ADVANCES IN THE ENDOVASCULAR TREATMENT FOR CEREBROVASCULAR DISEASES AND ITS COMPLICATIONS

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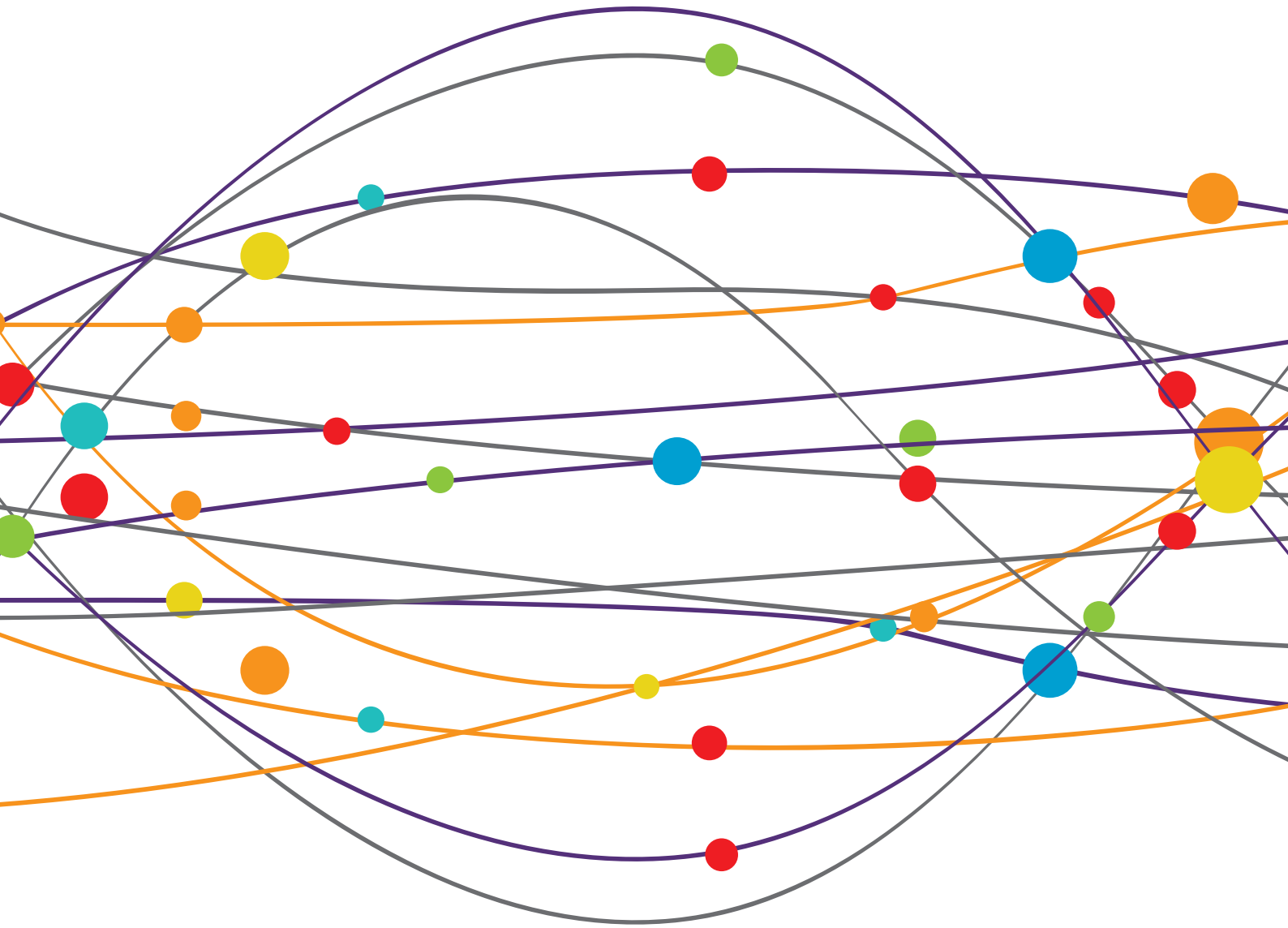

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ADVANCES IN THE ENDOVASCULAR TREATMENT FOR CEREBROVASCULAR DISEASES AND ITS COMPLICATIONS

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Symptomatic Atherosclerotic Non-acute Intracranial Vertebral Artery Total Occlusion: Clinical Features, Imaging Characteristics, Endovascular Recanalization, and Follow-up Outcomes

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Background and Objectives: Previous studies on symptomatic atherosclerotic non-acute intracranial vertebral artery total occlusion that was refractory to medical therapy are rare. We aimed to assess the clinical features, imaging characteristics, endovascular treatment feasibility and follow-up outcomes of patients with this condition.

Methods: Data from consecutive patients who had symptomatic atherosclerotic non-acute intracranial vertebral artery total occlusion and underwent endovascular recanalization from February 2016 to April 2020 were retrospectively collected in our prospective database. Clinical, imaging, procedural, and follow-up data were collected and analyzed.

Results: Thirty-one patients, predominantly males, were enrolled in this study. These patients presented with recurrent/progressive stroke in the posterior circulation despite aggressive medical therapy. Angiographic analysis revealed asymmetric vertebral arteries due to unilateral hypoplasia and intracranial vertebral artery total occlusions in the dominant vertebral arteries, which were characterized by long lesion length and high clot burden. Multiple infarctions and perfusion defects in the posterior circulation were demonstrated by diffusion-weighted imaging and arterial spin labeling, respectively. Successful endovascular recanalization was achieved in 87.1% of the patients. Over a median clinical follow-up duration of 11.0 months, 74.1% of patients with successful recanalization achieved favorable clinical outcomes (mRS score $\leq$2).

Conclusion: Symptomatic atherosclerotic non-acute intracranial vertebral artery total occlusion attributable to hypoperfusion is characterized by recurrent/progressive ischemic events, dominant intracranial vertebral artery total occlusion, long lesion length, and high clot burden. Endovascular recanalization of the dominant intracranial vertebral artery occlusion appears to be a feasible treatment for these patients.

Keywords: atherosclerosis, non-acute intracranial vertebral artery occlusion, features, endovascular treatment, outcome

INTRODUCTION

The intracranial vertebral artery (ICVA) is a common site of atherosclerotic occlusion that is often involved bilaterally; however, the ICVA has received the least attention, especially concerning the treatment of occlusive lesions (1). A subset of patients survive the acute ICVA occlusion stage and continue to suffer recurrent strokes and transient ischemic attacks (TIAs) in posterior circulation despite aggressive medical therapy in the subacute and chronic period (1–3). Hypoperfusion without adequate collateral circulation is a main mechanism for recurrent ischemic strokes and worsening symptoms, and it is highly likely that medical therapy will fail in these patients; rather, they will benefit from revascularization (4, 5).

Previous studies have been rare and are limited by small sample sizes of patients with symptomatic atherosclerotic non-acute ICVA total occlusion that was refractory to medical therapy (6–12). We aimed to assess the clinical features, imaging characteristics, endovascular treatment feasibility, and follow-up outcomes of these patients.

MATERIALS AND METHODS

Study Population

"Non-acute occlusion" was defined as symptomatic (TIA or stroke) complete occlusion of an intracranial artery of presumed atherosclerotic etiology in which endovascular therapy was performed more than 48 h from the time the patients was last seen well (6). We retrospectively reviewed our prospective stroke intervention database to identify consecutive patients who had symptomatic atherosclerotic non-acute ICVA total occlusion and underwent endovascular recanalization from February 2016 to April 2020. The Institutional Review Board of the First Affiliated Hospital of Shandong First Medical University approved the study.

The inclusion criteria were as follows: (1) intracranial atherosclerosis was the primary etiology; (2) experienced recurrent TIAs or stroke (neurological deterioration, such as deterioration of consciousness, hemiparesis, sensory disturbance, ataxia, dizziness, vertigo, dysarthria, dysphagia, diplopia, etc.) related to occluded vertebral artery despite aggressive medical treatment, which was defined as the treatment including dual-antiplatelet therapy, statin, blood pressure and glucose control, smoking cessation and an emphasis on healthy lifestyle; (3) total occlusion of dominant ICVA was confirmed by DSA; and (4) hemodynamic failure and hypoperfusion in the ICVA territory were confirmed based on the clinical and imaging evidence.

The exclusion criteria were as follows: (1) non-atherosclerotic occlusion, such as vasculitis, arterial dissection, or embolic disease; (2) clinical symptoms were stable with aggressive medical treatment; (3) contraindications to operation, such as known allergy or contraindication to aspirin, clopidogrel, or anesthesia; and (4) life expectancy<1 year because of other medical conditions.

Clinical Assessment

We assessed the patient demographic information and cardiovascular risk factors, including age, sex, hypertension, diabetes mellitus, hyperlipidemia, previous history of stroke, coronary artery disease, atrial fibrillation, and smoking. The modified Rankin scale (mRS) scores and the National Institutes of Health Stroke Scale (NIHSS) scores were determined by well-trained neurologists.

Radiological Assessment

ICVA total occlusion was initially assessed by non-invasive computed tomography angiography (CTA) or magnetic resonance angiography (MRA) and then confirmed by digital subtraction angiography (DSA). Total occlusion was defined as grade 0 antegrade flow distal to the occlusion by thrombolysis in the cerebral infarction (TICI) grading system on DSA. High-resolution magnetic resonance imaging (HRMRI) was used to analyze the occlusion etiology, occlusion course and luminal thrombosis of these patients. Magnetic resonance imaging (MRI) and arterial spin labeling (ASL) were used to assess multiple infarctions and regional hypoperfusion defects in the ICVA territory, respectively. Posterior circulation acute stroke prognosis early CT scores (pc-ASPECTS) on diffusion-weighted imaging (DWI), which were determined within 3 days before the procedure, were provided by well-trained neurologists.

Intervention Procedure

Dual antiplatelet treatment with 100 mg aspirin and 75 mg clopidogrel daily was routinely maintained for at least 5 days before the procedure, and thromboelastography platelet mapping was performed to guide the modulation of antiplatelet treatment. The details of the interventional procedure have been described previously (13, 14). The lesions were initially predilated with conventional balloons (Gateway balloon, Boston Scientific, USA). Drug-coated balloon (DCB) (SeQuent Please, B. Braun, Germany) have been applied after conventional balloon angioplasty to inhibit intimal hyperplasia and restenosis in later research (15, 16). When the residual stenosis was >50% and the antegrade perfusion was unstable, or there was vessel dissection after balloon angioplasty, remedial stenting implantation was performed (Wingspan stent, Stryker Neurovascular, USA; Solitaire AB stent, Medtronic, United States; Apollo stent, Microport Neuro Tech, China, Xience Prime stent, Abbott Vascular, United States) (17). Transcatheter aspiration was applied to reduce the clot burden prior to angioplasty when the clot burden was high proximal to the occlusion segment. Intravenous low dose tirofiban injection was administered when there were obvious clots at and around the occlusion lesions.

Post-procedural antegrade flow was graded using the TICI grading system, and technical success was determined by recanalization with a TICI grade ≥2b on post-procedural angiography. Procedure complications included perforating branch occlusion, embolization, hyperperfusion syndrome, intracranial hemorrhage (ICH), subarachnoid hemorrhage, vessel perforation and dissection.

TABLE 1 | Baseline clinical variables.

Baseline clinical variables	*N* = 31 (%)
Age(years), mean (SD)	58.9 ± 8.5
Male	27 (87.1)
Hypertension	29 (93.5)
Diabetes mellitus	14 (45.2)
Coronary artery disease	11 (35.5)
Previous history of stroke	8 (25.8)
Hyperlipidemia	2 (6.5)
Atrial fibrillation	2 (6.5)
Smoking	22 (71.0)
Pre-treatment NIHSS, median (IQR)	4 (2–7)
Pre-treatment mRS, median (IQR)	3 (2–4)
Pre-treatment pc-ASPECTS on DWI, median (IQR)	6 (5–7)

NIHSS, National Institutes of Health Stroke Scale; mRS, modified Rankin scale; pc-ASPECTS, posterior circulation acute stroke prognosis early CT score; DWI, diffusion-weighted imaging; SD, standard deviation; IQR, interquartile range.

Follow-up Outcomes

All patients were discharged on dual antiplatelets, consisting of aspirin and clopidogrel, and were required to remain on the dual antiplatelet regimen for 3 months for angioplasty and 6 months for stenting, after which they continued with one of the two drugs. Patients were also treated with statins and other risk factor controls.

These patients were followed up clinically at 1 month, and all the patients were followed up clinically in May 2020. They were scheduled for DSA at 3–6 months. Favorable functional outcome was defined as an mRS score 0–2. Restenosis was defined as a diameter of the stenosis >50% of the target artery segment. Symptomatic restenosis was defined as restenosis associated with ischemic symptoms of the treated vessel territory.

Statistical Analysis

Continuous data are expressed as the mean ± standard deviation (SD) or as the median with the interquartile range (IQR). Categorical data are expressed as numbers and percentages. Statistical analysis was performed using SPSS version 19.0 for Windows (SPSS Inc., Chicago, IL, United States).

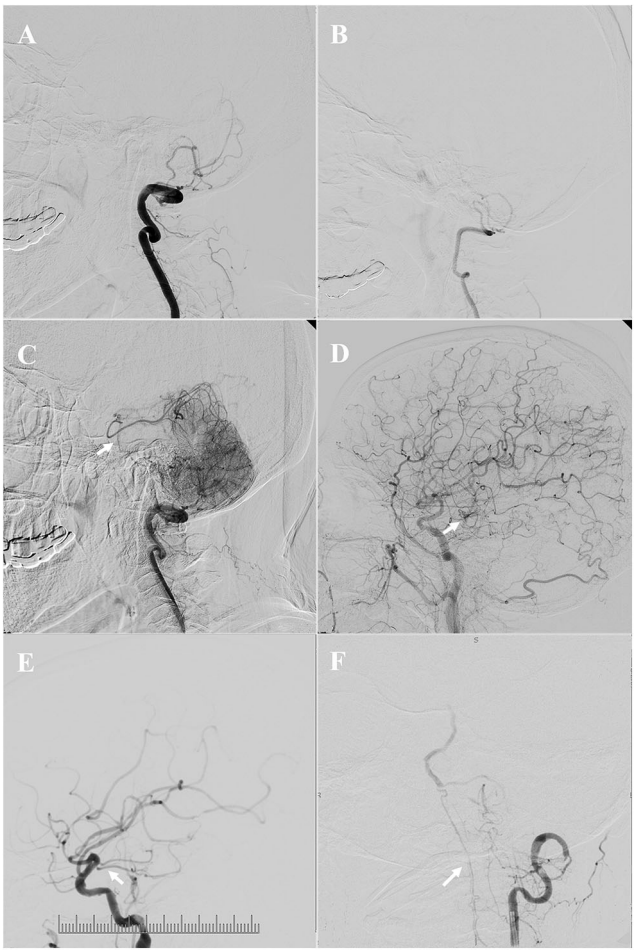

FIGURE 1 | Angiographic features and collateral circulation. Illustrative patient 18 **(A–D)**: asymmetric vertebral arteries (VA) due to unilateral hypoplasia, the dominant intracranial vertebral artery (ICVA) was totally occluded **(A)**, the blood flow of the contralateral hypoplastic VA was tenuous, and ended in the posterior inferior cerebellar artery (PICA) **(B)**; the collateral flow from posterior and anterior leptomeningeal anastomosis was limited at late arterial phases [**(C,D)**, the arrow indicates the top of the basilar artery]. Illustrative patient 1**(E)**: the arrow indicates a tiny posterior communicating artery (PComA). Illustrative patient 19 **(F)**: the arrow indicates upward retrograde flow through the anterior spinal artery (ASA).

RESULTS

Clinical Features

Thirty-one patients, predominantly males (27/31, 87.1%), were enrolled in this study (**Supplementary Table 1**). Baseline clinical characteristics are listed in **Table 1**. The mean age of the patients was 58.9 ± 8.5 years. The most common risk factors were hypertension (29/31, 93.5%), smoking (22/31, 71.0%), diabetes mellitus (14/31, 45.2%), coronary artery disease (11/31, 35.5%) and previous history of stroke (8/31, 25.8%).

All these patients were treated with aggressive medical therapy since presentation and still experienced recurrent and progressive strokes in the posterior circulation. Common symptoms included dizziness and vertigo, dysarthria, dysphagia, diplopia, blurred vision, ataxia, hemiparesis, sensory disturbance, headache, hearing loss, and so on. Lifestyle-limiting symptoms that were exacerbated by activity or decreases in blood pressure, such as aggravated dizziness and vertigo, blurred vision, ataxia, and headache after standing or walking, were prominent in these patients.

The pretreatment median mRS and NIHSS scores at baseline were 3 (IQR, 2–4) and 4 (IQR, 2–7), respectively. A total of 61.3% (19/31) of these patients had low NIHSS scores (<6), whereas these patients also had poor quality of life because of serious vertigo, dysphagia, diplopia, or ataxia.

Imaging Characteristics

Angiographic analysis revealed that the vertebral arteries (VA) of all these patients were asymmetric due to unilateral hypoplasia,

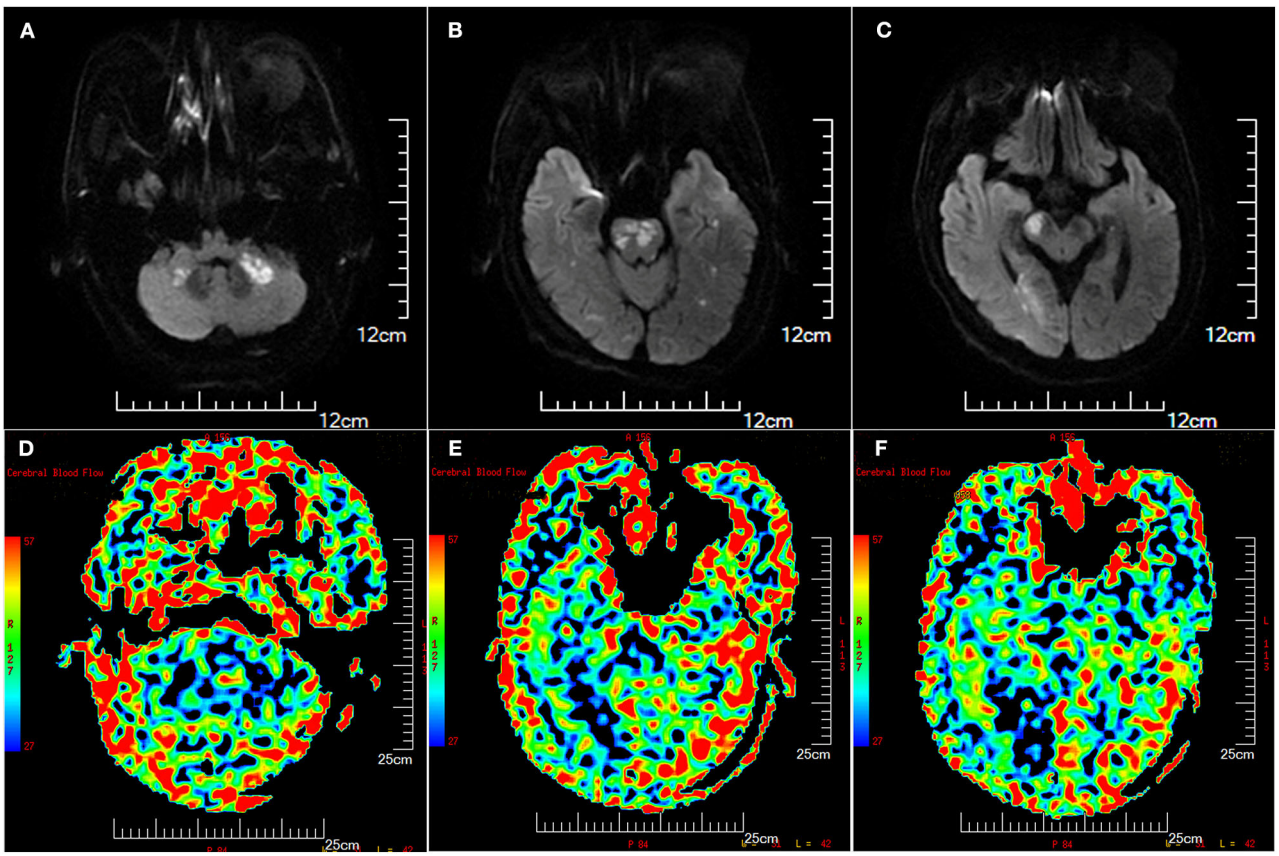

FIGURE 2 | Illustration of multiple infarctions and perfusion defects in the posterior circulation (patient 8), which were detected by diffusion-weighted imaging (DWI) **(A–C)** and arterial spin labeling (ASL) **(D–F)**, respectively. The Scale for ASL [image **(D–F)**] was color coded (red, largest cerebral blood flow; blue, least cerebral blood flow). ASL images showed larger perfusion deficits including the brain stem, cerebellum, and occipital lobe.

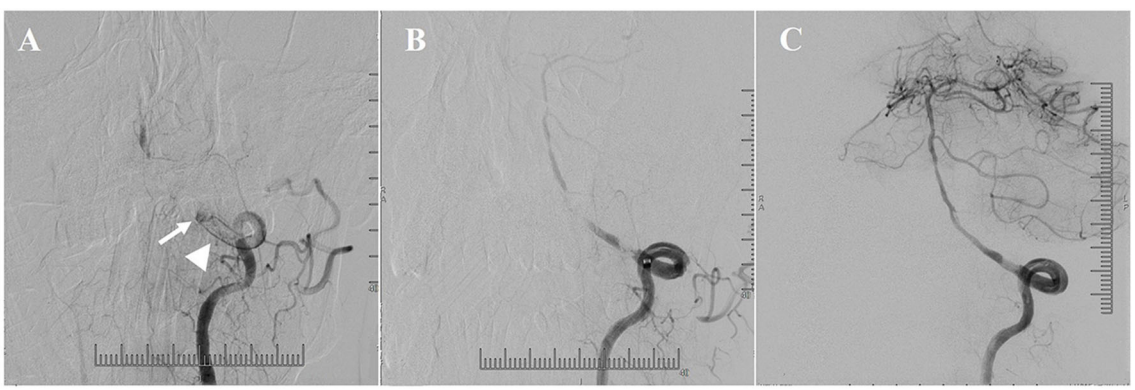

FIGURE 3 | Illustrative patient 20. **(A)** A lot of clots (arrowhead) proximal to the occlusion segment (arrow). **(B)** Angiographic result after transcatheter aspiration. **(C)** Favorable antegrade flow was obtained after conventional balloon and drug-coated balloon (DCB) angioplasty.

and ICVA total occlusions occurred in the dominant VA (**Figure 1**). The blood flow of the contralateral hypoplastic VA was tenuous, as 71.0% (22/31) of the contralateral hypoplastic VA ended in the posterior inferior cerebellar artery (PICA), 9.7% (3/31) of the contralateral hypoplastic VA ended before entering the skull, 6.5% (2/31) of the contralateral hypoplastic VA had multiple serious stenoses, and 12.9% (4/31) of the contralateral hypoplastic VA had whole-course extreme hypoplasia.

MRI revealed multiple infarcts in the cerebellum, medulla oblongata, pontine, midbrain, thalamus, splenium of the corpus

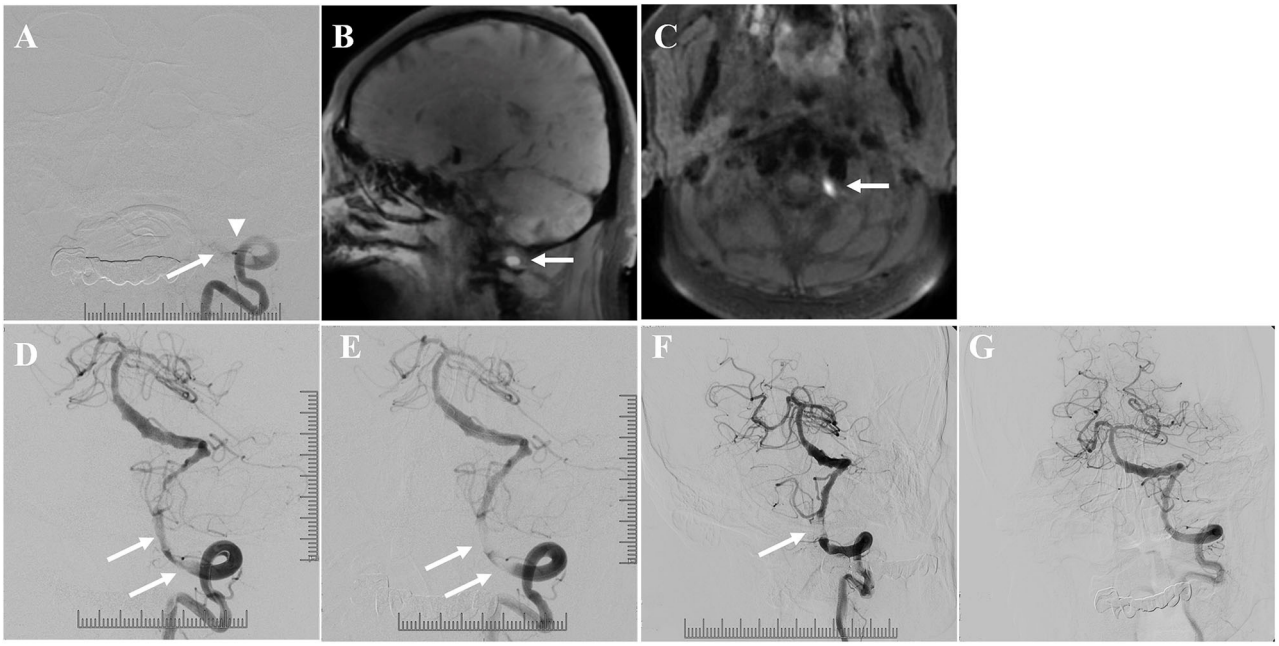

FIGURE 4 | Illustrative patient 14: **(A)** Total occlusion (arrow) of the ICVA with obvious clots at and proximal to the occlusion segment (arrowhead) on digital subtraction angiography (DSA). **(B,C)** Clots with high signal intensity (arrow) on pre-contrast T1-weighted high-resolution magnetic resonance imaging (HRMRI). **(D)** Angiographic result after conventional balloon angioplasty. There were obvious clots (arrow). **(E)** Angiographic results after stenting demonstrated favorable antegrade flow, despite persistent clots (arrow). **(F)** The patient was treated with intravenous low-dose tirofiban injection and dual antiplatelets for 7 days. DSA 7 days later showed good antegrade flow with interval reduction in clot burden (the arrow indicates the residual clots). **(G)** Then, the patient was treated with dual antiplatelets after discharge. DSA 5 months later showed that the antegrade flow was good, without restenosis or obvious clots.

callosum, and temporal and occipital lobes in the ICVA territory. Pre-treatment pc-ASPECTS on DWI was 6 (IQR, 5–7).

A total of 25.8% (8/31) of the patients had a posterior communicating artery (PComA), 38.7% (12/31) of the patients had upward retrograde flow through the anterior spinal artery (ASA), and 6.5% (2/31) of the patients had PComA and upward retrograde flow through the ASA. However, the PComA was tiny in these patients, and the collateral blood flow of these patients through PComA, ASA, and leptomeningeal anastomosis was tenuous and limited (**Figure 1**). The American Society of Interventional and Therapeutic Neuroradiology/Society of Interventional Radiology Collateral Flow Grading System score of all these patients was <3 on DSA. Relatively small and multiple infarctions on DWI with a large area of low perfusion assessed by ASL demonstrated hypoperfusion defects in the ICVA territory of these patients (**Figure 2**).

Obvious clots occurred in 41.9% (13/31) of the patients at or around the ICVA occlusion lesions, which was detected by DSA and HRMRI. The clots were divided into three categories according to the location: occlusion segment, distal to the occlusion segment, and proximal to the occlusion segment (**Figures 3**–**5**).

Endovascular Treatment

The endovascular procedure was applied for the dominant ICVA total occlusion of these patients. The median time from symptom onset to endovascular treatment was 23.0 days (IQR, 15.0–53.5 days), and the median time from image-documented ICVA total occlusion to endovascular treatment was 14.0 days (IQR, 7.0–29.5 days).

Transcatheter aspiration prior to angioplasty was able to effectively reduce the clot burden proximal to the occlusion segment (**Figure 3**). Favorable antegrade flow was achieved after angioplasty and stenting despite obvious clots at and proximal to the occlusion segment (**Figures 3**, **4**).

Successful recanalization was achieved in 87.1% (27/31) of the patients, with TICI 3 reperfusion in 25 cases (80.6%, 25/31) and TICI 2b reperfusion in 2 cases (6.5%, 2/31). The treatment modalities and outcomes of the patients are summarized in **Table 2**. DCBs were used in 15 cases after conventional balloon dilatation to inhibit intimal hyperplasia. A total of 44.4% (12/27) of the patients had a long lesion length and underwent stenting with a stent ≥20 mm in length. One patient was treated with two Wingspan stents (4 * 15 mm, 4.5 * 20 mm) because of the long lesion length, and the other 11 patients were treated with one stent that was ≥20 mm in length (one patient was treated with a Xience Prime stent that was 28 mm in length, three patients were treated with a Xience Prime stent that was 23 mm in length, six patients were treated with a Wingspan stent that was 20 mm in length, and one patient was treated with a Solitaire AB stent that was 20 mm in length). The median residual stenosis after the procedure was 15.0% (IQR, 10.0–25.0%).

The procedure failed in four patients because the guidewire could not traverse the occluded segment. Six patients experienced

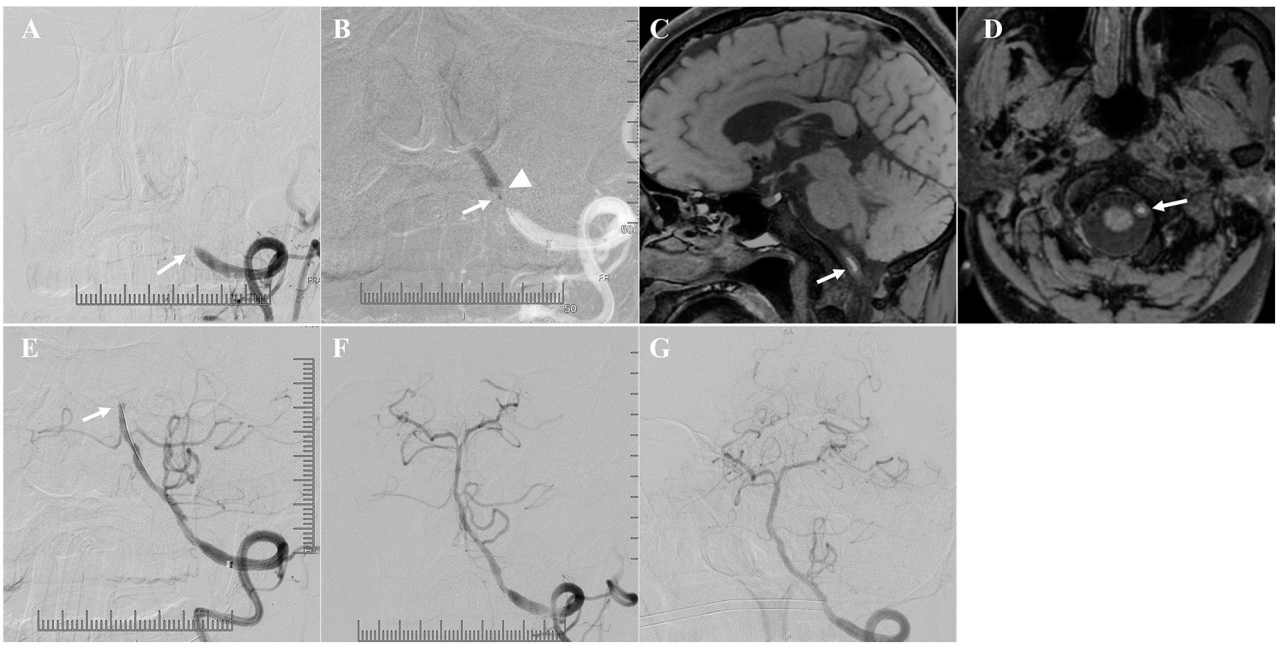

FIGURE 5 | Illustrative patient 30. **(A)** Total occlusion of the intracranial vertebral artery (ICVA) (arrow). **(B)** Microcatheter angiography (the arrow indicates the position of the microcatheter) showed a relatively short occlusion segment and obvious filling defects distal to the occlusion segment (arrowhead). The filling defects were clots distal to the occlusion segment. **(C,D)** Clots with high signal intensity distal to the occlusion segment on pre-contrast T1-weighted high-resolution magnetic resonance imaging (HRMRI) (arrow). **(E)** Angiographic results after conventional balloon and drug-coated balloon angioplasty demonstrated migration of the clots to the distal segment of the basilar artery. Distal antegrade flow could not be seen (arrow). **(F)** Favorable antegrade flow was obtained after emergency transcatheter aspiration. **(G)** Angiography 3 months later demonstrated favorable antegrade flow without restenosis.

procedural related complications, of whom only three patients were symptomatic. Perforating branch occlusion occurred in two patients, and symptomatic dissection occurred in one patient. The three patients had new infarcts in posterior circulation after the procedure, and their mRS scores were 1, 3, and 3 at the last follow-up, respectively.

Asymptomatic ICH occurred in one patient after the procedure. Hemorrhage was detected in the previous occipital lobe infarction, which may have resulted from hyperperfusion after recanalization. Asymptomatic embolization occurred in two patients who had clots distal to the occlusion lesions, and neither of them exhibited new clinical manifestations with emergency mechanical thrombectomy (MT) (**Figure 5**). Other periprocedural complications, such as subarachnoid hemorrhage or perforation, did not occur in this case series.

Clinical and Angiographic Follow-up Data

The clinical and angiographic follow-up outcomes of successfully treated patients are presented in **Table 3**. The lifestyle-limiting symptoms improved quickly within several days in the patients with successful recanalization. Unexpectedly, the symptom of hearing loss also improved quickly within several days after the procedure. The symptom improvement rate after the procedure was 85.2% (23/27) for these patients. At the first 30-day clinical follow-up, there were no recurrent cerebral ischemic events; 66.7% (18/27) of the patients achieved a favorable clinical outcome (mRS score$\leq$2), and 85.2% (23/27) of the patients achieved an acceptable clinical outcome (mRS score$\leq$3). Over a median clinical follow-up duration of 11.0 months, 74.1% (20/27) of the patients achieved a favorable clinical outcome (mRS score $\leq$2), and 88.9% (24/27) of the patients achieved an acceptable clinical outcome (mRS score $\leq$3) at the last follow-up. There was one death due to multiple organ failure.

During the 5.5 $\pm$ 2.6 months vessel imaging follow-up period, DSA was obtained for 18 patients, and CTA was obtained for 2 patients. Angiographic follow-up demonstrated continuous clot dissolution in these patients after successful endovascular recanalization (**Figure 4**). Restenosis occurred in 10% (2/20) of patients who had follow-up imaging: one presented with angiographic asymptomatic restenosis; whereas the other presented with symptomatic reocclusion 7.5 months after the procedure, and this patient was neurologically independent with emergency MT and stenting, the mRS of this patient was 0 before discharge. No recurrent stroke occurred in other patients with successful recanalization during the clinical follow-up period.

DISCUSSION

In our study, patients with symptomatic atherosclerotic non-acute ICVA total occlusion were treated with aggressive medical therapy since presentation, but they were still hemodynamically unstable and experienced recurrent and progressive ischemic

TABLE 2 | Procedural characteristics.

Variables	*N* = 31 (%)
Symptom onset to treatment (days), median (IQR)	23.0 (15.0–53.5)
Image-documented occlusion to treatment (days), median (IQR)	14.0 (7.0–29.5)
Technical success	27 (87.1)
Modality of recanalization	
CBA	3 (9.7)
CBA+stenting	9 (29.0)
CBA+DCBA	8 (25.8)
CBA+DCBA+stenting	7 (22.6)
Post-procedural perfusion	
TICI 3	25 (80.6)
TICI 2b	2 (6.5)
TICI 0	4 (12.9%)
Residual stenosis, median (IQR)	15.0% (10.0–25.0)
Complication rate	6 (19.4)
Perforating branch occlusion	2 (6.5)
Embolization	2 (6.5)
Dissection	1 (3.2)
Asymptomatic ICH	1 (3.2)
Symptomatic complication rate	3 (9.7)
Perforating branch occlusion	2 (6.5)
Dissection	1 (3.2)

CBA, conventional balloon angioplasty; DCBA, drug-coated balloon angioplasty; TICI, thrombolysis in cerebral infarction; ICH, intracranial hemorrhage; IQR, interquartile range.

TABLE 3 | Clinical and angiographic outcomes of successfully treated patients.

Variables	*N* = 27 %	Median (IQR)
Follow-up time(months)		11.0(5.0–26.5)
Symptom improved post-procedure	23 (85.2)	
30-day mRS score ≤2	18 (66.7)	
30-day mRS score ≤3	23 (85.2)	
mRS score at last follow-up ≤2	20 (74.1)	
mRS score at last follow-up ≤3	24 (88.9)	
Ischemic event during follow-up	1 (3.2)	
Death	1 (3.2)	
Restenosis on follow-up image	10% (2/20)	

mRS, modified Rankin scale; IQR, interquartile range.

events despite aggressive medical therapy. Therefore, they were transferred to our comprehensive stroke center for further treatment. These patients had asymmetric VA due to unilateral hypoplasia, and ICVA total occlusions occurred in the dominant VA. The blood flow of the contralateral hypoplastic VA was tenuous, and most of them ended in the PICA. This condition exposed these patients to the risk of a catastrophic stroke in the basilar artery territory.

Limitations of NIHSS include a focus on limb and speech impairments and less emphasis on cranial nerve lesions. Patients with symptomatic ICVA total occlusions may have low NIHSS scores, whereas the mRS scores of these patients can be high because of serious vertigo, dysphagia, diplopia, or ataxia, so we did not stratify the patients by NIHSS score. Pc-ASPECTS on DWI is helpful in predicting functional outcome in posterior circulation ischemic stroke (18), and the low pretreatment median pc-ASPECTS (6, IQR, 5–7) on DWI indicated a poor prognosis for these patients.

The collateral flow from PComA, ASA and leptomeningeal anastomosis was limited and failed to provide sufficient blood flow and perfusion. We speculate that serious hypoperfusion without adequate collateral circulation was the main mechanism for medical therapy failure and recurrent ischemic events in these patients. The mechanism of artery-to-artery embolism based on hypoperfusion may also contribute to recurrent and progressive stroke in these patients (19). The ICVA occlusions caused hypoperfusion, and the resulting sluggish blood flow promoted the formation of clots that formed emboli. Obvious clots occurred in 41.9% (13/31) of these patients at and around the ICVA occlusion lesions in this study. Hypoperfusion and related changes in the dynamics of blood flow in the cerebral arteries also prevented the clearing of distal emboli.

The management of these patients is a medical dilemma. Patients who have hemodynamic compromise and comparatively slow infarct growth are highly likely to benefit from delayed recanalization. We demonstrated that endovascular recanalization appeared to be feasible for symptomatic atherosclerotic non-acute ICVA total occlusion attributable to hypoperfusion in this study. Based on our single-arm study results, we are not able to draw conclusions about the efficacy of delayed endovascular recanalization for these patients. However, all these patients presented with recurrent and progressive stroke despite aggressive medical therapy before the procedure, and it is encouraging to see that the hypoperfusion related lifestyle-limiting symptoms improved quickly within several days after the procedure in patients with successful recanalization. Over a median clinical follow-up duration of 11.0 months for the patients with successful recanalization, 74.1% (20/27) of these patients achieved a favorable clinical outcome (mRS score ≤2), and 88.9% (24/27) of these patients achieved an acceptable clinical outcome (mRS score ≤3). Except for one patient suffering symptomatic reocclusion 7.5 months after the procedure, there was no recurrent stroke during the clinical follow-up period in other patients with successful recanalization.

Although the symptomatic complication rate in this study was not very high (9.7%, 3/31), it should be emphasized that endovascular recanalization for non-acute ICVA occlusion is a high-risk procedure. Together failed procedure and symptomatic complication was 22.5% of patients, and all complications and failed procedures occurred in 32.3% of patients. Symptomatic atherosclerotic non-acute ICVA occlusion features a long lesion length (44.4%,12/27) and high clot burden (41.9%, 13/31), which makes the endovascular recanalization procedure more challenging in these patients than in patients who with non-acute middle cerebral artery occlusion or non-acute basilar artery (BA) occlusion (13, 14). The management of clots based on ICVA occlusion lesions was critical during the procedure. Transcatheter aspiration prior to angioplasty can effectively reduce the clot burden proximal to the occlusion segment, and

this is a potential treatment to obtain better reperfusion and improve the prognosis. Angiographic follow-up demonstrated that continuous clot dissolution was achieved after successful recanalization in these patients. Embolization risk is very high and difficult to prevent in patients with clots distal to the occlusion segments. The clots breaking up and embolizing the distal segment of BA can cause life threatening complications. HRMRI is helpful in the diagnosis of ICVA occlusion and luminal thrombosis (20) and can help us to identify the subset of patients with high embolism risk before the procedure. At present, there is no embolic protection device to reduce embolization complications. The intervention procedure must be cautiously performed by experienced interventionalists, and emergency MT is critical for patients suffering embolization complications. The selection of eligible patients and the correct treatment for complications are equally critical.

There are several limitations of our study. First, this study is a single-center study; thus, selection bias may be possible. Other main limitations are its retrospective nature and a lack of a control arm. Prospective randomized controlled trials are needed to investigate whether endovascular recanalization compares favorably with aggressive medical management in these patients.

CONCLUSIONS

Patients with symptomatic atherosclerotic non-acute ICVA total occlusion presented with recurrent and progressive ischemic events despite aggressive medical therapy. These patients had asymmetric VA due to unilateral hypoplasia, and ICVA total occlusions occurred in the dominant VA. The dominant ICVA total occlusion was characterized by long lesion length and high clot burden. These patients had relatively small multiple infarctions and large perfusion defects in the posterior circulation. Hypoperfusion without adequate circulation played a critical role in the recurrent ischemic events and lifestyle-limiting symptoms in these patients and endovascular recanalization appeared to be a technically feasible treatment for these patients.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary materials, further inquiries can be directed to the corresponding author.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Institutional Review Board of the First Affiliated Hospital of Shandong First Medical University. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

WZ contributed to the design of the study, acquisition, analysis and interpretation of the data, drafting of the article and revision of the content, and final approval of the paper. JuZ, YM, and YZ contributed to the analysis of the data and the revision of content and the final approval of the article. JiZ, YS, LS, and MZ contributed to the analysis of the data and the final approval of the article. WW and HY contributed to the statistical analysis and the final approval of the article. JH contributed to the conception and design of the study, acquisition and analysis of the data, drafting of the article, revision of the content, and final approval of the article. All authors contributed to the article and approved the submitted version.

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SUPPLEMENTARY MATERIAL

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ORIGINAL RESEARCH
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Hemodynamic Effect of the Last Finishing Coils in Packing the Aneurysm Neck

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Background: Using the finishing coils to densely pack the aneurysm neck is necessary. However, the exact hemodynamic effect of finishing coils in packing the aneurysm neck is unknown.

Objective: To evaluate the hemodynamic characteristics of finishing coils to densely pack the aneurysm neck, using finite element method simulation.

Methods: A computational study was performed based on a 44-year-old female patient with an unruptured wide-necked carotid-ophthalmic artery aneurysm treated with low-profile visualized intraluminal support stent-assisted coil embolization. Four computational fluid dynamics models including pre-treatment, post-stenting, common stent-assisted coil embolization (SACE), and common SACE with finishing coils were evaluated qualitatively and quantitatively.

Results: Compared with the baseline of pretreatment model (100%), sac-averaged velocity in post-stenting, common SACE, and common SACE with finishing coil models decreased to 95.68%, 24.38%, and 13.20%, respectively; high flow volume (>0.1 m/s) around the aneurysm neck decreased to 92.19%, 9.59%, and 5.57%, respectively; and mean wall shear stress increased or decreased to 107%, 25.94%, and 23.89%, respectively.

Conclusion: Finishing coils to densely pack the aneurysm neck can generate favorable hemodynamic modifications, which may decrease the recurrence.

Keywords: hemodynamics, intracranial aneurysms, stent, coiling, recurrence

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INTRODUCTION

Coil embolization for intracranial aneurysms (IAs) is an effective treatment modality which is far less invasive than the long-standing convention of surgical clipping (1). However, recanalization and coil compaction after embolization is not uncommon, with recurrence rates as high as over 30% reported in the literature (2, 3). One factor that may contribute to recurrence after coiling is residual inflow in the aneurysmal sac (4). Therefore, coiling density is an important factor to predict post-coiling outcomes, and usually aneurysms are packed as densely as possible to avoid coil compaction (5–7). Stent-assisted coiling embolization (SACE) has also been found to reduce the recurrence of wide-necked aneurysm embolization (8). However, some wide-necked aneurysms after SACE can still be found recanalized especially at the aneurysm neck. Consequently, densely coiling the aneurysm neck is necessary.

The coils to pack the aneurysm sac could be divided into frame coils, filling coils, and finishing coils. However, the exact hemodynamic effect of finishing coils in packing the aneurysm neck is unknown. This study aims to investigate the hemodynamic characteristics of finishing coils to densely pack the aneurysm neck, using finite element method (FEM) simulation.

METHODS

Computational Fluid Dynamics (CFD) Study Protocol Design

The hemodynamics of four models including pre-treatment, post-stenting, common SACE, and common SACE with finishing coils were evaluated qualitatively and quantitatively. Packing density is defined as the ratio between the inserted coils and aneurysm volume.

Aneurysm Model

A 44-year-old female patient with an incidentally found right carotid-ophthalmic artery wide-necked aneurysm (dome and neck dimension: 5.45 mm/3.37 mm) was treated with low-profile visualized intraluminal support (LVIS) stent-assisted densely coiling aneurysm neck technique and included in this CFD study (**Figure 1**).

The carotid-ophthalmic aneurysm was reconstructed in this study for demonstrating the hemodynamic effect of finishing coils to densely pack the aneurysm neck. 3D rotational angiography images were obtained and 3D reconstruction in surface-triangulation format and isolation of the region of interest were performed through the open source software, VMTK (www.vmtk.org). For the FEM analysis, CFD meshing, and flow simulation, a 3D segmented geometry was cleared by using Geomagic tool (Geomagic, Morrisville, NC).

Finite-Element Method Modeling of Coiling and Stent Deployment

LVIS stent (3.5 × 15 mm; MicroVention-Terumo, Tustin, CA) was generated virtually using SolidWorks (Dassault Systemes; SolidWorks, Waltham, MA) and transformed into finite element analysis (FEA) software ABAQUS (SIMULIA, Providence, RI) to perform the stenting of aneurysm. Meanwhile, frame and helical coils were generated in MATLAB (MathWorks, Natwick, MA) and the shape of these coils was simplified by using a centerline (9). A continuous cylindrical structure in 3D shape was assumed for the coils and then the coils were swept to 3D configuration after deployed in the aneurysm sac (10, 11).

The FEA-based workflow for stent deployment modeling was performed in ABAQUS/Explicit v6.14, and the stent was modeled with nitinol super-elasticity material and the parameter values were obtained from previous studies by Reedlunn et al. (9). The simulation consists of three steps: crimping, delivery, and deployment. The crimping of stent was performed and used for the initial condition for the delivery process through the predefined field tool in ABAQUS. A delivery path was generated with central points of the cross-sections of the blood vessel and the crimped stent within microcatheter was delivered through the path to the orifice of the aneurysm according to the process of delivery of a stent during clinical treatment. The crimped stent was assembled in a microcatheter in the global coordinate system and delivered to the aneurysm orifice of the pre-treated model through a displacement load according to the central points of the arterial wall along the delivery path. With the predefined stress–strain field, the stent was released in the next step. A "general contact" algorithm in ABAQUS was used for the complex interactions during the stent delivery and deployment procedures, with a friction coefficient value of 0.15.

After the stent deployment, SACE with small hyper-soft coils densely packing the aneurysm neck model was created after 11 coils including one 6 mm × 20 cm coil, one 5 mm × 20 cm coil, one 3 mm × 8 cm coil, two 3 mm × 6 cm coils, one 1.5 mm × 4 cm coil, four 1.5 mm × 3 cm coils, and one 1 mm × 3 cm coil (MicroPlex-10; MicroVention, Aliso Viejo, CA). All the coils were swept to 3D solid model using ABAQUS/CAE with the real diameter of the coils and were then successively deployed into the aneurysm. Common SACE model was built without deploying the last two hyper-soft coils to keep the configuration of the previous coils under out of the outline of adjacent parent artery according to the actual operation (**Figure 1B**). To the end, the surface-based aneurysm and vessel model with the 3D representation of coils and the stent was subsequently used for the CFD analysis. The detailed process and methods in simulation of patient-specific endovascular stenting and coiling for intracranial aneurysm using FEM can be found in our previous study (12).

CFD Simulation

The aneurysm model was meshed with polyhedral grids and four-layer wall prism elements (for accurate boundary layer resolution) consisting of ∼2 million elements for pre-treatment model and up to 20 million cells for SACE model using ICEM-CFD meshing tool (Ansys, Canonsburg, PA). Incompressible Navier–Stokes equations under steady flow conditions was used to obtain the numerical solution by using the finite volume CFD solver, CFX V19 (Ansys, Canonsburg, PA). The mean flow rate for ICA inlet was 4.6 ml/s and used as inlet boundary conditions. Traction-free boundary conditions were applied at the outlet and the mass flow rate through each outlet vessel was set to be proportional to the cube of its diameter based on the principle of optimal work (13). With a density of 1,056 kg/m^3 and a dynamic viscosity of 0.0035 N·s/m^2, the blood was modeled as a Newtonian fluid material. The vessel walls were modeled as a rigid wall with no-slip boundary conditions.

For qualitative analysis, the aneurysmal flow streamlines, iso-velocity surface (high flow region around the neck plane), and wall shear stress (WSS) were analyzed. Taking the pre-treatment model as the baseline (100%), sac-averaged velocity, high velocity regions, and sac-averaged WSS were analyzed quantitatively. High velocity regions were defined where flow velocity magnitudes are larger than 0.1 m/s. WSS indicated the friction force between blood and inner surface of arterial wall, which was found to have an essential influence on aneurysm initiation, growth, and rupture (14, 15).

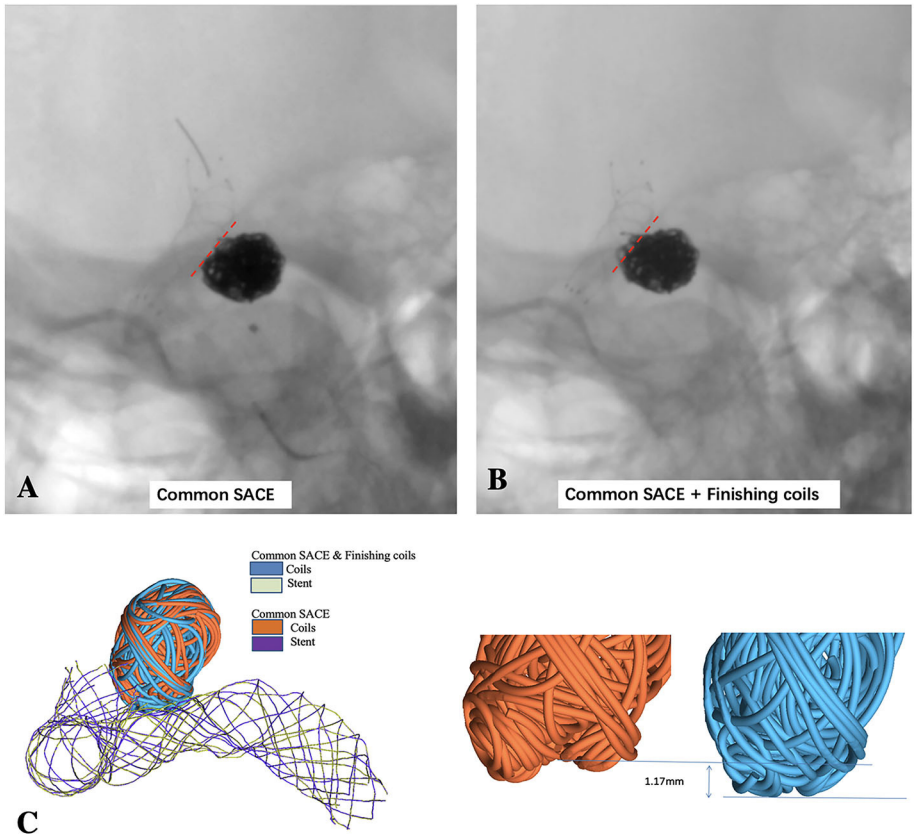

FIGURE 1 | LVIS stent-assisted common coiling without deploying the last two small coils to keep the coil configuration under out the outline of the parent artery **(A)** and LVIS stent-assisted coiling with small hyper-soft coils densely coiling the aneurysmal neck **(B)** are observed in the un-subtracted angiographies; **(C)** schematic diagram of LVIS stent-assisted coiling with small coils densely packing aneurysmal neck model and common SACE model using finite element method (FEM) simulation.

RESULTS

Qualitative Analysis of CFD

CFD simulations for four models were performed with color-coded streamlines, iso-velocity surface, and WSS, respectively (**Figure 2**). For flow streamlines, high flow volume via iso-velocity surface, and WSS in the aneurysmal sac, compared with the pre-treatment model, the other models decreased dramatically except the stenting model. In the four models, the reduction in high flow regions around the common SACE with finishing coils model was mildly stronger than for common SACE, whereas WSS in aneurysmal sac was comparable with that of common SACE model.

Quantitative Analysis of CFD

The aneurysmal volume was 123.61 mm^3 and the packing density is 33.49% in the common coiling models. Compared with the baseline of pretreatment model (100%), sac-averaged velocity in stenting, common SACE, and common SACE with finishing coil models decreased to 95.68%, 24.38%, and 13.20%, respectively; high flow volume (>0.1 m/s) around the aneurysm neck decreased to 92.19%, 9.59%, and 5.57%, respectively; and mean WSS increased or decreased to 107%, 25.94%, and 23.89%, respectively (**Figure 3**).

DISCUSSION

The present study simulated the procedure of the LVIS stent-assisted coil embolization in a carotid-ophthalmic aneurysm and evaluated its CFD characteristics qualitatively and quantitatively. Two main findings were obtained from our numerical modeling and data analyses. First, this study is the first to simulate LVIS SACE with small hyper-soft coils densely packing the sidewall aneurysm neck using finite element methods. Second, common SACE with finishing coil model substantially reduced the flow for both sac-averaged velocity and high flow volume compared with common SACE. To our knowledge, this study is the first to evaluate the hemodynamic characteristics of last finishing coils based on CFD simulation and provide a proof of concept of hemodynamic modifications resulting from small hyper-soft coils densely coiling the aneurysm neck.

It has been hypothesized that the decreased blood flow in the aneurysmal sac induced by coiling may initiate thrombosis, subsequent clot formation, and fibrosis (16). Residual blood

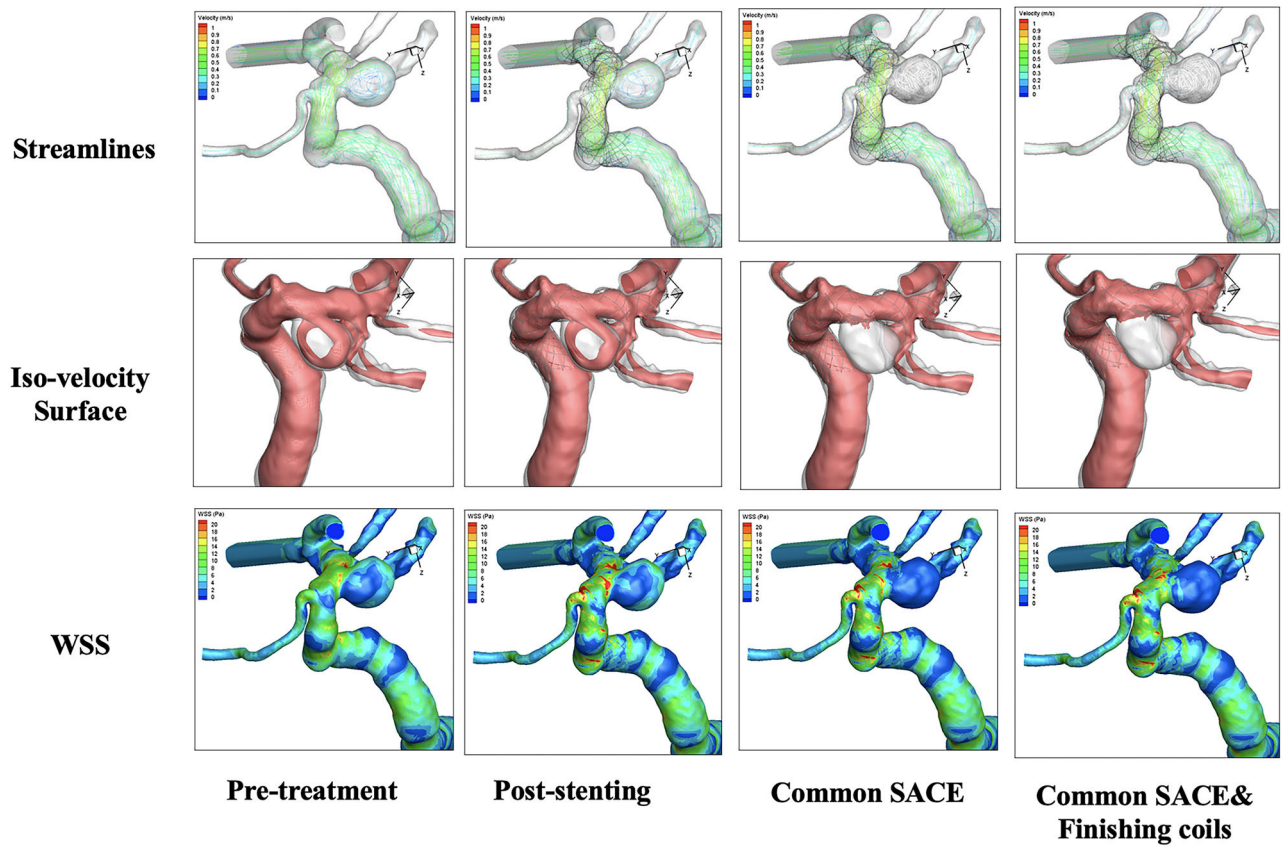

FIGURE 2 | Qualitative comparison was performed in the four models including pre-treatment, post-stenting, common SACE, and common SACE with finishing coils.

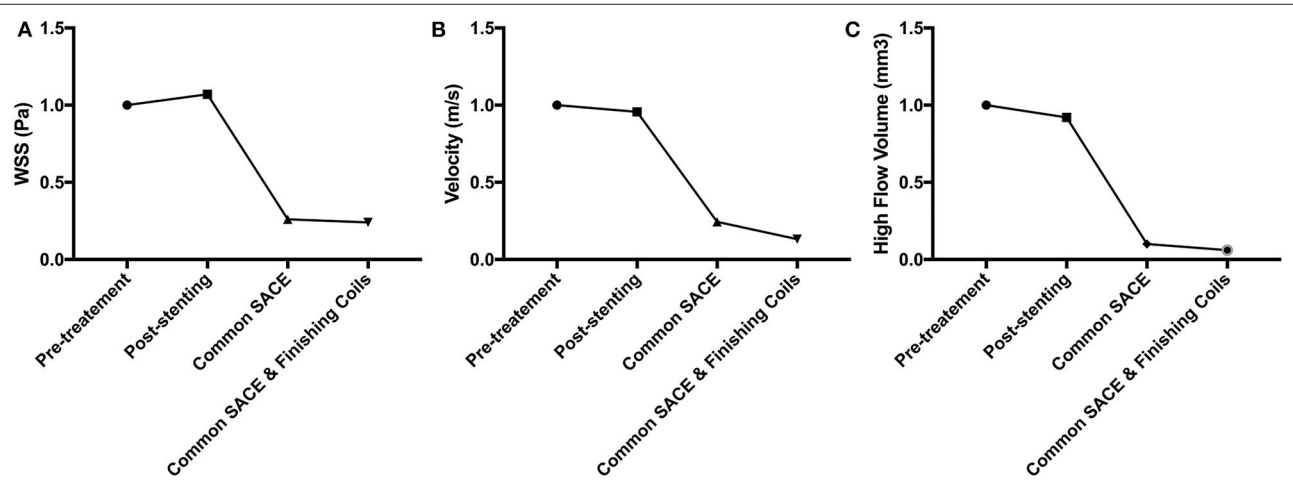

FIGURE 3 | CFD simulation results for WSS magnitude **(A)**, average velocity **(B)**, and high flow volume (>0.1 m/s) **(C)** in the aneurysm for the four models were compared quantitatively.

flow in the aneurysmal sac prevents thrombus organization and endothelial cell proliferation across the neck, which may lead to eventual aneurysmal recanalization (17, 18). In the present study, the finishing coils could induce substantial reduction, especially in the region of aneurysmal neck, which might facilitate thrombosis and decrease the recurrence rate. In clinical practice,

Wan et al. found that embolization of aneurysm neck was an effective and safe modality for the ruptured aneurysms with bleb formation (19).

Interestingly, in the post-stenting model, the mean velocity of aneurysmal sac and high flow volume around the neck just decreased which is consistent with previous studies (20, 21). However, the WSS increased to 107% of pre-treatment model, which may be due to the high jet flow through the stent mesh. In another aspect, it might indicate that the LVIS stent not only can divert flow but also can generate unfavorable hemodynamic effect.

In this study, common SACE with finishing coil model performed better in aneurysmal hemodynamic modification compared with common SACE model. These findings were obtained by qualitative observations and quantitative data analyses of CFD simulation. Velocity and high flow volume reductions within the aneurysm were observed in the all models, consistent with previous CFD-based studies (22–25). Of particular note, in this study high flow volume (>0.1 m/s) around the aneurysmal neck plane was significantly reduced in common SACE with finishing coil model. Furthermore, the high flow volume in the common SACE with finishing coils model was almost only half that of common SACE model. Babiker et al. (4) revealed that increased coiling density was accompanied with reduced cross-neck flow rate. Furthermore, Morales et al. (22) found that coil configuration initially played an important role in intra-aneurysmal hemodynamics until a high coiling density (nearly 30%) was achieved. Sluzewski et al. (6) reported that in aneurysms with coiling density between 20 and 23.9%, compaction did not occur if the aneurysm volume was <200 mm^3. Because the packing density (33.49%) in this study is high, consequently it was unnecessary to evaluate coil configuration in this study, while the aneurysmal volume was ∼124 mm^3.

Several limitations in this study should be noted. First, this one-sample proof-of-concept study just represents this innovative technique. Further prospective studies with greater sample sizes and longer follow-up are needed to verify our study results. Second, this technique is solely appropriate for wide-necked sidewall aneurysms with median size. For the large or giant sidewall aneurysms, flow diverter or parent artery occlusion may be optimal alternative modalities. Third, we adopted several commonly used assumptions to make CFD tractable. Due to a lack of patient-specific information, we assumed a constant, location-based inlet flow rate. Inlet velocities were scaled according to the inlet diameter. This study utilized the pre-treatment model as a baseline and evaluated the relative, not absolute, hemodynamic change.

CONCLUSION

This study demonstrated the last finishing coils to densely pack the aneurysm neck could generate more favorable hemodynamic modifications compared with common SACE, which can accelerate the thrombus formation in the aneurysmal neck and likely decreases the recurrence risk.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Huashan Hospital, Fudan University. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

XZ and JX had the idea for the article. HW, GLi, and XL performed the computational fluid study. HW, LH, GLu, LG, and YJ performed the literature search. HW wrote the article. XZ and JX are the guarantors. All authors contributed to the article and approved the submitted version.

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Hybrid Recanalization for the Treatment of Carotid/Vertebral In-stent Restenosis or Occlusion: Pilot Surgery Experiences From One Single Center

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Background : The hybrid recanalization of internal carotid artery (ICA) and vertebral artery (VA) in-stent restenosis or occlusion using a combination of endarterectomy and endovascular intervention has achieved technical success. We present our surgical experiences to further evaluate the safety and efficacy of the hybrid technique for the treatment of in-stent restenosis and occlusion.

Methods : A cohort of 12 refractory patients with in-stent restenosis or occlusion who underwent hybrid recanalization, a combination of endarterectomy and endovascular intervention, were retrospectively analyzed. Medical records, including presenting symptoms, comorbidities, contralateral ICA/VA findings, use of antiplatelet drugs, postoperative complications, and angiographic outcomes, were collected.

Results : Among 415 consecutive patients with ICA, common carotid artery, and V1 segment lesions, 12 refractory patients (2.89%) with 13 cases were enrolled in our study (1 female and 11 male). All patients underwent successful hybrid recanalization. There were no cases of postoperative stroke or death. Only two patients sustained hoarseness, but it resolved within 2 weeks after surgery. Three patients were treated with dual antiplatelet (aspirin and clopidogrel), seven with single antiplatelet (aspirin), one with single antiplatelet (clopidogrel), and one with single antiplatelet (ticagrelor). All patients were followed up in the outpatient department according to the protocol, with a mean follow-up period of 13 months (range, 6–24 months). No death or recurrent symptoms occurred during the regular follow-up period.

Conclusion : The hybrid technique maybe a safe and feasible treatment option to recanalize in-stent restenosis or occlusion with acceptable complications.

Keywords: endarterectomy, hybrid recanalization, occlusion, restenosis, stent

INTRODUCTION

Stroke derived from carotid or vertebral artery stenosis or occlusion poses a major problem worldwide and is associated with a high risk of recurrence and poor outcome. Although stent implantation in the carotid or vertebral stenosis has been acknowledged as a safe option for reducing long term stroke risk, high rates of stroke recurrence due to in-stent restenosis (ISR) and occlusion (ISO) after carotid artery stenting (CAS; 5–11%) or vertebral artery stenting (VAS; 18–43%) have been reported (1–4). Different treatment strategies, including pharmacological therapy, endovascular therapy, and surgery, are applied for the revascularization of ISR or ISO; however, no optimal therapeutic approach is recommended at present (2, 5). To our knowledge, hybrid techniques are less utilized mainly because of the high demand for hybrid operation rooms and neurosurgeons (6, 7). Moreover, previous studies of hybrid revascularization are mainly limited to an article on the chronically occluded internal carotid artery and to case reports of VA ISO or ICA ISR (3, 6, 8, 9). Therefore, in this single-center study, the pilot experiences of hybrid recanalization in 12 patients with 13 cases of carotid/vertebral ISR or ISO were reported.

METHODS

Patients

From October 2016 to June 2020, 415 consecutive patients with internal carotid artery (ICA) and V1 segment stenosis or occlusion were admitted to our center for ischemic stroke. Written informed consent was obtained from the individuals for the publication of any potentially identifiable images or data included in this article. All patients underwent digital subtraction angiography (DSA) to confirm the lesion. Medical treatment including single antiplatelet therapy (aspirin 100 mg/d, clopidogrel 75 mg/d, or ticagrelor 180 mg/d for 90 days) plus statin and the management of risk factors (e.g., hypertension, diabetes, and lifestyle) was performed. In this study, patients were included if they met the following criteria: (1) ISR ($\geq$70%) or occlusion of the ICA, the common carotid artery (CCA), or the V1 verified by DSA; (2) recurrent strokes or transient ischemic attacks (TIA) refractory to best medical treatment; (3) primary treatment performed using stent angioplasty; (4) available clinical and angiographic follow-up data after primary treatment and after hybrid recanalization for ISR or ISO. Exclusion criteria were: (1) lack of clinical or imaging information and (2) primary treatment only performed using balloon angioplasty or endarterectomy.

Abbreviations: ICA, internal carotid artery; VA, vertebral artery; ISR, in-stent restenosis; ISO, in-stent occlusion; CAS, carotid artery stenting; VAS, vertebral artery stenting; DSA, digital subtraction angiography; CCA, common carotid artery; TIA, transient ischemic attacks; CEA, carotid endarterectomy; VEA, vertebral endarterectomy; CTA, CT angiography; IPH, intraplaque hemorrhage; PICA, posterior inferior cerebellar artery; PSV, Peak systolic velocity; EDV, end-diastolic velocity.

Hybrid Revascularization Technique

Under general anesthesia, transfemoral access was performed first. Then, a standard carotid endarterectomy (CEA) or vertebral endarterectomy (VEA) surgery was performed to remove the plaque with the stent. After endarterectomy, a continuous suture was performed if there was retrograde blood flow. In case of no bleeding, a Fogarty balloon (4F for CEA/3F for VEA) thrombectomy was performed through the exposed proximal ICA or V1 segment to remove the distal thrombus. Then, a balloon-expandable (for VA) or self-expanding (for ICA and CCA) stent was implanted if there was distal stenosis or dissection through rechecked angiography. Finally, angiography was performed to ensure vascular patency. Heparin anticoagulation therapy was maintained during the temporary clamping and endovascular procedure. Blood pressure was tightly controlled postoperatively. Patients were prescribed single antiplatelet treatment after endarterectomy or balloon thrombectomy, and dual antiplatelet medications after additional stent implantation.

Clinical and Imaging Follow-Up

Clinical follow-up was performed by telephone interview or clinic visits at 1, 3, and 6 months after the intervention and yearly thereafter. Clinical events including TIA, stroke (of both anterior and posterior circulation), myocardial infarction, and death were recorded as clinical outcomes. Postoperative CT angiography (CTA) follow-up was mostly performed at 3 and 6 months after the intervention and then yearly. DSA and magnetic resonance imaging (MRI) assessment was performed according to the decision of the physicians once the patient presented with recurrent stroke or TIA.

RESULTS

Clinical Characteristics

Of 415 consecutive patients with ICA, CCA, and V1 segment lesions, 12 refractory patients (2.89%) were enrolled in our study (1 female and 11 male). The mean age was 65 years (range, 44–79 years). Comorbidities included tobacco smoking in 4 (33.33%) patients, hypertension in 10 (83.33%), hyperlipidemia in 1 (8.33%), coronary heart disease in 2 (16.67%), and diabetes mellitus in 4 (33.33%). All patients had recurrent TIA despite aggressive medical therapy (antiplatelet, statin, antihypertensive, etc.). Of the 12 patients, 7 had CAS-ISR, 1 had CAS-ISO, 3 had VAS-ISO, and 1 had concomitant CAS-ISR and VAS-ISO.

Surgery, Antiplatelet Therapy, and Follow-Up Evaluation

All patients underwent successful hybrid recanalization. Among them, two patients underwent balloon thrombectomy and three had additional stent implantation. There were no cases of postoperative stroke or death. Only two patients sustained hoarseness, but it resolved within 2 weeks after surgery. All patients underwent thromboelastography platelet mapping analysis, and ticagrelor was used as an alternative if the test indicated no response to a dual antiplatelet regimen. As a result, three patients were treated with dual antiplatelet (aspirin and

TABLE 1 | Baseline characteristics, clinical data, and outcomes.

No	Sex/age (years)	Recurrent symptoms	Smoking history	Hypertension	Hyperlipidaemia	Coronary heart disease	Diabetes	ISR/ISO type	Period from stenting to recurrence (month)	Contralateral ICA/VA	Additional endovascular device	Postoperative complications	Plaque topography and composition	Antiplatelet drugs	CTA follow-up	Follow-up time (month)
1	M/60	Limb weakness, slurred speech	−	+	−	−	−	CAS-ISO	30	ICA occlusion	Balloon, stent	None	Concentric, long-segmental	Aspirin, clopidogrel	Normal	6
2	M/66	Limb numbness	+	+	−	−	+	CAS-ISR	8	ICA moderate stenosis	None	None	Eccentric, proximal	Aspirin	Normal	12
3	M/79	Limb weakness	−	+	−	−	−	CAS-ISR	14	Normal	None	None	Eccentric, proximal	Aspirin	Low grade stenosis	16
4	M/70	Limb weakness, syncope	−	+	−	−	−	CAS-ISR	26	Normal	None	None	Eccentric, proximal	Clopidogrel	Normal	24
5	F/70	Limb numbness, slurred speech	−	−	−	−	−	CAS-ISR	5	Normal	None	None	Eccentric, proximal	Aspirin	Low grade stenosis	24
6	M/62	Limb weakness, slurred speech	−	+	−	−	+	CAS-ISR	7	Normal	None	None	Eccentric,proximal, stent fracture	Ticagrelor	Normal	6
7	M/67	Limb numbness	+	+	−	+	+	CAS-ISR	19	Normal	None	None	Eccentric, proximal	Aspirin	Normal	6
8	M/69	Limb weakness	−	−	−	−	−	CAS-ISR	10	Normal	None	None	Eccentric, proximal	Aspirin	Normal	6
9	M/54	Dizziness, walking instability	+	+	−	−	−	VAS-ISO	5	VA dominance, PICA deficiency	None	Hoarseness	Concentric, long-segmental	Aspirin	Normal	22
10	M/65	Dizziness, slurred speech	−	+	−	−	−	VAS-ISO	5	Normal	None	None	Concentric, long-segmental	Aspirin	Normal	12
11	M/70	Dizziness	−	+	−	−	−	VAS-ISO	10	V4 mild stenosis	Stent	None	Concentric, long-segmental	Aspirin, clopidogrel	Normal	12
12	M/44	Transient dizziness, limb numbness	+	+	+	+	+	CAS-ISR, VAS-ISO	3	Normal	Balloon, stent	Hoarseness	CAS- Eccentric, proximal; VAS- Concentric, long-segmental	Aspirin, clopidogrel	Normal	6

CAS, carotid artery stenting; ICA, internal carotid artery; ISO, in-stent occlusion; ISR, in-stent restenosis; VAS, vertebral artery stenting; VA, vertebral artery.

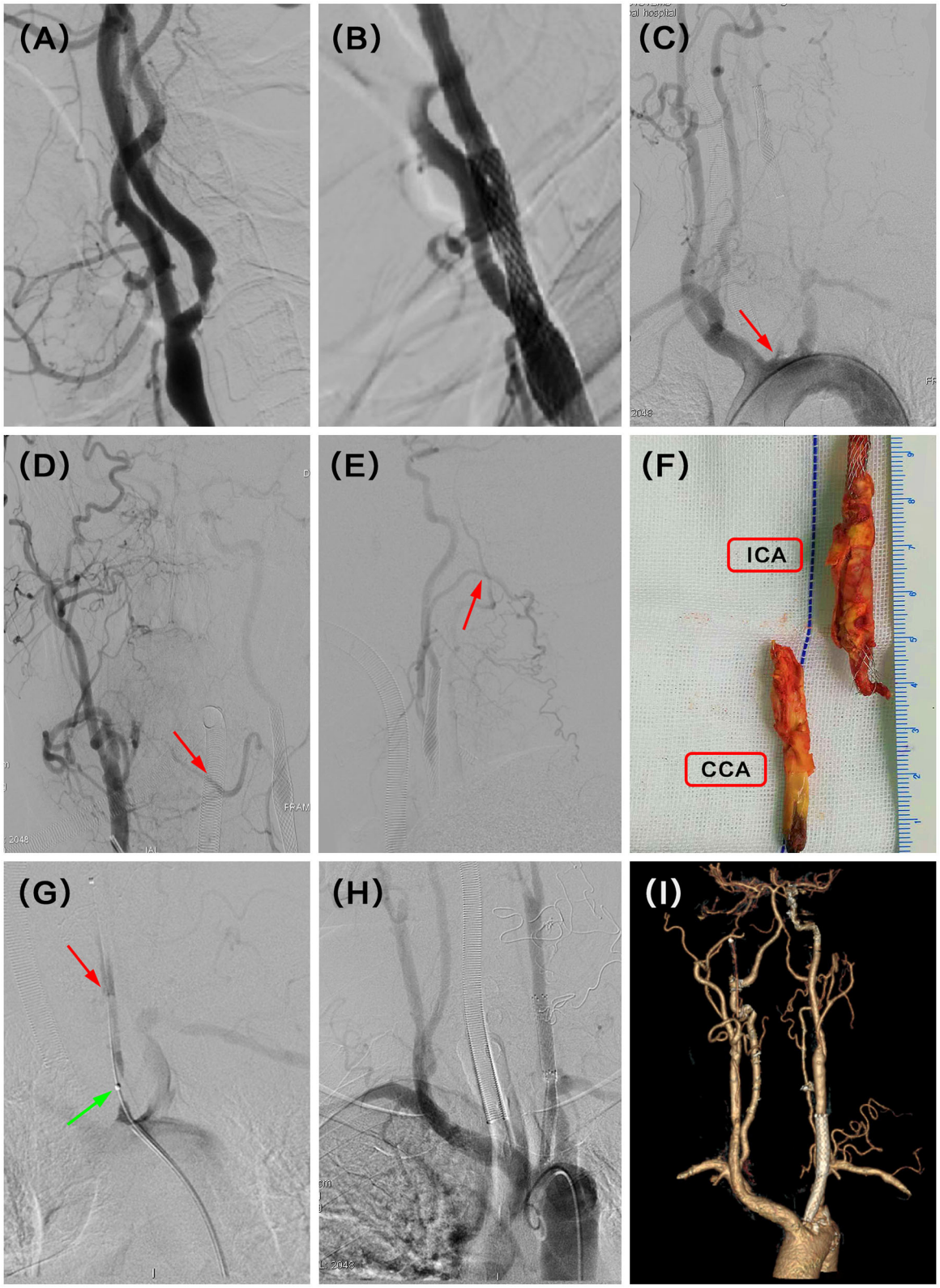

FIGURE 1 | (A) Severe stenosis of the left proximal internal carotid artery (ICA) was observed in the digital subtraction angiography (DSA). **(B)** Revascularization was achieved with balloon and stent angioplasty. **(C)** DSA showed recurrent left proximal common carotid artery (CCA) occlusion at the 30 months follow-up (red arrow). **(D)** Intraoperative angiography demonstrated that complementary inflow was reconstituted by collaterals from right lingual branches (red arrow). **(E)** Another

(Continued)

FIGURE 1 | complementary inflow was also reconstituted by collaterals from left occipital branches (red arrow). **(F)** Carotid endarterectomy (CEA) combined with Fogarty balloon thrombectomy was performed to remove the plaque with a stent, and the stent was seen clearly in the gross specimen. **(G)** After that, intraoperative angiography in the beginning of CCA showed tandem severe stenosis (green arrow) and dissection (red arrow) at the proximal and median CCA, respectively. **(H)** Successful recanalization was then achieved with further stent angioplasty with balloon dilation. **(I)** CT angiography (CTA) indicated the patency of the left CCA at the latest follow-up time (6 months) after hybrid surgery.

clopidogrel), seven with single antiplatelet (aspirin), one with single antiplatelet (clopidogrel), and one with single antiplatelet (ticagrelor). All patients were followed-up in the outpatient department according to the protocol, with a mean follow-up period of 13 months (range, 6–24 months). Only two patients showed a low grade stenosis (<30%), and the rest remained a normal luminal diameter after rechecking the latest imaging (CTA) follow-up. No death or recurrent symptoms occurred during the regular follow-up period. The clinical data and outcomes are summarized in **Table 1**.

Topography and Composition of the Plaque

Postoperative plaque topography (eccentric/concentric, proximal/long-segmental lesion) and morphology (stent fracture) were recorded. Plaque topography revealed eccentric plaques in eight (66.67%) CAS cases and proximal plaques in eight (66.67%) CAS cases. However, VAS cases were more prone to concentric and long-segmental lesions. Plaque morphology revealed stent fracture in one (8.33%) CAS case.

Representative Case Illustrations

Patient 1

A 60-year-old man presented with dizziness. He additionally demonstrated paroxysmal limb weakness and slurred speech despite the best pharmacological option. DSA demonstrated occlusion of the left CCA 30 months after CAS (**Figures 1A–C**). CCA was reconstituted by collaterals from the contralateral lingual and ipsilateral occipital branches (**Figures 1D,E**). He underwent successful hybrid recanalization for the left CCA and the stent was clearly seen in the gross specimen (**Figures 1F–H**), and the 6-month postoperative CTA showed persistent patency (**Figure 1I**).

Patient 9

A 54-year-old man presented with recurrent dizziness. He later developed walking instability. DSA demonstrated left V1 occlusion 5 months after stenting (**Figures 2A,B**). V1 was reconstituted by collaterals from muscular and thyrocervical branches (**Figure 2C**). Although the right VA was dominant, the deficiency of the right posterior inferior cerebellar artery (PICA) and hypoperfusion of the left PICA resulted in recurrent and aggravating symptoms (**Figures 2D,E**). He underwent hybrid recanalization for the left VA and the stent was clearly seen in the gross specimen (**Figures 2F,G**), and the 22-month postoperative CTA showed persistent patency (**Figure 2H**).

DISCUSSION

The rates of ischemic cerebrovascular events involving the carotid bifurcations or the vertebro-basilar circulation have been estimated at 7–20% and 25%, respectively (10–13); these are considered high rates. Stenting is regarded as the preferred option for carotid and vertebral artery stenosis surgery for its low invasiveness, low patient discomfort, and short hospitalization time, among other reasons (14, 15). However, the widespread use of CAS and VAS leads to the occurrence of early and late complications, like ISR or ISO. The benefits of stenting in the prevention of future stroke may be hampered by the high rate of ISR or ISO (2, 16). In our study, we presented a hybrid recanalization treatment in 12 patients with carotid or vertebral ISR/ISO with good follow-up results. In addition, the illustrative cases demonstrate the challenges that a neurosurgeon or neurointerventionalist can face when managing such cases.

ISR has been defined by an angiography cutoff value of ≥50 or ≥70% in several studies (3, 5, 15). We used the latter as our standard in all cases after angiographic calculation. Duplex ultrasonography also correlated very well with catheter-based angiography. Peak systolic velocity (PSV) of 300 cm/s, end-diastolic velocity (EDV) of 140 cm/s, and ICA/CCA of 3.8 are, as well, optimal cutoff points to detect 70% restenosis after stenting (17, 18).

With respect to the pathogenesis of this process, early ISR (<6 weeks) is caused by myointimal hyperplasia and vascular remodeling, and late ISR is a consequence of recurrent neo-atherosclerosis (19, 20). Compared with VA plaques, ICA plaques were more prone to eccentric lesions; this was largely due to less shear stress on the lateral wall, where most plaques occurred (21, 22). Stent fracture has also been previously reported to predict plaque formation due to abnormal endothelial proliferation caused by mechanical disruption of the fracture. An incidence of stent fracture up to 4–25% has been reported in previous studies, but the stent fracture incidence in our cohort was lower, probably due to the specific inclusion criteria (23).

The risk factors for ISR may originate from three sources: the patients, physician skill, and stent characteristics (5, 24, 25). The first source includes factors such as smoking, hypertension, hyperlipidemia, atrial fibrillation, diabetes mellitus, C-reactive protein (>5 mg/l), and coronary artery disease. These could be controlled by pharmacological and lifestyle management (5, 24). The second source includes high postoperative residual stenosis caused by the lack of skill of the surgeon. A high degree of residual stenosis with a corresponding small vascular diameter is an independent risk factor for ISR, and technical success is mostly defined as residual stenosis < 30% (24). Finally, the third source includes a small stent diameter, which is consistent with a small artery size and has been reported as another predictor of ISR (25).

Standard pharmacological management of ISR-including antiplatelet, statin, and antihypertensive drugs-is the first step before further treatment (2, 5). The efficacy of medication in reducing the long-term stroke risk remains controversial.

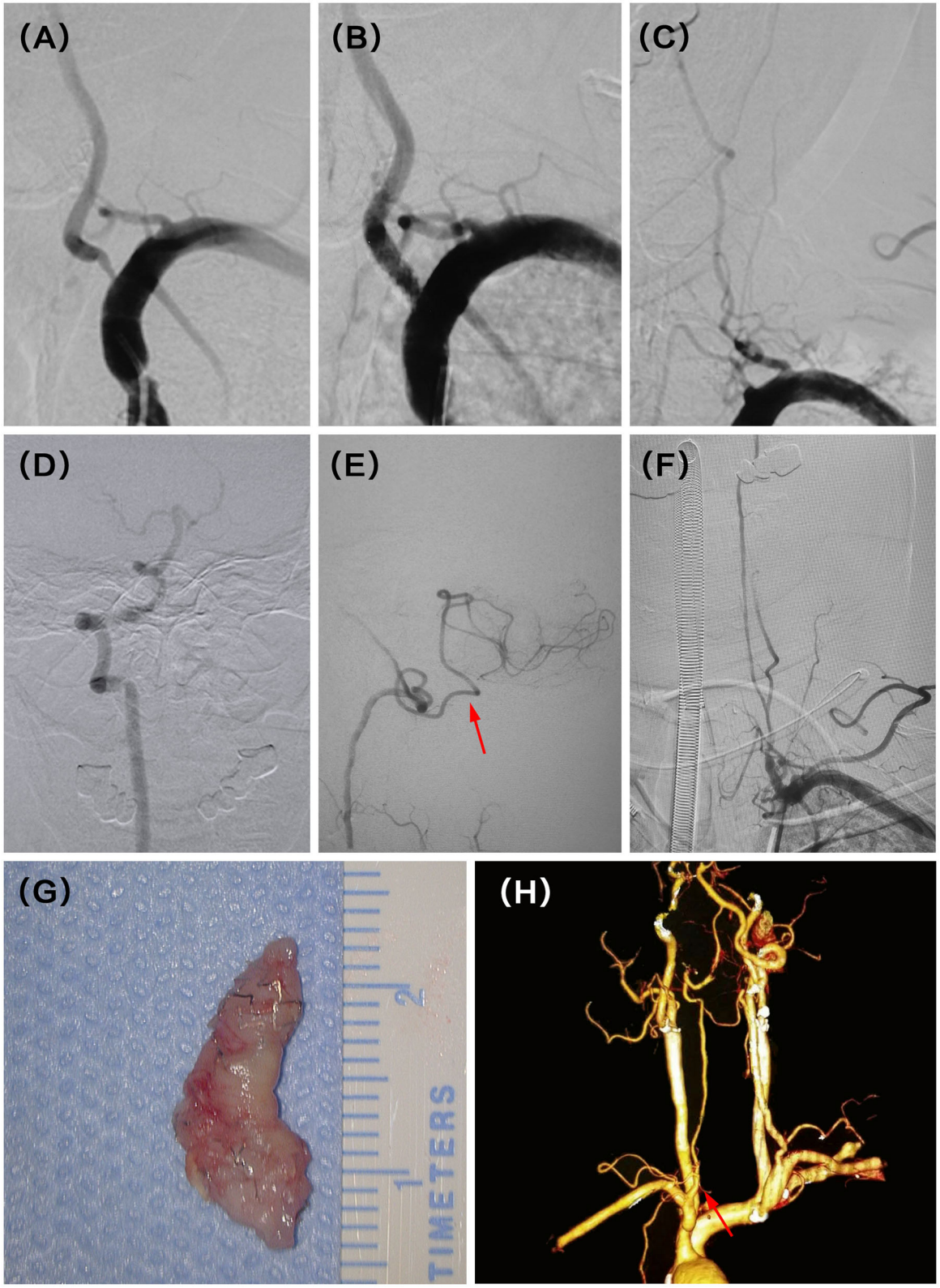

FIGURE 2 | (A) Severe stenosis of the left vertebral artery (VA) ostium was observed in the digital subtraction angiography (DSA). **(B)** Revascularization was achieved with balloon and stent angioplasty. **(C)** DSA showed recurrent left V1 occlusion at the 5 months follow-up. **(D)** Intraoperative angiography demonstrated dominant right VA with the deficiency of ipsilateral PICA. **(E)** Intraoperative angiography also demonstrated symptomatic non-dominant left VA with a thin posterior inferior

(Continued)

FIGURE 2 | cerebellar artery (PICA) (red arrow). **(F)** Successful recanalization was then achieved with stent removal after vertebral endarterectomy (VEA). **(G)** The stent was seen clearly in the gross specimen. **(H)** CT angiography (CTA) indicated the patency of the left VA at the latest follow-up time (22 months) after hybrid surgery (red arrow).

The Vertebral artery Ischemic Stenting Trial (VIST) showed that pharmacological treatment was preferred in cases of intracranial vertebral stenosis because of high operative risk; the Vertebral Artery Stenting Trial (VAST) demonstrated a higher same territory stroke risk in the stented group than in the pharmacological treatment group (26, 27). However, the Warfarin–Aspirin Symptomatic Intracranial Disease (WASID) study group concluded that many patients with symptomatic VA ostitum disease continued to have ischemic events despite optimal pharmacological therapy. A previous study also demonstrated that recurrent symptoms still appeared in patients treated with maximal pharmacological therapy, and 18% of the ICA stenosed patients developed a severe disability or died during the follow-up (28, 29).

Endovascular treatment mainly included balloon or stent angioplasty. Balloon is considered preferable to stent angioplasty because of its higher patency rates during short-term follow-up and because of the challenge of passing the catheter through the in-stent restenosis (5). However, multiple studies have demonstrated a trend toward choosing stenting over balloon angioplasty for its lower restenosis rates during long-term follow-up (30, 31). Different types of the stent also resulted in different ISR rates. A prospective randomized trial reported a lower ISR rate of 3.1% in the self-expanding stent group compared with 22.9% in the balloon-expandable stent group; the favorable outcome of the self-expanding stent is likely due to its flexibility and compliance to the tortuous vessels. Previous studies have also shown that drug-eluting stents were associated with a lower restenosis rate (11%) than were bare metal stents (19.4–30%) due to their ability to inhibit endothelial proliferation (32, 33).

Surgical revascularization includes primary endarterectomy, transposition, and a hybrid technique. CEA is a conventional treatment that can remove plaque with a stent, while VEA is not widely used due to its technical challenge and the lack of supporting findings from randomized trials (6, 7). VA transposition is a good alternative treatment for proximal VA occlusive disease, but it is difficult to achieve recanalization of the distal VA (1). Therefore, a hybrid technique that combines endarterectomy and endovascular intervention has emerged as an alternative procedure to achieve recanalization, especially for long-segmental occlusion. Open surgery could not only obtain proximal revascularization but also make the real lumen (the interface between the plaque and vessel wall) visible (7, 34). A technique reported in previous studies was the insertion of a microwire into the real lumen of the VA to ensure the completion of subsequent thrombectomy and stenting (6, 35). However, considering the mostly straight anatomy of the proximal ICA and the V1 segment and the performance of preoperative angiography evaluation, the Fogarty balloon was directly inserted through the exposed proximal ICA or V1 segment to conduct the surgical thrombectomy in our center. In addition, complementary endovascular thrombectomy or stenting could also achieve distal recanalization and avoid destroying the collaterals from the thyrocervical or costocervical trunk (35). In addition to wound hematomas and infections, Horner syndrome and chylothorax are inherent risks of the process of VA endarterectomy and transposition (1, 7). In our study, two patients in the VAS group developed transient nerve dysfunction after surgery, whereas none of the CAS group developed this complication. There were two main reasons for this disparity. First, the endarterectomy required a delicate operative maneuver under the microscope. Second, the operation area of CEA was always limited to the carotid sheath after it was cut open, observing little injury to the cranial nerve. In addition, the surgical ligation of the left thoracic duct was performed to prevent postoperative chylothorax in VA hybrid recanalization.

This study had several limitations. To begin with, it was a retrospective, small sample size, single-center design, and one hybrid technique study. Furthermore, a longer and sufficient follow-up including cranial MRI, is needed to evaluate neurologic improvement, the patency of the recanalized ICA or VA, and the efficacy of hybrid surgery. Prospective multicenter randomized control and larger sample size studies are needed to confirm the safety and efficacy of hybrid recanalization strategy.

Symptomatic post-stenting restenosis or occlusion of ICA or VA stenosis poses a challenging dilemma to neurosurgeons and neurointerventional radiologists. Symptomatic patients with post-stent restenosis or occlusion of the ICA or the VA refractory to pharmacological treatment are candidates for a revascularization procedure. The present study demonstrates that a hybrid procedure for ICA and VA post-stenting restenosis or occlusion maybe a feasible treatment strategy. A large sample size and long-term follow-up are necessary to confirm these findings.

CONCLUSION

A hybrid technique that combines endarterectomy and endovascular intervention maybe a safe and feasible treatment option to recanalize in-stent restenosis or occlusion with acceptable complications.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary materials, further inquiries can be directed to the corresponding author/s.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Ethics committee of Qilu hospital

of Shandong University (KYLL-2020(KS)-533). The patients/participants provided their written informed consent to participate in this study. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

AUTHOR CONTRIBUTIONS

DW and XL made substantial contributions to the conception and design of the work. The Operation and data acquisition were performed by PZ, TS, and MH. YW and WW performed the data analysis. CW drafted the manuscript and all of the other authors revised it critically for important intellectual content. All authors read and approved the final version to be published and they agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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The Enterprise2 Stent for Endovascular Treatment of Intracranial Aneurysms: Short-Term Results From a Single Center Experience

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Background: Self-expanding devices, such as the Enterprise VRD (EP-VRD) have widely used for stent-assisted coiling treatment in wided-necked aneuryms while some thromboembolic complications were reported due to its incomplete stent apposition (ISA). We report our experiences on the novel Enterprise2 (EP-VRD2) stent *in vivo* in the treatment of intracranial and cranial cervical junction aneurysms.

Methods: Twenty-five consecutive patients with intracranial or cranial cervical junction aneurysms were treated with EP-VRD2 stents retrospectively collected in our institution. We use the 'jailing' technique in all cases and deployed the stent by using pushing over the outer curve technique. The 3- or 6-monthS follow-up was done regularly by DSA.

Results: Twenty-five EP-VRD2 stents were implanted to treat 21 aneurysms at the siphon segment of internal carotid artery (ICA), one at the petrous segment, two at the cervical segment, one at the verteral artery with five accompanied with stenosis. Two patients had kinking during the procedure and were solved by microwire or microcatheter massaging. Four patients with a larger arc angle and a smaller radius of the parent vessel was detected ISA. No patient underwent the ischemic event after the operation. Twenty-three of 25 patients were evaluated after 3- or 6-months by DSA, 22 showed complete occlusion (RROC1), one slight re-stenosis in the follow-up within those five patients with stenosis. A length of 23 mm seemed associated with ISA ($p < 0.01$).

Conclusion: The EP-VRD2 performed well in our small patient series; however, ISA could still occur with a sharp angle of the parent vessel.

Keywords: aneurysm, endovascular treatment, stent, enterprise 2 stent, incomplete stent apposition (ISA)

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INTRODUCTION

Currently, novel endovascular devices and technologies have increased opportunities for treatment of intracranial aneurysms (IAs). These include surgical clipping, even in complex aneurysms. Among these, stent-assisted coiling (SAC) has become the modality of choice for treatment of wide-necked aneurysms due to its lower recurrence rates compared to coiling alone (1–4). The Enterprise Vascular Reconstruction Device (EP-VRD, Codman Neurovascular, Raynham, MA, USA) is a self-expandable laser device that is the first closed-cell designed stent. It has been

widely used in SAC treatment of IAs (5–7). Nevertheless, there remain some drawbacks limiting its application. Johnson et al. reported that 4.4–6.4% (8) of patients who underwent SAC treatment had thromboembolic complications partially due to the incomplete stent apposition (ISA) in blood vessels with large diameters and curvatures (9).

To overcome this weakness, the Enterprise2 stent (EP-VRD2) was developed; it is the second-generation Enterprise stent, featuring improved design in terms of geometry. EP-VRD2 showed better wall apposition in curved vessels than did EP-VRD in an *in vitro* study (10). Clinicians could further reduce ISA in curved vessels by pushing over the outer curve deploying technique (11). Nevertheless, little is known about its performance *in vivo* except first experiences reported by Herweh et al. (12).

In this study, we enrolled a series of 25 cases of intracranial or cranial cervical junction aneurysms treated with EP-VRD2 as well as its short-term follow-up results. We then preliminarily analyzed its wall apposition performance to confirm its safety and efficacy in a Chinese population.

MATERIALS AND METHODS

Patients

We retrospectively collected the data from 25 patients with intracranial or cranial cervical junction aneurysms treated with EP-VRD2 from November 2018 to December 2019 at our institution. Informed consent for participants was obtained from the patients or their legal representatives, and the protocol was approved by our ethical committee.

Standard dual-antiplatelet therapy (100 mg/d aspirin and 75 mg/d clopidogrel, loading dose 300 mg once each) was administered 5 days prior to the procedure for unruptured cases and continued thereafter. For ruptured aneurysms, patients were loaded with an appropriate weight-based dose of tirofiban (6 μg/kg once, and then 0.1 μg/kg per minute for 12 h) at the moment of stent deployment then changed to loading-dosed dual-antiplatelet drugs for 6–8 h and discontinuation of tirofiban. General anesthesia was used in all patients. We measured aneurysms using digital subtraction angiography (DSA) and 3-dimensional (3D) rotational angiography. After the procedure, patients were given standard dual-antiplatelet therapy for 3 months and only aspirin (100 mg/d) thereafter. The procedure-related complications and immediate and 3–6 monthly follow-up DSA results were reviewed.

Procedure

All endovascular procedures were performed using Allura Xper FD20 angiographic system (Philips, Netherlands). We used the "jailing" technique in all cases. Either a 6-F guide catheter or a combination of a 6-F-long sheath and a 6-F intermediate catheter was positioned into the carotid or vertebral artery, depending on the distortion of the vascular access. 3D imaging and 2D imaging of the target aneurysms were performed to evaluate the tortuous conditions and measure related aneurysmal morphological parameters. A pre-shaped 0.014-inch 200-cm micro-guidewire (Synchro, Stryker, Kalamazoo, MI, USA) and a 0.021-inch microcatheter (Prowler Select Plus, Codman Neurovascular, Raynham, MA, USA) for stent delivery according to the manufacturer's instructions were positioned at least 10 mm past the distal location of the aneurysm neck. Coil embolization was performed using a 0.017-inch microcatheter (Echelon-10, ev3 Endovascular, Plymouth, MN, USA). The distal markers of the stent were positioned distally across the aneurysm neck. The distal part of stent was unsheathed by slowly withdrawing the microcatheter and carefully pushing or pulling the delivery wire of stent for adequate expansion and neck coverage. After coil embolization, the delivery wire was further advanced to a position along the outer curve of the parent artery, and the stent was then pushed out completely with the delivery wire maintained along the outer curve (pushing over outer curve technique). Each deploying procedure included an angiography and an Xper CT with diluted contrast (1:5) right after complete deployment to confirm its correct stent placement and satisfactory vessel wall apposition.

Complications and Follow-Up

In our institution, short-term follow-up DSA was routinely performed 3–6 months after treatment. Telephone or outpatient interview was conducted monthly to investigate potential complications. Procedure-related complications included aneurysm rupture and embolic events [such as transient ischemic attack [TIA] or symptomatic ischemic stroke]. The post-procedure potential-related complications were evaluated with the modified Rankin score (mRS). Occlusion rates were evaluated during the immediate post-embolization and follow-up DSA images for every aneurysm with the Raymond–Roy occlusion classification (RROC) (13): I, complete occlusion; II, neck remnant; and III, residual sac. Any further contrast remnant of the neck or sac during follow-up was defined as "recurrence".

Statistical Analysis

Continuous data were presented as mean ± SD. A comparative analysis between the complete and incomplete stent apposition groups was performed using an independent-samples *t*-test. Statistical significance was defined as $P < 0.05$. Statistical analysis was carried out with SPSS Statistics for Windows, Version 26.0 (SPSS Inc., Chicago, Illinois, USA).

RESULTS

Twenty-five patients with intracranial or cranial cervical junction aneurysms were included. Fourteen patients were male, with ages ranging from 48 to 78 years (mean ± SD, 65.08 ± 9.08 years). All aneurysms were unruptured except two. Treatments were performed successfully in all patients. Patient demographics and parent aneurysm artery features including location, diameter, radius, arc angle, stent details, follow-up information, and complications are shown in **Table 1**. Two aneurysms were located at the cervical segment of ICA, one at the petrous segment, seven at the cavernous segment, seven at the ophthalmic segment, seven at the posterior communicating segment, and one at the transverse segment of the vertebral artery. Among five patients with a stenosis of the parent artery (two mild, three severe), only

TABLE 1 | Summary of patient data and details of vessel anatomy.

No.	Sex	Target lesion	stenosis	Stent length (mm)	Diameter (mm)		Angle	Radius(mm)	Stent markers		Stent apposition		Initial RROC	FU-RROC	Complication	
					Distal	Prox.			Prox.	Distal	Inner	Outer			Procedural	Post
1	M	C7	-	23	3.26	4.7	61	4.63	A	A	C	C	I	I	-	-
2	F	C6	-	23	2.8	4.1	78	2.8	A	A	C	I	I	I	-	-
3	M	C4	-	30	2.89	3.22	87	3.39	A	A	C	C	I	I	-	-
4	M	C7	-	30	3.68	4.51	96	4.63	A	A	C	C	I	I	-	-
5	M	C7	Mild	23	2.88	4.04	139	2.96	A	A	I	C	I	I	Kinking	-
6	M	C4	Severe	30	3.31	3.67	71	3.35	A	A	C	C	I	I	-	-
7	F	C4	-	39	3.50	6.15	150	5.71	A	S	C	C	II	II	-	-
8	M	C6	-	23	3.53	4.83	36	3.51	A	A	C	C	I	N/A	-	-
9	F	C7	Severe	30	3.44	5.6	76	3.78	S	A	C	C	I	I	-	-
10	F	C6	Severe	23	3.74	3.96	70	3.85	A	S	C	C	I	I	-	-
11	F	C4	-	39	2.6	3.96	79	3.83	A	A	C	C	I	I	-	-
12	F	C6	-	23	3.35	4.78	56	4.3	S	A	C	C	I	I	-	-
13	M	C7	-	23	3.55	4.32	120	3.48	A	A	C	C	I	N/A	-	-
14	F	C7	-	23	3.71	4.45	101	3.8	A	A	I	C	I	I	-	-
15	F	C7	-	23	4.67	5.04	125	4.3	S	A	C	I	I	I	Kinking	-
16	F	C6	-	23	3.54	4.93	109	3.67	S	A	C	C	I	I	-	-
17	M	C6	-	23	3.66	4.63	100	3.84	S	A	C	C	I	I	-	-
18	M	C4	-	23	3.37	4.63	104	3.98	S	S	C	C	I	I	-	-
19	M	C2	-	39	5.12	5.69	150	5.83	S	S	C	C	I	I	-	-
20	M	C1	-	30	3.90	4.59	141	4.01	S	S	C	C	I	I	-	-
21	M	C1	-	30	4.42	4.66	97	4.65	S	S	C	C	I	I	-	-
22	F	V2	-	30	4.23	4.54	-	-	S	S	C	C	I	I	-	-
23	M	C4	-	30	3.56	3.98	-	-	S	S	C	C	I	I	-	-
24	M	C6	Mild	30	3.42	3.89	-	-	S	S	C	C	I	I	-	-
25	F	C4	-	16	3.76	4.03	-	-	S	S	C	C	I	I	-	-

C1-C7 the seven segments of ICA according to Heller and Malek (14), RROC Raymond-Roy occlusion classification, A asymmetrical, S symmetrical, C complete, I incomplete, V2 the transverse segment of the vertebral artery, N/A non-applicable, FU follow up, Angle of arc subtended by stent and curvature radius were determined according to Roy and Milot (13).

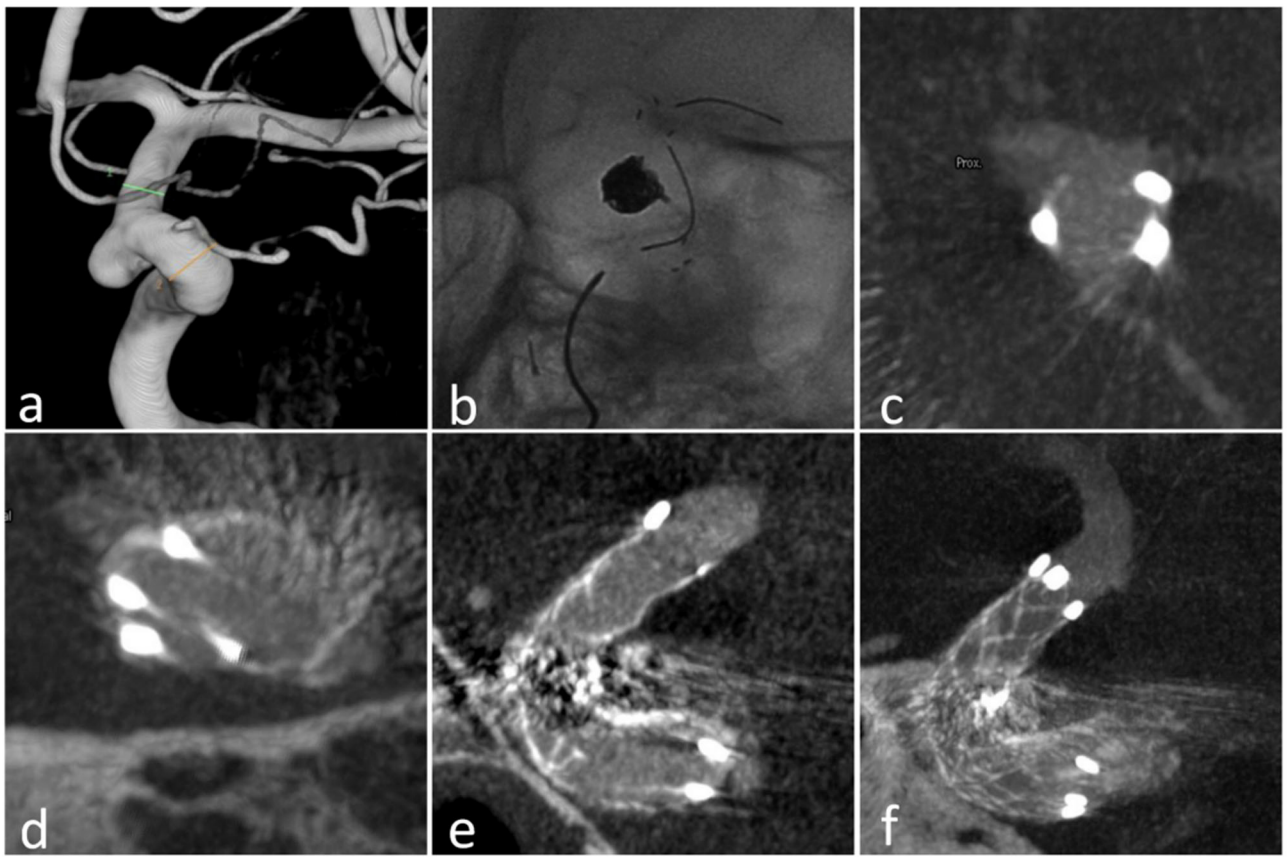

FIGURE 1 | Case 18: **(a)** the aneurysm at the ophthalmic arterial segment of ICA; **(b)** the stent (23 mm) in the ICA; **(c)** the proximal markers were asymmetrical; **(d)** the distal markers were symmetrical; **(e)** sagittal view of the stent in Xper CT; **(f)** correct stent wall position of the deployed stent with larger thickness in Xper CT.

one patient's stent was incompletely apposed. All were examined using Xper CT to confirm the stent wall apposition (**Figure 1**). Five patients had accompanying atherosclerotic stenosis. Stent kinking was observed in two aneurysms using Xper CT during the operation that were then corrected by massaging the stent via microcatheter or microwire (**Figure 2**). Mild crescent signs in four aneurysms were all implanted the 23-mm stent (**Figure 3**). The reason was that the larger angle of arc was subtended by the stent with the smaller curvature radius, which were determined according to a previous study (14).

Incomplete stent apposition occurred in four aneurysms. Possible related factors were compared (**Table 2**). There was significant difference in stent length between complete apposition group and incomplete apposition group ($P = 0.001$). A length of 23 mm appeared to be associated with ISA. No significant differences were found in terms of degree of stenosis, angle, radius, distal and proximal diameters, or diameter gradients of the parent artery.

No patient underwent ischemic event after the operation. Two ruptured patients with acute treatment recovered well without developing further rupture or hemorrhage during hospitalization. Twenty-four aneurysms showed angiographic complete occlusion (RROC1) immediately after procedure, and one patient (Case 7) had residual neck filling (RROC 2) due to multiple nearby aneurysms on the same parent artery. Twenty-three patients were evaluated after 3–6 months by DSA. Among them, 22 showed RROC1 and Case 7 had residual neck filling with slight increase (RROC2). One re-stenosis was observed in the follow-up DSA with severe stenosis of the parent artery (**Figure 4**). Two patients (Case 3 and Case 12) were back after 3 and 12 months by DSA. Both showed RROC1 and had no stenosis on the parent arteries (**Figure 5**). No migration of the stents was observed during the deployment or follow-up.

DISCUSSION

Stent-assisted coiling has been demonstrated to have a higher rate of complete occlusion and a lower rate of recurrence in the long-term follow-up compared with conventional coiling especially for treatment of wide-necked aneurysms (15). However, it remains challenging because of potential stent-related embolic events of the parent artery (16). The common stents include Neuroform EZ, Enterprise, Lvis, Solitaire, Pipeline, and other flow diverters.

Diameters of wide-necked aneurysms located in the clinoid segment of ICA are usually about 5 mm or more (17), which the sizes of EP-VRD and Neuroform EZ cannot reach. Solitaire, a

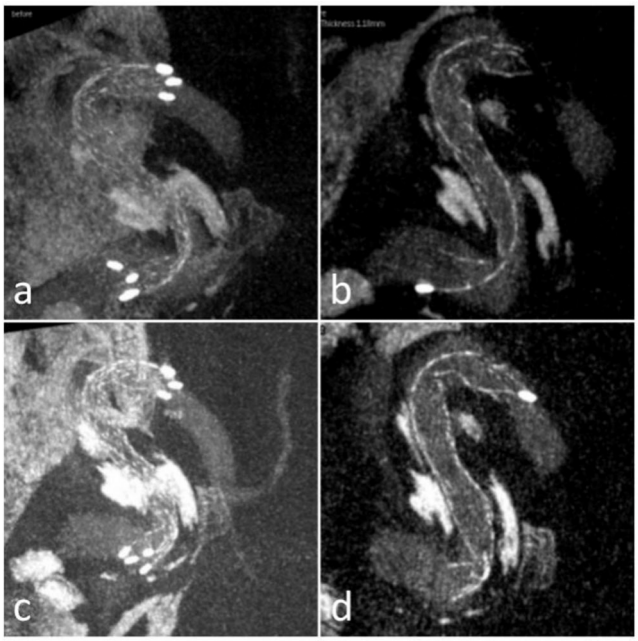

FIGURE 2 | Case 23 **(a,b)** sagittal views of the stent in Xper CT during the procedure showed the kinking; **(c,d)** sagittal views of the stent after massaging via microcatheter or microwire showed the kinking improved.

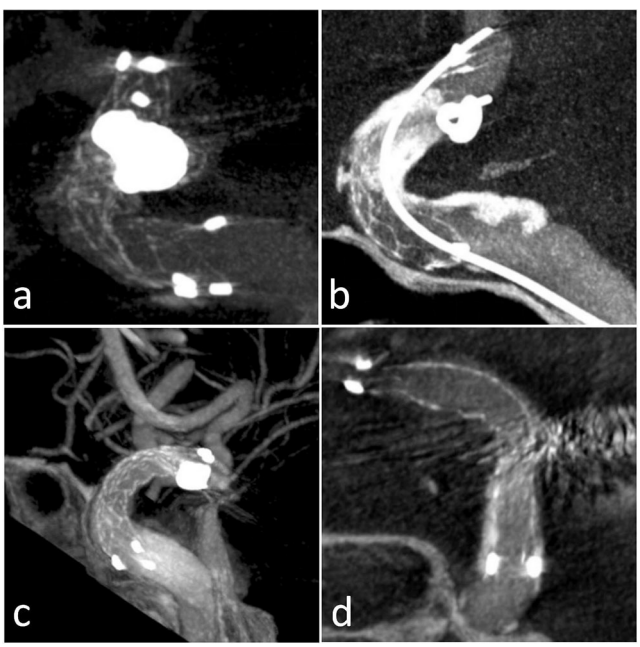

FIGURE 3 | Four patients with ISA presentation in Xper CT: **(a)** Case 2 outer curve ISA; **(b)** Case 5 inner curve ISA; **(c)** Case 14 inner ISA; **(d)** Case 15 outer curve ISA.

TABLE 2 | Comparison of complete apposition and incomplete apposition.

		Complete apposition ($n = 21$)	Incomplete apposition ($n = 4$)	*P*-value
Stenosis		0.48 ± 1.08	0.25 ± 0.50	0.689
Stent length		27.95 ± 6.09	23 ± 0	0.001
Artery diameter	Distal	3.61 ± 0.52	3.52 ± 0.87	0.764
	Proximal	4.54 ± 0.69	4.41 ± 0.46	0.726
Artery angle		94.29 ± 32.72	110.75 ± 26.89	0.364
Artery radius		4.14 ± 0.74	3.47 ± 0.71	0.113
Diameter gradient		0.93 ± 0.66	0.89 ± 0.42	0.925

*Stenosis means the stenosis degree of parent artery: normal-0, mild-1, moderate-2, severe-3. The angle and radius of parent artery were the same data in **Table 1**. Diameter Gradient is the difference between the distal diameter and proximal diameter of parent artery.*

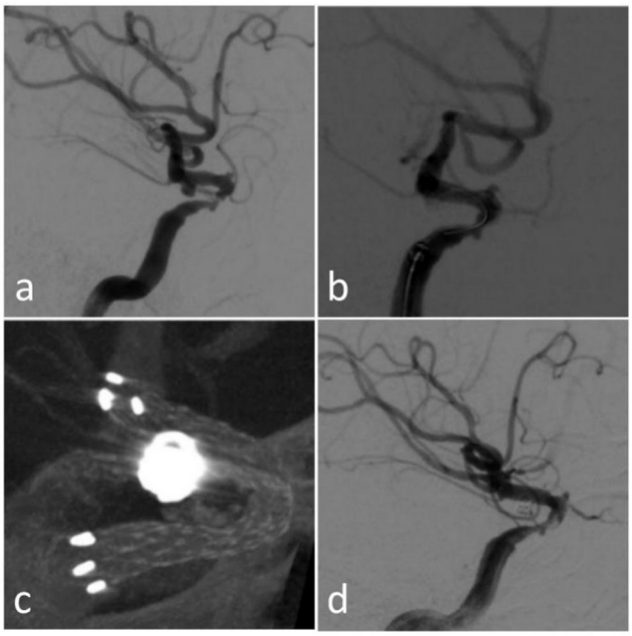

FIGURE 4 | Case 9 **(a)** original DSA; **(b)** immediate angiography after the endovascular treatment; **(c)** Xper CT during the procedure; **(d)** follow-up angiography after 3 months.

retrial stent with a large mesh, may lead to coil herniation and arterial occlusion if herniation loops are tangled inside the stent, giving rise to unsatisfactory complete occlusion rate on long-term follow-up (18). The rate of all thromboembolic events and the risk of in-stent stenosis were higher with the LVIS stent than with the Enterprise stent (16). A pipeline device and other flow diverters have been indicated for the endovascular treatment for large or giant wide-necked intracranial aneurysms in the petrous to the superior hypophyseal segments of ICA demonstrated by the Food and Drug Administration in 2011(19).

Enterprise VRD2 extended the body diameter of EP-VRD from 4.5 to 5 mm and enlarged the expanded diameter of the flare ends from 7 to 7.3 mm (**Figure 6**). Though the adaptation vessel diameters of both types remain the same, from 2.5 to 4.5 mm,

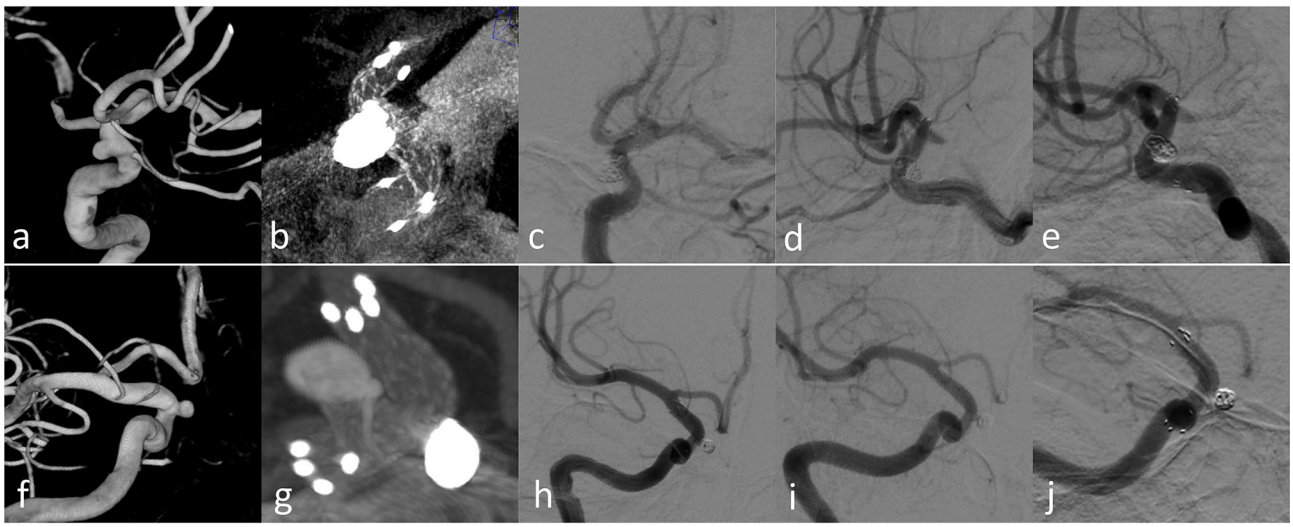

FIGURE 5 | Case 3 **(a–e)** and Case 12 **(f–j)** with longer-term radiographic follow-up: **(a,f)** 3D images before treatment; **(b,g)** Xper CT immediately after SAC treatment; **(c,h)** immediate angiography after the endovascular treatment; **(d,i)** follow-up angiography after 3 months; **(f,j)** follow-up angiography after 12 months.

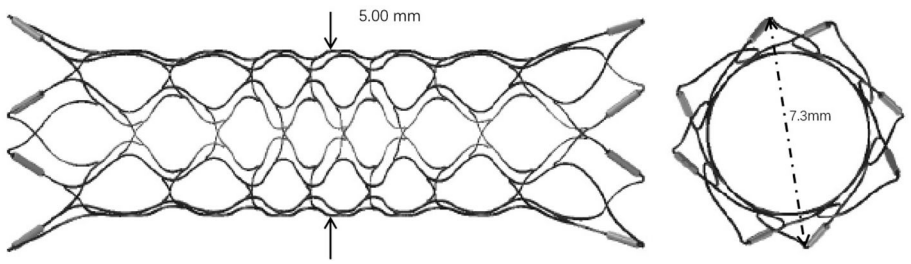

FIGURE 6 | EP-VRD2 diameter extends to 5 mm, the diameter of the flare ends expands to 7.3 mm.

the EP-VRD2 is supposed to perform better in larger vessels than EP-VRD (11). In our series, 21 of 25 aneurysms were located in the carotid siphon, the proximal diameter ranged from 3.22 to 5.60 mm, and the mean diameter was 4.53 mm, which was the most frequent location. Two stents were located in the cervical segment with the proximal diameter of the parent artery larger than 4.5 mm (one was 4.59 mm, the other 4.66 mm).

Enterprise, with a closed-cell design, has been shown to recapture and reposition including complete withdrawal and ovalization in curved vascular segments to keep coils staying within aneurysms, protecting the parent artery (20). However, the incomplete stent apposition (ISA) could also occur (20) associated with its closed-cell design and the angle of the vessel, which could be observed in the radiological images as well as clinical signs such as ischemic stroke or TIA, immediately (21) and on follow-up (9). Heller et al. detected ISA of the Enterprise on 3T-MRA with an unsatisfactory rate in 19/39 patients (49%) (14). EP-VRD2, a modified version, was designed to improve its apposition performance and reduce the incidence of ISA.

An *in vitro* study (11) found that EP-VRD2 achieved better vessel wall apposition than did the EP-VRD. In the present study, some ISAs (16%, 4/25) were observed on the parent artery in treatments with EP-VRD, two even using the pushing over outer curve technique during the deployment of the stent. However, none of the patients experienced cerebral ischemic events.

The angle and the radius of the parent artery have a significant influence on the wall apposition of the stent. The EP-VRD, in turn, exhibited significant kinking (consecutive flattening and narrowing of the stent lumen) when coming across an angle of 90° and more (14). In our cases, stent kinking occurred in two aneurysms during the procedure by Xper CT. Heller et al. demonstrated this phenomenon also *in vivo* (14) and found that this phenomenon was more likely to occur in larger vessels (4 mm vs. 3.7 mm), constituting curves with smaller radius (7.5 mm vs. 9.8 mm) and subtending large angles (140° vs. 95°) (9). The struts of EP-VRD2 were designed to allow the stent to elongate more on the outer curvature and to compress more on the inner curvature to increase its flexibility and its adherence to the vessel wall. We observed kinking of EP-VRD2 by Xper CT in two patients; one (case 5) had a small radius (2.96 mm), a larger angle (139°), and a larger difference between the radius of proximal (4.04 mm) and distal (2.88 mm) of the parent artery. This was eliminated by

massaging the stent by a microcatheter. The other kinking was on the second curve of the parent vessel, which was also improved by massaging the stent by a "J-type" microwire. EP-VRD2, with a closed-cell stent, can also be repositioned and adjusted after the deployment, which cannot be achieved when using the open-cell stents as Neuroform EZ.

All stents were deployed by using the pushing over outer curve technique. Mild crescent signs (CS) were observed in four cases indicating ISA in Xper CT: Case 2 had the smallest radius of 2.8 mm but a small curve angle of 87°, Case 5 had a large angle of 139° and a smaller radius of 2.96 mm, and Cases 14 and 15 had a larger vessel diameter and a little smaller radius. All four cases used the stent length of 23 mm while the proximal markers were all located asymmetrically. The stent length influenced the stent apposition significantly especially for the length of 23 mm. Perhaps we should avoid the use of the 23-mm EP-VRD2. However, none of these four patients developed new neurological ischemic events, either immediately or on follow-up (3–6 months). More cases are needed to perform statistical analysis to validate this finding. We also observed that the stent lumen could be completely apposed to the vessel wall; even the proximal markers were located asymmetrically. This finding was similar to that of a previous study (12). In particular cases of EP-VRD, secondary migration was observed (22), while no migration was observed at deployment or on follow-up of EP-VRD2.

Limitations

Our study has some limitations. First, our main limitation is the relatively small number of cases; however, it remains important to have a preliminary evaluation of this new stent in Chinese people. Second, angiographic evaluation of mid-term and long-term follow-up is needed to confirm its efficacy on recurrence rate and restenosis rate especially for those with stenosis. Third, Xper CT was not performed in the follow-up angiography especially for those four ISA patients and two stent-kinking patients during the procedural.

CONCLUSION

EP-VRD2 stent may be a safe and effective device for embolization of intracranial wide-necked aneurysms with a good performance in large vessels that possess a relatively small-curved vessel radius. However, incomplete vessel wall apposition also occurred in the curves with the larger angle and smaller radius.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary materials, further inquiries can be directed to the corresponding author/s.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Ethics committee of Zhejiang Hospital. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

LC and SW: planning, conduct, and reporting of the work described in the article. CZ, JW, JG, and YG: reporting of the work described in the article. All authors contributed to the article and approved the submitted version.

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The Utility of Diffusion-Weighted MRI Lesions to Compare the Effects of Different Heparinization Schemes in Intracranial Aneurysms Treated by Endovascular Intervention

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Objective: Heparinization is applied to prevent ischemic complications in the endovascular treatment of intracranial aneurysms, but there is no unified heparinization scheme. Diffusion-weighted imaging (DWI) can be used to evaluate ischemia after endovascular therapy for intracranial aneurysms. The goal of this study is to apply DWI to evaluate the effects of different heparinization schemes on intracranial aneurysms treated with endovascular therapy.

Methods: We retrospectively reviewed 141 patients with 149 aneurysms treated with endovascular interventions from July 2019 to April 2020 at our center, including 96 aneurysms treated with local heparinization and 53 aneurysms treated with systemic heparinization. We collected the basic information of the patients, including age, sex, comorbidities, and aneurysm characteristics, and associated treatment data. New ischemic lesions detected by DWI were categorized belonging to four types. Multivariate logistic regression was used to compare the effects of different heparinization schemes on intracranial aneurysms treated with endovascular therapy.

Results: There were no significant differences in age, sex, hypertension, diabetes, and aneurysm size or location between the two groups. The incidence and distribution types of DWI abnormalities in the local heparinization groups and systemic heparinization groups were not significantly different ($P > 0.05$). There was a correlation between the laser engraving stent and postoperative DWI abnormalities ($P < 0.003$). Multivariate logistic regression analysis showed that the laser engraving stent was significantly correlated with postoperative DWI abnormalities (odds ratio, 4.71; 95% CI: 1.51–14.58; $P = 0.007$).

Conclusion: Compared with systemic heparinization, local heparinization does not increase the incidence of DWI abnormalities after endovascular treatment, and its application in this group of patients is safe and effective.

Keywords: intracranial aneurysm, heparinization, diffusion-weighted imaging, endovascular treatment, vascular disorders

INTRODUCTION

Endovascular treatment has become the main treatment method for intracranial aneurysms, but ischemic complications are the main risk of endovascular treatment (1). Diffusion-weighted imaging (DWI) is a sensitive method for detecting acute ischemic strokes. Studies have found that the incidence of ischemic lesions is between 10 and 77% after endovascular treatment of intracranial aneurysms, and ischemic lesions may be associated with cognitive decline, depression, and future stroke in patients (2–5). The causes of these associations of ischemic lesions include fragile plaques, thrombosis exfoliation in aneurysms, and thrombosis caused by the catheter (6). Previous studies have also shown that age, aneurysm size, and use of complex embolization techniques are risk factors for ischemic complications (7, 8).

Heparinization is an important method to prevent ischemic complications; however, there is no unified scheme for heparinization. The commonly used schemes are systemic heparinization and local heparinization. The goal of this study is to apply DWI to evaluate the effects of different heparinization schemes on intracranial aneurysms with endovascular treatment.

METHODS

We retrospectively collected patients who received endovascular treatment for intracranial aneurysm in our center from July 2019 to April 2020. The inclusion criteria were a saccular intracranial aneurysm (for ruptured aneurysms, the Hunt-Hess grade was 0–2) and MRI examination within 72 h after operation, while the exclusion criteria were dissecting aneurysm, blood blister-like aneurysm, aneurysms with moyamoya disease or arteriovenous malformation, previous use of antithrombotic drugs (including anticoagulants or antiplatelet aggregation drugs), or no MRI examination. The clinical data of the patients were collected, including age, sex, combined diseases (hypertension, diabetes, and hyperlipidemia), history of stroke, aneurysm characteristics, heparinization method, operation time, intraoperative hypotension, and endovascular technique. The aneurysms were classified according to location as anterior cerebral artery aneurysms (including anterior communicating aneurysm and A1 segment of anterior cerebral artery and distant arterial aneurysm), middle cerebral artery aneurysms, internal carotid artery aneurysms (including cavernous sinus segment aneurysm, clinoid process segment aneurysm, ophthalmic artery segment aneurysm, and communicating segment aneurysm) and posterior circulation aneurysms (including vertebral artery aneurysm, basilar artery aneurysm, post-erosuperior cerebellar artery aneurysm and posterior cerebral aneurysm). An intraoperative duration of more than 120 min was used as a marker of a long duration operation. The diagnostic criterion for intraoperative hypotension were systolic blood pressure <90 mmHg or a systolic blood pressure drop of more than 1/3 of baseline, except for anesthetic factors. This study was supported by our hospital, and all patients provided informed consent.

In the local heparinization group, no antiplatelet drugs were used before operation, and the catheter flushing solutions contained 2,000 U of heparin per 500 ml of fluid during the operation. For patients treated with coiling alone in the local heparinization group, no additional heparin or antiplatelet therapy was given during the perioperative period. For patients treated with stent-assisted embolization in the local heparinization group, tirofiban (10 μg/kg) was given during the operation and was continuously administered via a venous pump (0.15 μg/kg/min) 1 h later. A loading dose of aspirin (300 mg) and clopidogrel (300 mg) was given 6 h after the operation. Tirofiban and antiplatelet drugs should be used in combination and were overlapped at least 6 h before stopping antiplatelet drugs. The scheme of the systemic heparinized group was treated with intravenous injection according to the standard heparinization regimen (70 U/kg); then, 1,000 U heparin was administered every hour. For patients treated by stent-assisted embolization in the systemic heparinized group, aspirin (100 mg/days) and clopidogrel (75 mg/days) were administered for 3–7 days before the procedure. After the operation, daily clopidogrel (75 mg) was maintained for 1 month, and daily aspirin (100 mg) was maintained for 6 months. For patients treated with coiling alone in the systemic heparinized group, no antiplatelet therapy was given before or after the operation.

A laser engraving stent and dense network stent were used in the procedure. The laser engraving stent was either the Enterprise stent (Codman; USA), Solitaire stent (EV3; USA), or Neuro Form EZ stent (Boston Scientific; USA). The dense network stent either the LVIS stent (Microvention; USA), Pipeline stent (Medtronic; USA), or Tubridge stent (MircoPort; Shanghai).

All patients received an MRI examination with diffusion-weighted imaging (MRI-DWI), 1.5T or 3.0T, within 72 h after endovascular treatment. All MRIs were reviewed by two experienced neuroradiologists. Ischemic lesions were identified by DWI and were categorized as the following types: (A) unilateral 1∼3 DWI points <10 mm; (B) unilateral >3 DWI points <10 mm or flaky DWI points >10 mm; (C) bilateral 1∼3 DWI points <10 mm; and (D) bilateral >3 points <10 mm or flaky DWI points >10 mm.

Statistical Analysis

The independent samples *T*-test was applied for comparison of continuous variables, and the chi-square test or Fisher's exact test was used for analysis of categorical variables. Logistic regression was used for multiple analysis to evaluate the relation between asymptomatic ischemic lesions and other factors after endovascular treatment. A $p < 0.05$ was considered significant. We used standard commercial software SPSS version 22 (IBM Corp., Armonk, NY, USA).for statistical analysis.

RESULTS

During the study period, a total of 255 patients received endovascular treatment for intracranial aneurysms at our center, and 141 patients with 149 aneurysms met the inclusion criteria. The mean age was 58.7 ± 10.3 years, and 102 (72.3%) patients were female. Endovascular operations were performed in 149 aneurysms (ruptured and unruptured aneurysms), including 41 anterior communicating artery aneurysms, 26 middle cerebral aneurysms, 73 internal carotid artery aneurysms, and nine

posterior circulation aneurysms. Of all aneurysms, 72 aneurysms received coil embolization, and 77 aneurysms were treated by stent-assisted embolization, including 43 (55.8%) laser engraving stents (38 Enterprise stents, three Neuro Form EZ stents, and two Solitaire stents) and 34 (44.2%) dense network stents (31 LVIS stents, one Pipeline stent, and two Tubridge stents).

In total, 91 patients with 96 aneurysms were treated with endovascular embolization in the local heparinization group, and 50 patients with 53 aneurysms were treated with endovascular embolization in the systemic heparinization group. The demographic parameters were evenly distributed among the groups (female: 69.2 vs. 78.0%, $p > 0.05$; age: 59.74 ± 10.7 years vs. 56.94 ± 9.5 years, $p > 0.05$). The differences between the two groups were the treatment type and the type of stent. More patients in the local heparinized group received coiling alone and more patients in the systemic heparinized group received stent-assisted embolization (56.3 vs. 66%, $P = 0.009$). Dense network stents were more commonly used in the local heparinization group than in the systemic heparinization group (57.1 vs. 28.6%, $P = 0.012$). **Table 1** shows comparative data between the local heparinization group and systemic heparinization group.

In the local heparinization group, 67 (69.8%) patients had abnormal DWI after the operation, including 37 (38.5%) patients in the coil embolization group and 30 (31.3%) patients in the stent-assisted embolization group.

A total of 36 cases (67.9%) with abnormal DWI after the operation were found in the systemic heparinization group, including 10 cases (18.9%) in the coil embolization group and 26 cases (49.1%) in the stent-assisted embolization group. There were no statistically significant differences in the incidence of DWI abnormalities between the local heparinization group and systemic heparinization group, including the subgroups (**Table 2**).

The most common type of DWI abnormality in the systemic heparinization group was A (50%, 18/36). The most common type of DWI abnormality in the local heparinization group was also A (32.8%, 22/67). In the subgroups receiving coiling alone and stent-assisted coiling, the most common type of DWI abnormality in the systemic heparinization group was A, and the most common type of DWI abnormality in the coiling alone group with local heparinization was A (40.5%, 15/37). But, the most common DWI abnormality in the stent-assisted coiling group with local heparinization was C (36.7%, 11/40). The distribution of DWI abnormalities in the different groups showed no significant difference [($P > 0.05$) (**Table 3**, **Figure 1**)].

The univariate analysis results showed that there were no significant differences among age, sex, history of arterial hypertension, diabetes, hyperlipidemia, location and size of aneurysm, ruptured aneurysm, heparinization scheme, intraoperative hypotension, operation time ≥ 120 min, embolization mode of the aneurysm and postoperative DWI abnormality ($P > 0.05$). Compared with the dense network stent, the laser engraving stent was more prone to DWI abnormalities (66.1 vs. 33.9%, $P = 0.003$) (**Table 4**).

Variables including female gender, age >60 years old, aneurysm on the left side, location and size of aneurysm, local heparinization, intraoperative hypotension, operation

TABLE 1 | Demographic parameters and distribution of patients who received local and systemic heparinization treatment for aneurysms.

	Local heparinization	Systemic heparinization	*p*-value
No. of patients	91 (64.5)	50 (35.5)	
Age (years), mean ± SD	59.74 ± 10.7	56.94 ± 9.5	0.125
Female sex	63 (69.2)	39 (78.0)	0.265
Arterial hypertension	49 (53.8)	31 (60.8)	0.350
Diabetes mellitus	4 (4.4)	4 (8.0)	0.454
Aneurysm size no. (mm)	96 (64.4)	53 (37.6)	0.322
<5	54 (56.3)	23 (43.4)	
5–10	38 (39.6)	27 (50.9)	
>10	4 (4.2)	3 (5.7)	
Aneurysm site			0.538
Anterior communicating artery aneurysm	30 (31.3)	11 (20.8)	
Middle cerebral aneurysm	15 (15.6)	11 (20.8)	
Internal carotid artery aneurysm	45 (46.9)	28 (52.8)	
Posterior circulation aneurysm	6 (6.3)	3 (5.7)	
Treatment type			
Coiling alone	54 (56.3)	18 (34.0)	0.009
Stent–assisted coiling	42 (43.8)	35 (66.0)	
Type of stent			
Laser engraving stent	18 (42.9)	25 (71.4)	0.012
Dense network stent	24 (57.1)	10 (28.6)	

TABLE 2 | Grouping of the heparinization schemes and analysis of cerebral ischemia.

Heparinization schemes	Abnormalit, No. (%)	No DWI abnormality, No. (%)	*P*–value
Systemic heparinization	36 (67.9)	17 (32.1)	0.813
Local heparinization	67 (69.8)	29 (30.2)	
Systemic heparinization Coil embolization	10 (18.9)	8 (15.1)	0.551
Stent–assisted coiling	26 (49.1)	9 (17.0)	
Local heparinization Coil embolization	37 (38.5)	17 (17.7)	
Stent–assisted coiling	30 (31.3)	12 (12.5)	

TABLE 3 | Distribution results of the heparinization method and DWI abnormality.

Heparinization way	A, No. (%)	B, No. (%)	C, No. (%)	D, No. (%)	P–value
Systemic heparinization	18 (50.0)	6 (16.7)	6 (16.7)	6 (16.7)	0.307
Local heparinization	22 (32.8)	11 (16.4)	20 (29.9)	14 (20.9)	
Systemic heparinization Coil embolization	4 (40.0)	3 (30.0)	2 (20.0)	1 (10.0)	0.520
Stent–assisted embolization	14 (53.8)	3 (11.5)	4 (15.4)	5 (19.2)	
Local heparinization Coil embolization	15 (40.5)	6 (16.2)	9 (24.3)	7 (18.9)	
Stent–assisted embolization	7 (23.3)	5 (16.7)	11 (36.7)	7 (23.3)	

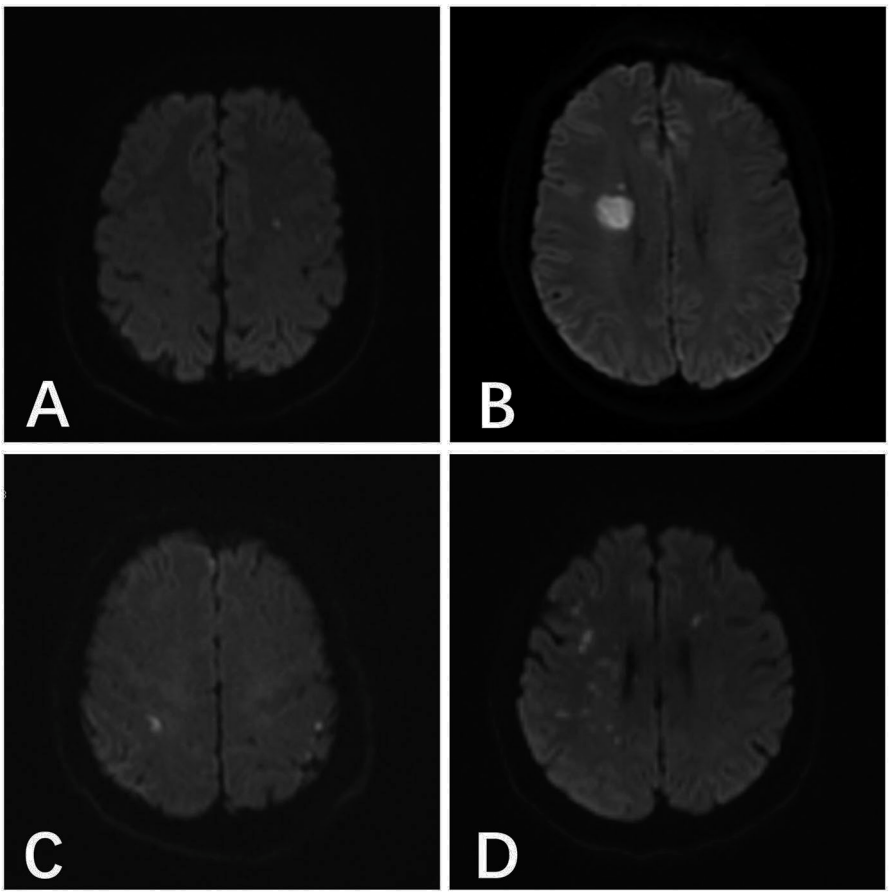

FIGURE 1 | (A) A 46-year-old male patient with anterior communicating aneurysm underwent pure spring coil embolization under systemic heparinization, and the postoperative result indicated the acute cerebral infarction focus in the left parietal temporal lobe. **(B)** A 48-year-old male patient with right posterior communicating aneurysm underwent stent-assisted embolization under local heparinization, and the postoperative result indicated the acute cerebral infarction in the right lateral ventricle. **(C)** A 54-year-old male patient with right posterior communicating aneurysm underwent pure spring coil embolization under local heparinization, and the postoperative result indicated the abnormal DWI signals in the bilateral parietal lobes. **(D)** A 55-year-old female patient with a right middle cerebral aneurysm underwent stent-assisted embolization under systemic heparinization, the postoperative result indicated the acute cerebral infarction in the right parietal temporal lobe and the left frontal lobe.

time $\geq$120 min and stent usage were included in the multivariate logistic regression analysis as independent variables. (**Appendix Table A1**). The results showed that there was no significant correlation among female gender, age >60 years old, aneurysm on the left side, location and size of aneurysm, local heparinization, intraoperative hypotension, operation time $\geq$120 min and DWI abnormalities after endovascular treatment for intracranial aneurysms. There was a significant correlation between the engraving stent (OR 4.711, 95% CI 1.512–14.584, $P = 0.007$) and DWI abnormalities after endovascular treatment for intracranial aneurysms (**Table 5**).

Among 103 cases of abnormal DWI lesions, 91 patients (88.3%) had no symptoms and 12 patients (11.7%) had symptoms, including five patients with headache, three patients with vomiting, two patients with allergies, one patient with somnolence, and one patient with chest distress. All patients recovered well without a secondary hemorrhage or neurological sequelae when discharged from the hospital.

DISCUSSION

Intracranial aneurysm is a highly dangerous hemorrhagic cerebrovascular disease. Rebleeding in patients with ruptured intracranial aneurysms may occur at any time during the acute phase, thus requiring a more timely operation to achieve the purpose of treatment, especially for patients with a large amount of blood loss, who may need other invasive operations immediately after embolization. The existence of these factors challenges the safety and necessity of traditional systemic heparinization. In this study, 91 patients with 96 acute hemorrhagic aneurysms were treated by endovascular embolization with local heparinization, including 67 cases

TABLE 4 | Univariate analysis results of DWI abnormalities after endovascular treatment for intracranial aneurysms.

Clinical factors		DWI abnormality, No. (%)	No DWI abnormality, No. (%)	*P*–value
Age (year)	≤60	54 (55.7)	27 (61.4)	0.526
	>60	43 (44.3)	17 (38.6)	
Sex	Male	26 (26.8)	13 (29.5)	0.736
	Female	71 (73.2)	31 (70.5)	
Diabetes	Yes	7 (7.2)	1 (2.3)	0.435
	No	90 (92.8)	42 (97.7)	
History of stroke	Yes	9 (9.3)	2 (4.5)	0.503
	No	88 (90.7)	42 (95.5)	
Hypertension	Yes	58 (59.8)	22 (50.0)	0.277
	No	39 (40.2)	22 (50.0)	
Hyperlipidemia	Yes	68 (70.1)	26 (65.0)	0.558
	No	29 (29.9)	14 (35.0)	
Ruptured	Yes	67 (65.0)	29 (63.0)	0.813
	No	36 (35.0)	17 (37.0)	
Aneurysm is on the left	Yes	55 (53.4)	26 (56.5)	0.724
	No	48 (46.6)	20 (43.5)	
Aneurysm location	Anterior communicating artery aneurysm	25 (24.3)	16 (34.8)	0.324
	Middle cerebral aneurysm	20 (19.4)	6 (13.0)	
	Internal carotid artery aneurysm	50 (48.5)	23 (50.0)	
	Posterior circulation aneurysm	8 (7.8)	1 (2.2)	
Aneurysm size (mm)	<5	57 (55.3)	20 (43.5)	0.399
	5–10	41 (39.8)	24 (52.2)	
	>10	5 (4.9)	2 (4.3)	
Wide neck aneurysm	Yes	28 (27.2)	9 (19.6)	0.320
	No	75 (72.8)	37 (80.4)	
Heparinization mode	Local heparinization	67 (65.0)	29 (63.0)	0.813
	Systemic heparinization	36 (35.0)	17 (37.0)	
Intraoperative hypotension	Yes	37 (36.6)	17 (37.0)	0.970
	No	64 (63.4)	29 (63.0)	
Operation time ≥120min	Yes	61 (59.2)	23 (50.0)	0.294
	No	42 (40.8)	23 (50.0)	
Stent used	Yes	56 (54.4)	21 (45.7)	0.325
	No	47 (45.6)	25 (54.3)	
Type of stent	Laser engraving stent	37 (66.1)	6 (28.6)	0.003
	Dense network stent	19 (33.9)	15 (71.4)	

TABLE 5 | Multivariate analysis results of clinical data.

Clinical data		OR (95% CI)	*P*–value
Sex (female)		0.822 (0.317–2.131)	0.687
Age (>60 years)		1.395 (0.603–3.224)	0.436
Left side		0.879 (0.391–1.974)	0.754
Location of aneurysm	Anterior communicating artery aneurysm	0.167 (0.017–1.688)	0.129
	Middle cerebral aneurysm	0.530 (0.049–5.780)	0.603
	Internal carotid artery aneurysm	0.254 (0.027–2.399)	0.231
Size of aneurysm (mm)	<5	0.931 (0.126–6.853)	0.944
	5–10	0.502 (0.066–3.791)	0.504
Local heparinization		1.742 (0.725–4.183)	0.214
Intraoperative hypotension		0.880 (0.373–2.078)	0.770
Operation time ≥120min		0.988 (0.427–2.290)	0.978
Dense network stent		0.699 (0.282–1.734)	0.440
Laser engraving stent		4.711 (1.521–14.584)	0.007*

*$P < 0.05$.

(69.8%) who showed DWI abnormalities. These findings are consistent with the incidence rate of visible ischemic lesions on DWI after postoperative intravascular treatment reported by previous studies, which is between 10 and 77% (2–5). Thus, it can be seen that the application of local heparinization does not increase the risk of intraoperative cerebral ischemic events. In terms of postoperative DWI abnormalities, there was no significant difference (69.8 vs. 67.9%, $P = 0.813$) in its incidence in the local heparinization group and systemic heparinization group. In the subgroup analysis of coiling alone and stent-assisted coiling, there were no significant differences in DWI abnormalities. At the same time, there were no bleeding events in the two groups during hospitalization, which indicated that the application of local heparinization in the endovascular treatment of intracranial aneurysms did not increase the risk of bleeding and ischemic complications compared with systematic heparinization.

The anticoagulant effect of heparin is mediated largely through its interaction with antithrombin III(ATIII).this produces a conformational change in ATIII and so markedly accelerates its ability to inactivate the coagulation enzymes thrombin (factor IIa), factor Xa, and factor IXa. Heparin is probably the most commonly used intraoperative drug that is considered to reduce the risk of intraoperative thromboembolic events (9–11). Most centers apply systemic heparinization in the endovascular treatment of intracranial aneurysms. Usually, the heparin dosage for vein mass injection at the beginning of the operation ranges from 3,000 to 5,000 U, followed by a continuous intravenous drip at a rate of 20–40 U/kg/h, and the activated clotting time (ACT) is maintained between 200 and 300 s to avoid the complications of thromboembolism (9, 12–14). The World Federation of Interventional Neuroradiology (WFITN) recommends 5,000 U of heparin for intravenous infusion, followed by a 1,000 U/h continuous intravenous drip, while maintaining an ACT value of 200 s (13). We studied the replacement of systemic heparinization with local heparinization in the treatment of ruptured aneurysm. The catheter flashing

solution contained 2,000 U of heparin per 500 ml. Through the analysis of the distribution of different heparinization schemes and cerebral ischemia events on DWI, we found that the most common type of ischemic event distribution was A ($n = 40$, 38.8%) in this series. Meanwhile, the comparison of ischemic event distribution types between the systemic heparinization group and the local heparinization group did not show significant differences, which indicated that different schemes of heparinization did not affect the distribution of abnormal ischemic events on DWI, and there was no difference between the different methods of heparinization and DWI abnormalities. At the same time, the distribution of aneurysms at different locations showed no difference in this study ($P = 0.298$). We considered that these DWI abnormalities may be related to the operation of the patient, and these lesions are correlated with the specific locations of the aneurysm according to reports by some researchers (15, 16).

The incidence of thromboembolic events after cerebral aneurysm coil embolization was still high, and previous studies have shown that various factors are positively correlated with postoperative ischemic events, including older age, dyslipidemia, diabetes, history of ischemic stroke, leukodystrophy, rupture of aneurysms, multiple aneurysms, larger neck size and longer operation time (5, 15–18). Stent-assisted embolization was also considered to be the cause of the significant increase in the risk of embolism (19). In our study, the incidence of DWI abnormalities of the two types of stents after the operation showed statistical significance (laser engraving stent, n=37, 66.1%; dense network stent, $n = 19$, 33.9%; $P = 0.007$). In the subsequent multivariate analysis, it was indicated that engraving stents were also correlated with asymptomatic ischemic events ($P < 0.05$), which may be related to the stent parameters, stent implantation operation method, whether the stent was well-attached during the operation, and the influence of stent implantation on hemodynamics. These factors may influence the conversion of intracranial aneurysms.

Previous studies have found that patients with an intracranial aneurysm on the left side had a higher incidence of postoperative cerebral ischemia. The results of this study showed that the aneurysm located on the left side ($n = 55$, 53.4%) showed abnormal DWI after operation, but there was no correlation on the left side in univariate analysis. In a prospective study of 39 patients with unruptured aneurysms, Sim et al. (16) proposed that the left admission passage may increase the possibility of asymptomatic multiple sporadic microemboli after the aneurysm embolization operation. It was suggested that the left great vessels, especially the left common carotid artery, tended to be more difficult to perform surgery on due to their larger angle with the aortic arch, so left-sided aneurysms undergoing surgery were more prone to these ischemic complications. At the same time, some authors have speculated that these multiple microemboli may originate from the intraoperative removal of small blood clots, the atherosclerotic plaque from the aortic arch or the great vessel wall via catheter operation (20). However, there was no significant difference in the location of DWI abnormalities in our study.

The operation time as a risk factor for postoperative cerebral ischemia has also been documented in previous studies. The incidence of cerebral ischemia lesions after embolization of the aneurysm increased with the increase of the operation time (17). In this study, we took an operation time $\geq$120 min as a marker of a long operation. Correlation analysis between a single factor and multiple factors with DWI abnormalities was conducted, and none of the results showed statistical significance. Park et al. (21) verified that the occurrence of microemboli was positively correlated with the operation time in univariate analysis; however, such a relation was not confirmed in subsequent multivariate analysis. A longer duration of the operation may mean that the aneurysm grows in difficult locations and the operator encounters increased difficulties during the operation. Lee et al. (17) suggested that shortening of the operation time is the most effective way that surgeons can reduce the incidence of thromboembolic events after embolization. Therefore, before the operation, the operator should work out a detailed operation plan according to the patient's condition and aneurysm condition to ensure the operation goes smoothly and to reduce intraoperative and postoperative complications of the patient. At the same time, we also assessed the relation between intraoperative hypotension and the occurrence of DWI abnormalities for the first time. Although intraoperative hypotension means that the patient has lower cerebral perfusion and a greater risk of embolization events, a correlation between intraoperative hypotension and DWI abnormalities was not shown in our results.

No significant correlation was found between ruptured aneurysms and postoperative DWI abnormalities ($P > 0.05$) in our study. In the treatment of ruptured aneurysms, some studies have shown that thrombolytics, such as tirofiban, can effectively dissolve the thrombus or embolus during the operation (22). Tirofiban is a non-peptide antagonist of platelet glycoprotein (GP) IIb/IIIa receptor, which can inhibit platelet aggregation, and the patient's normal platelet function is restored within 4 h after drug withdrawal (23). We used tirofiban to prevent thromboembolic events during stent-assisted embolization with local heparinization. Although the incidence of DWI abnormalities with local heparinization was 69.8%, no further rupture or bleeding occurred after the operation, which indicated that the application of tirofiban was safe with local heparinization, even though long-term injection of tirofiban may have a risk of cerebral hemorrhage.

How to reduce ischemic complications in clinical applications has always puzzled clinicians. One strategy is to use antiplatelet drugs prior to the selective aneurysm coil embolization operation, as it has been proven to reduce the risk of clinical thromboembolic events (24, 25). How to reduce the occurrence of microemboli events with abnormal DWI during the aneurysm operation has also been studied by many researchers. Kim et al. (26) obtained the incidence of diffusion-weighted imaging-high signal intensity (DWI-HIS) lesions in a conventional group (89.2%, 33/37) and an improved group (26.5%, 9/34) in a study of 71 patients with unruptured cerebral aneurysms by deliberately aspirating the contents of the microcatheter after releasing each spring coil, and the difference was statistically significant ($P < 0.0001$). Lim et al. (27) showed that prior use of a heparin bolus

dosage above 2,000 U during cerebral aneurysm embolization may reduce cerebral ischemic events after embolization. The use of new-generation blood flow guides can also reduce the incidence of such complications. Pikis et al. (28) found that new-generation blood flow guides significantly reduced the incidence of such complications in a study of 33 patients with unruptured aneurysms, with a DWI positive lesion rate of 16.66%, which also requires further study.

Limitations

Our study has several limitations. First, this is our single center's exploration of different heparinization schemes. Second, we cannot exclude the effect of ruptured aneurysms on vascular stimulation and ischemia in this study. Third, since we did not conduct preoperative MRI examinations, some ischemic lesions observed on DWI after the operation may have occurred before the treatment of intracranial aneurysms.

CONCLUSION

Our study shows that local heparinization is safe and effective in endovascular embolization for intracranial aneurysms and does not increase the risks of cerebral ischemia and bleeding complications compared with traditional systemic heparinization. DWI abnormalities after intracranial aneurysm embolization are a serious problem, and how to reduce the occurrence of DWI abnormalities may require more clinical data experiments and basic experimental studies.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary materials, further inquiries can be directed to the corresponding author/s.

AUTHOR CONTRIBUTIONS

LZ contributed to the preparation of the manuscript and data collection. XZ contributed to revising the manuscript. YL and CD contributed to data analysis and interpretation. YW and HY contributed to the experi-mental design and manuscript revision. All authors contributed to the article and approved the submitted version.

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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APPENDIX

TABLE A1 | Assignment table of single-factor and multi-factor logistics regression analysis for DWI abnormalities after endovascular treatment for intracranial aneurysms.

Item	Assignment
DWI abnormality	Yes = 1, No = 0
Sex	Female = 1, Male = 2
Age	Above 60 years = 1, Below 60 years = 2
Aneurysm is on the left	Left side = 1, Right side = 2
Ruptured	Yes = 1, No = 2
Aneurysm location	Anterior communicating artery aneurysm = 1, Middle cerebral aneurysm = 2, Internal carotid artery aneurysm = 3, post-circulation aneurysm = 4 (dummy variable)
Aneurysm size	<5 = 1, 5–10 = 2, Above 10 = 3 (dummy variable)
Heparinization mode	Local heparinization = 1, Systemic heparinization = 2
Intraoperative blood pressure condition	Hypotension occurred during operation = 1, Hypotension did not occur during operation = 2
Operation duration	Operation time ≥120 min = 1, Operation time < 120 min = 2
Stent usage condition	Dense network stent = 1, Laser engraving stent = 2, Unused stent = 3 (dummy variable)

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ORIGINAL RESEARCH
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Possibility of Worsening Flow Diversion Effect Due to Morphological Changes of a Stented Artery With Multiple Overlapping Stents for Partially Thrombosed Vertebral Artery Aneurysms

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Background: Morphological changes of a stented artery can cause a flow diversion effect to reduce intra-aneurysmal flow; however, there is a potential for the negative effect of increased intra-aneurysmal flow. We present cases with multiple overlapping stents for a partially thrombosed vertebral artery aneurysm and characterize the hemodynamic properties of a recurrent case by focusing on the morphological changes of the stented artery.

Methods: Between October 2017 and April 2019, four consecutive cases of symptomatic unruptured large and giant partially thrombosed vertebral artery aneurysms were treated with multiple overlapping low-profile visualized intraluminal support stents and no coils. Both angiographic and clinical outcomes were assessed. Computational fluid dynamics analysis was performed to clarify hemodynamic features. The degree of pressure elevation was calculated as the pressure difference (Pd). Wall shear stress (WSS) was also calculated.

Results: In three of the four cases, successful flow reduction was achieved with no morphological change of the stented arteries. The patients' symptoms were gradually improved. The remaining case required additional stents after the initial treatment. In the recurrent case, Pd was noticeably elevated at the aneurysm neck after treatment, and WSS was generally increased in the area due to altered blood flow into the aneurysm dome caused by morphological changes of the stented artery.

Conclusion: Overlapping stents can be used for the treatment of large and giant thrombosed vertebral artery aneurysms with flow diversion effect; however, morphological changes of the stented artery requires careful attention as it may lead to an increase in the intra-aneurysmal flow, causing negative outcomes.

Keywords: overlapping stents, posterior circulation, vertebral artery aneurysm, computational fluid dynamics, morphological change

INTRODUCTION

In endovascular surgery using neck-bridge stents and flow diverters (FDs), the flow diversion effect is an important factor in occlusion of cerebral aneurysms and is caused by metal coverage at the aneurysm orifice as well as straightening of the stented parent artery (1–4). Reduction of intra-aneurysmal flow often contributes positively to the treatment of cerebral aneurysms. However, unpredictable flow changes are possible with this treatment (5–7). Previous computational fluid dynamics (CFD) studies have shown that multiple low-profile visualized intraluminal support (LVIS) devices have flow diversion effects (8). We treated unruptured large and giant partially thrombosed vertebral artery aneurysms by overlap stenting using multiple LVIS stents, because the use of FD for posterior circulation aneurysms is unauthorized in our country, and we focused on the morphological change of the stented artery. Also, CFD analysis was performed for understanding hemodynamic changes after stent replacement.

MATERIALS AND METHODS

Patients

Between October 2017 and April 2019, four patients with large and giant partially thrombosed vertebral artery aneurysms were treated by overlap stenting using LVIS stents (MicroVention, Aliso Viejo, CA, USA). Their clinical information is summarized in **Table 1**. For the flow diversion effect, multiple LVIS stents were placed in the parent artery of the aneurysms. No coils were used in the treatment of any of the aneurysms described in this

TABLE 1 | Clinical information.

Case	Age	Dome size (mm)	Symptoms	Number of LVIS stent	Morphological change of parent artery	Angiographic outcome	Clinical outcome
1	60–65	18	Dizziness	2	No	Complete occlusion at 2 years	Improved
2	70–75	23	Left hemiparesis, dysphasia	2	No	Complete occlusion at 2 weeks	Improved
3	50–55	38	Left hemiparesis	2	No	Almost complete occlusion at 6 months	Partially improved
4	50–55	35	Vertigo, left hemifacial spasm	5	Yes	Worsened	Worsened

LVIS, low-profile visualized intraluminal support.

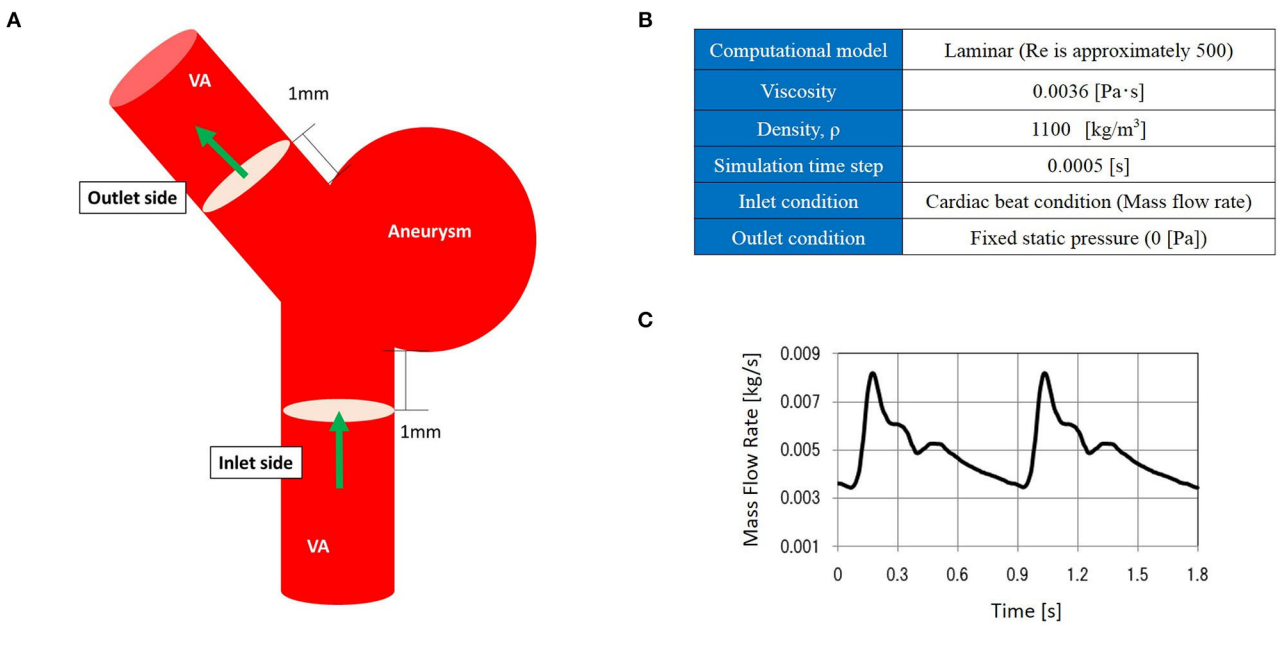

FIGURE 1 | The computational fluid dynamics (CFD) model. CFD analysis domain **(A)**, CFD analysis condition **(B)**, and inlet mass flow rate **(C)**.

study. After treatment, patient follow-up included conventional digital subtraction angiography (DSA) and magnetic resonance imaging (MRI). We assessed both angiographic and clinical outcomes. The O'Kelly-Marotta (OKM) grading scale was used to assess the degree of angiographic filling and contrast stasis in the aneurysms.

For the treatment, antiplatelet therapy was administrated with 100 mg of aspirin and 75 mg of clopidogrel per day for 7 days before the procedure. After the procedure, the dual antiplatelet therapy was continued for at least 6 months, and clopidogrel was continued for 1–2 years.

CFD Modeling and Analysis of Hemodynamic Parameters

CFD analysis was performed to evaluate hemodynamics at the treatment site. Aneurysm and parent vessel geometries were extracted from DSA images via manual cropping and image thresholding. This information was subsequently converted to a triangulated surface using Amira Software (FEI Company, Hillsboro, OR, USA). A commercial software package (ANSYS ICEM CFD 18.21, ANSYS Inc., Canonsburg, PA, USA) was used to generate an unstructured computational volumetric mesh. This mesh mainly comprised tetrahedrons along with several prism element layers near the wall surface to increase the analytic precision of the boundary layer. The numbers of grid elements were ∼1,500,000. After assuming a pulsatile laminar flow, pressure of 0 (Pa) at the outlet, and rigid blood vessel walls with non-slip conditions, the blood flow along the computational mesh was simulated using Navier–Stokes equations. The analysis domain encompassed the whole aneurysm dome from the aneurysm inlet side to the outlet side. **Figure 1** shows additional details regarding the CFD modeling.

We investigated several hemodynamic parameters, focusing on pressure-related parameters. As previously described (9), the pressure difference (Pd) was defined as the degree of pressure elevation at the aneurysm wall. It is calculated by subtracting the average pressure (Pave), the mean pressure value in this domain, from the pressure of the target area (P). To normalize this value, it was divided by the dynamic pressure at the side of the aneurysm inlet.

$$\textit{Pressure difference} = \frac{P - Pave}{\frac{1}{2}\rho Vin^2} \quad (1)$$

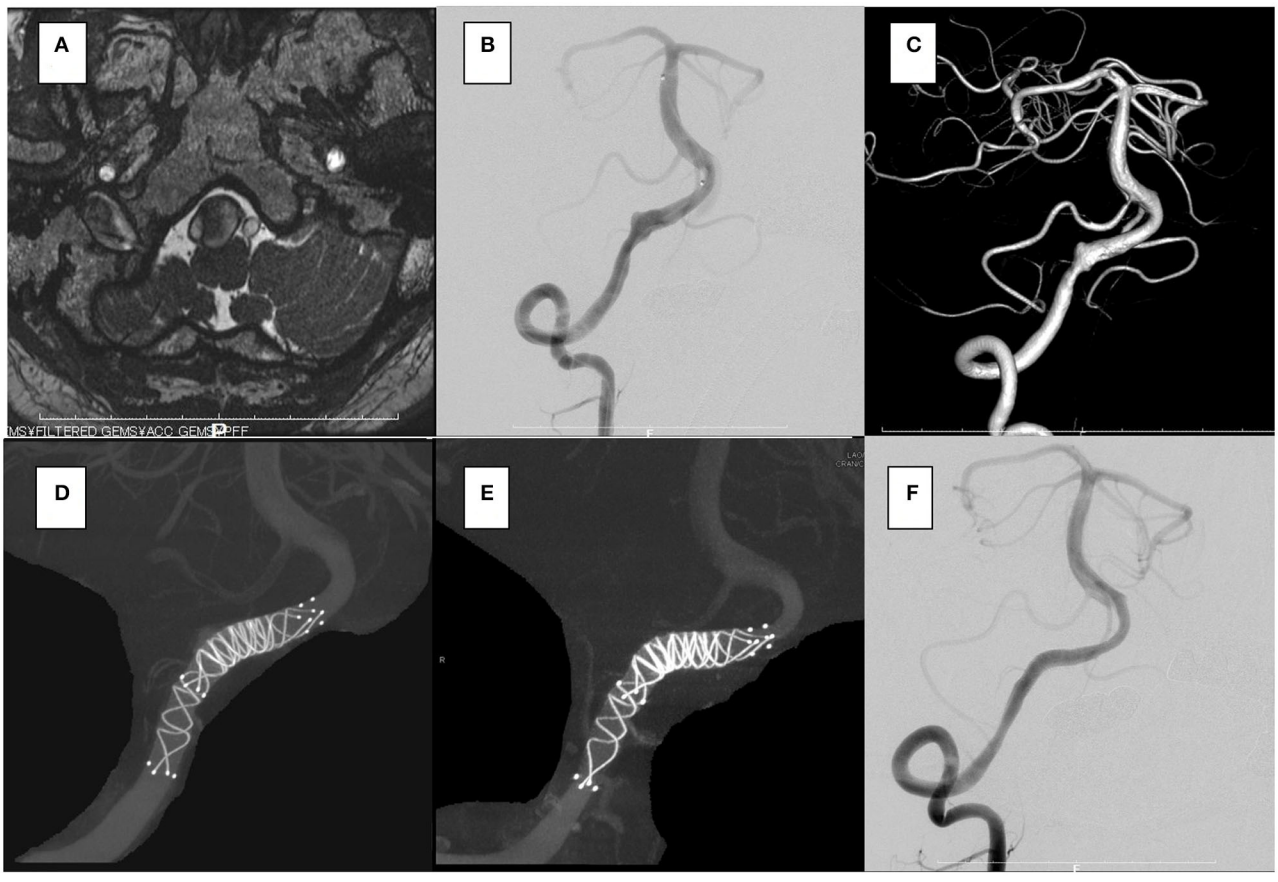

FIGURE 2 | In the case 1, the patient presented with dizziness. The brain stem was compressed by a large partially thrombosed vertebral artery aneurysm. **(A–C)** Overlapping stents with double low-profile visualized intraluminal support (LVIS) were placed (two of 4.5 × 32 mm). **(D)** After 2 years, the follow-up angiography shows that the aneurysm was closed off **(E,F)**, and his symptoms were resolved.

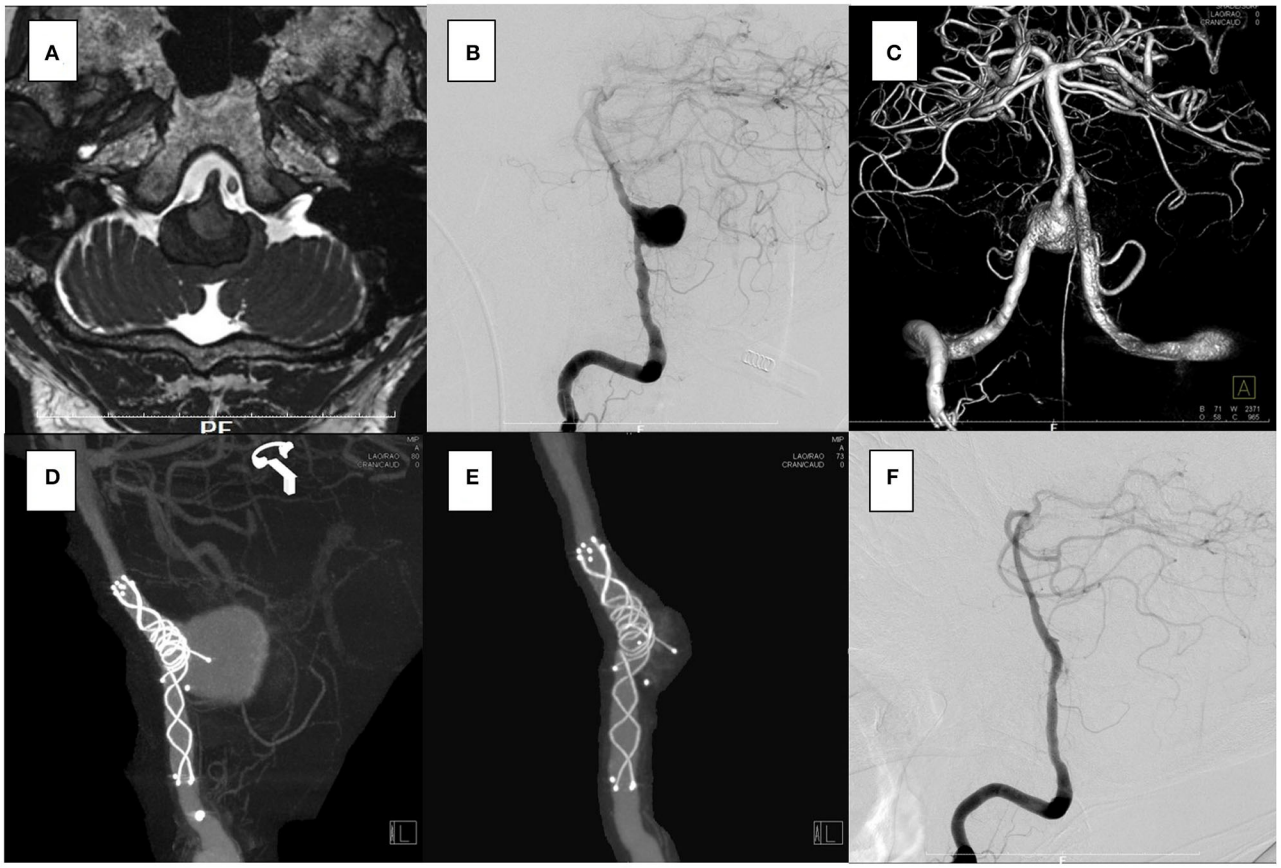

FIGURE 3 | In the case 2, the patient presented with left hemiparesis and dysphasia. His brain stem was compressed by a large partially thrombosed vertebral artery aneurysm. **(A–C)** Overlapping stents with double low-profile visualized intraluminal support (LVIS) were placed (3.5 × 22 mm, 4.5 × 32 mm). The first stent was shortened when a micro catheter was advanced to the distal end of the vertebral artery, but it covered the aneurysm orifice. **(D)** After 2 weeks, the follow-up angiography showed that the aneurysm was closed off. **(E,F)** No recanalization has been seen for 2 years.

P: pressure [Pa], Pave: average pressure [Pa]
ρ: 1,100 [kg/m^3], Vin: mean velocity of the aneurysm inlet [m/s]

We also assessed wall shear stress (WSS) in the aneurysm dome, defined as the frictional force of blood flow along the aneurysm wall.

RESULTS

The aneurysm domes were occluded in two aneurysms and almost occluded in one aneurysm in the follow-up angiography (**Figures 2**–**4**). The clinical symptoms gradually resolved in the three cases. On the contrary, one giant vertebral thrombosed aneurysm was uncontrollable after overlap stenting with triple LVIS stents. Additional double LVIS stents were placed 12 months after the initial treatment; however, this worsened the aneurysm further by increasing inflow into the aneurysm dome and causing the enlargement of the thrombosed aneurysm (**Figure 5**). The morphological change of the parent artery was seen in the recurrent case after the initial treatment (**Figure 6**) and CFD analysis reveals that this change led to pressure elevation around the aneurysm neck. The highest Pd at the area increased from 0.08 to 1.17, while WSS generally remained elevated (**Figure 7**).

DISCUSSION

Recently, FDs have been widely used for the treatment of cerebral aneurysms (10, 11). The effectiveness of FDs for large and giant thrombosed aneurysms has been reported, with curative thrombosis of the aneurysm sac caused by reducing flow, without the use of coils (12). Posterior circulation thrombosed aneurysms are particularly difficult to treat because of the high rate of recanalization and compression of the brainstem, which coil embolization has the potential risk of worsening (13, 14). The effect of flow diversion is, at least theoretically, useful for the treatment of such aneurysms. In our study, overlap stenting with braided stents was used because FD is unauthorized for use in posterior circulation aneurysms in our country. Flow reduction was achieved in three out of four aneurysms by overlap

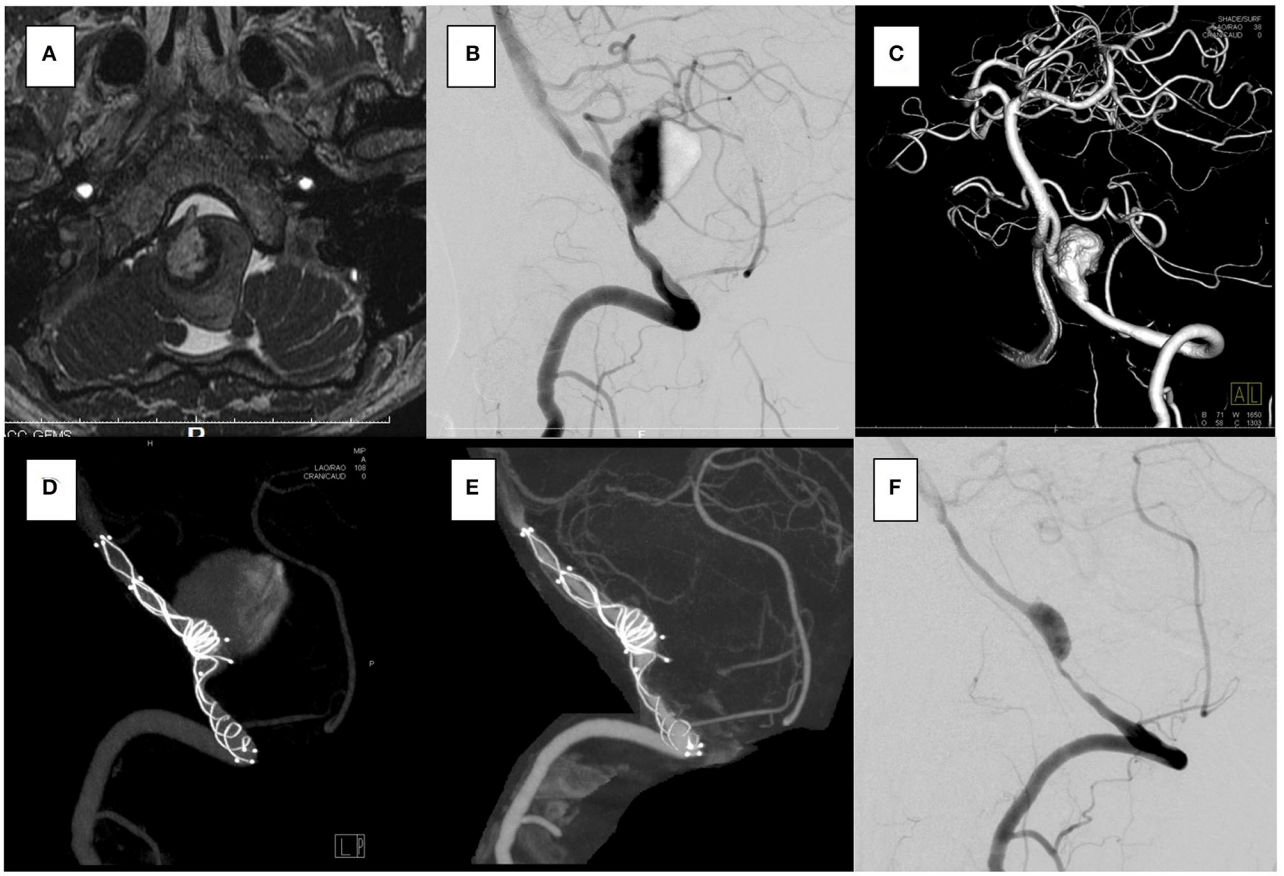

FIGURE 4 | In the case 3, the patient presented with left hemiparesis. The brain stem was compressed by a giant partially thrombosed vertebral artery aneurysm. **(A–C)** Overlapping stents with double low-profile visualized intraluminal support (LVIS) were placed (4.0 × 22 mm, 4.5 × 32 mm). The first stent was shortened when a micro catheter was advanced to the distal end of the vertebral artery, but it covered the aneurysm orifice. **(D)** After 6 months, the follow-up angiography showed that the aneurysm was almost closed off. **(E,F)** No recanalization was seen for 1 year.

stenting. It has been reported that multiple overlapping LVIS stents have a similar flow diversion effect as that of FD (6, 8). Metal coverage of the aneurysm orifice is one of the important factors causing a flow diversion effect. The porosity of the braided stents also contributes to decreased flow into the aneurysms (15, 16). We especially focused on the morphological changes in the stented parent artery, which previous studies have reported as contributing to a flow diversion effect (1–4). Ishii et al. analyzed unruptured large aneurysms with and without a stent and reported that the neck-bridging stent prevents recanalization caused by the straightening effect of the parent artery, most likely caused by significant angular change (1). Additionally, Larrabide et al. studied aneurysms in the internal carotid artery using CFD before and after FD treatment (4). They reported that successful blood flow reduction to the site of the aneurysm was related to aneurysm position and orientation with respect to the parent vessel, in addition to the morphology of the aneurysm. These studies reported that flow diversion after morphological changes of the stented parent artery can result in a positive outcome. Interestingly, in case 4, the morphological changes of the parent artery caused by multiple overlapping stents led to increased pressure and WSS in the aneurysm. Additional stents were not effective, even though the mesh porosity was theoretically much lower than that of FD. These results highlight that flow diversion effects with morphological changes to the parent artery can worsen due to blood flow into an aneurysm sac. Previous studies have reported adverse events associated with aneurysm rupture after treatment with FD, and the researchers speculated that flow diversion causes inflow jet and pressure elevation in the aneurysm sac (17–20). Some studies reported that failure to prevent increases in intra-aneurysmal pressure can occur because of parent artery configuration and curvature (20, 21). In addition, the elevation of WSS on the neck wall caused by altered blood flow is thought to increase the risk of recanalization (22, 23). Although recent engineering studies have analyzed the hemodynamic changes after stenting, it remains unclear how and to what extent the parent artery changes after stent placement (24, 25).

From a different perspective, the vasa vasorum is thought to play an important role in wall remodeling in the progressive

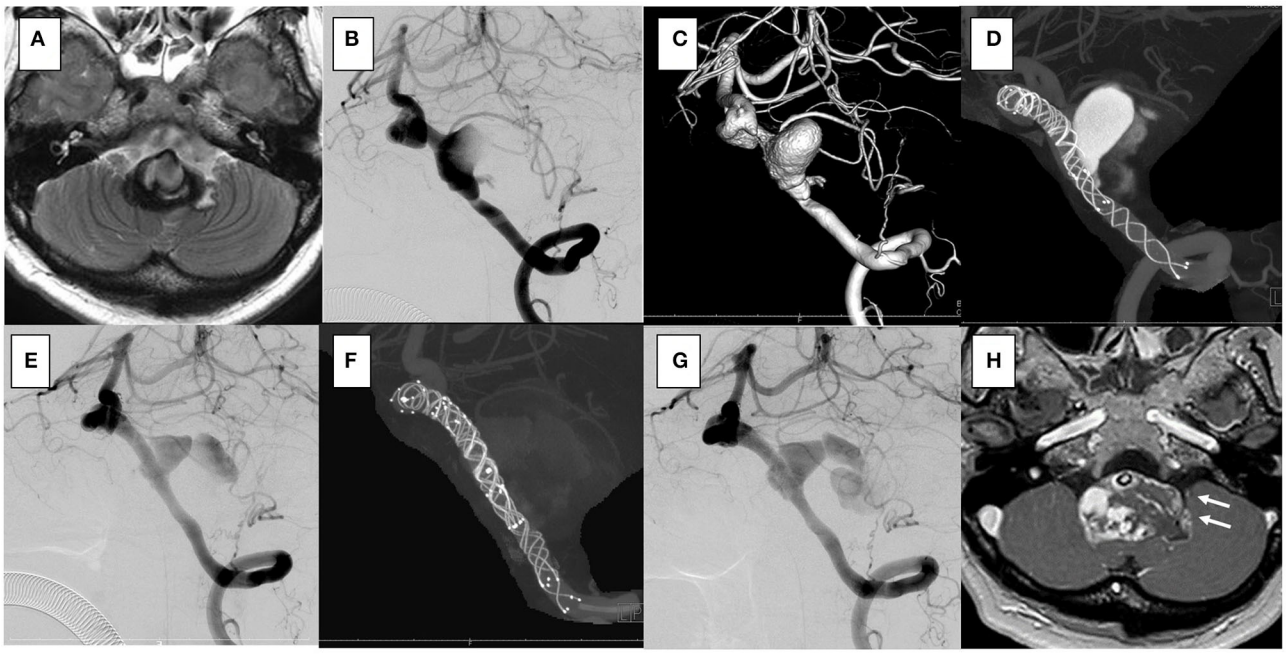

FIGURE 5 | In the case 4, the patient presented with vertigo and left hemifacial spasm. The brain stem was compressed by a giant partially thrombosed vertebral artery aneurysm. **(A–C)** Overlapping stents with triple low-profile visualized intraluminal support (LVIS) were placed (three of 4.5 × 32 mm), and stagnation of flow occurred soon after treatment. Her symptoms were resolved. **(D)** After 1 year, the follow-up angiography showed recanalization. **(E)** Additional stents with double LVIS were placed (4.5 × 18 mm, 4.5 × 23 mm). **(F)** However, it was uncontrollable and further recanalization was seen in the 6-month follow-up angiography **(G)**; furthermore, progressive aneurysmal enlargement occurred and aneurysm wall enhancement indicating the vasa vasorum was observed [**(H)**; white arrow]. Clinically, she presented vertigo and hemifacial spasm again, and slight hoarseness was apparent.

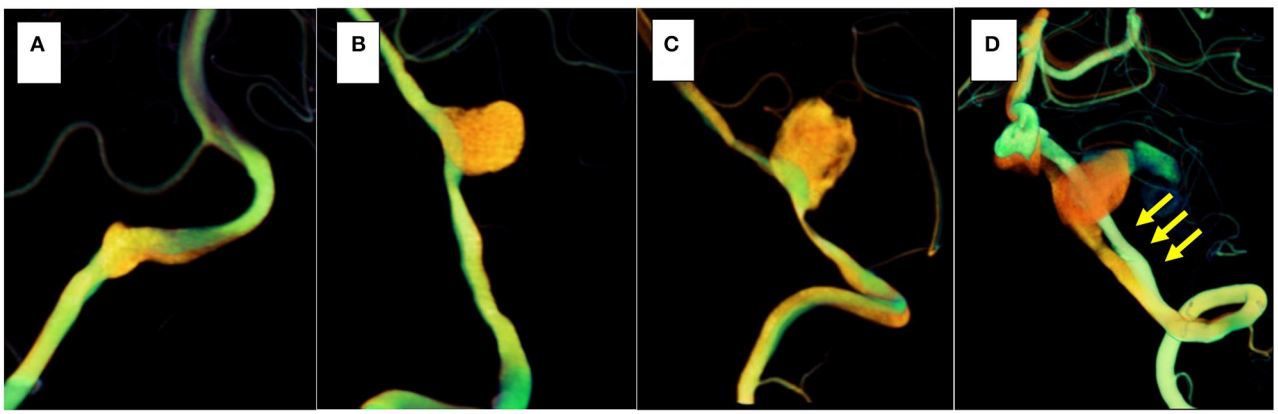

FIGURE 6 | The orange vessel is pre-treatment, and the green vessel is post-treatment. In three cases (cases 1–3), morphological changes in the stented parent artery were not seen **(A–C)**; however, in the recurrent case (case 4), the parent artery straightened after stent placement (yellow arrows) **(D)**.

growth of thrombosed large and giant aneurysms, and the image of aneurysm wall enhancement on MRI indicates inflammatory etiology including the vasa vasorum, which suggests malignant behavior of the aneurysm growth (26, 27). This finding was observed in the recurrent case even after retreatment and suggested intractable aneurysm due to worsening inflammation (**Figure 5H**).

Our study is the first to report a flow diversion effect by overlapping neck-bridge stents without coils for large and giant partially thrombosed vertebral artery aneurysms; however, CFD analysis of a recurrent case revealed that negative outcomes were related to changes in blood flow dynamics due to morphological changes in the stented parent artery.

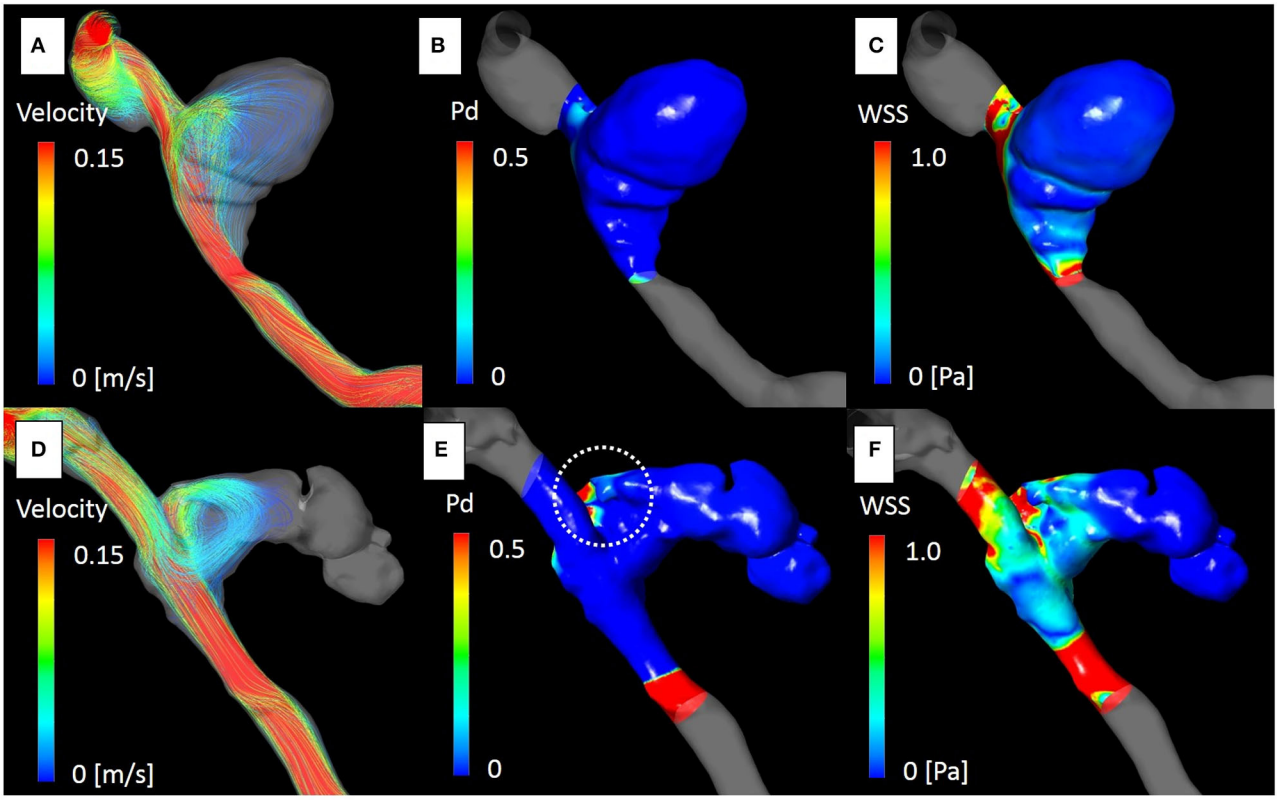

FIGURE 7 | The computational fluid dynamics study of case 4. Streamline, pressure difference (Pd) and wall shear stress (WSS) at the peak systolic phase before [**(A–C)**, respectively], and after treatment [**(D–F)**, respectively]. Blood flow into the aneurysm dome was altered after placement of the overlapping stents due to morphological changes in the parent artery **(D)**. Pd around the aneurysm neck was significantly elevated [**(E)**; white dot circle]. The maximum Pd identical to the impingement zone of the aneurysm dome was elevated from 0.08 to 1.01. WSS was generally elevated around the area **(F)**.

There are some limitations to this study. First, multiple stents were not simulated because it is not possible to acquire the morphological data of multiple LVIS stents, and this may influence the validity of our results. Second, the number of cases for analysis was small. Additional studies describing larger series are required. Third, the follow-up period may have been inadequate to determine whether the treatment was curative. Fourth, vasa vasorum is one of the important factors that causes the enlargement of thrombotic aneurysms. However, the other three cases of vasa vasorum were not available as contrast enhanced MRI was not performed routinely at our institution, and therefore, these could not be included for a comparison in this series.

CONCLUSION

Overlapping stents can be used to treat large and giant thrombosed vertebral artery aneurysms with a flow diversion effect. However, morphological changes of the stented parent artery may increase intra-aneurysmal flow causing a negative outcome, and careful attention is needed in this regard.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author/s.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by The ethics committee of Niigata University Medical and Dental Hospital (approval number: 2020-0027). Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

TS designed the study, acquired and analyzed the data, and drafted the article. All authors critically revised the article for important intellectual content and approved the final version for publication.

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Neurology

ORIGINAL RESEARCH
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Endovascular Treatment of Tiny Aneurysms With Low-Profile Visualized Intraluminal Support Devices Using a "Compressed" Stent Technique

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Objective: To investigate the safety and efficacy of low-profile visualized intraluminal support (LVIS) stent-assisted coiling of intracranial tiny aneurysms using a "compressed" stent technique.

Methods: We retrospectively analyzed patients with tiny aneurysms treated in our hospital with LVIS devices using a compressed stent technique. We analyzed patients' imaging outcomes, clinical outcomes, and complications.

Results: Forty-two tiny aneurysms in 42 patients were included in this study cohort; 8 patients presented with subarachnoid hemorrhage at admission. The immediate postoperative complete embolization rate was 76.2% (32/42). After an average of 8.5 months of imaging follow-up, the complete embolization rate was 90.5% (38/42), and no aneurysm recanalization occurred. After an average of 24.4 months of clinical follow-up, 95.2% (40/42) of the patients achieved favorable clinical outcomes (modified Rankin scale = 0/1). Operation-related complications occurred in two patients (4.8%); one intraoperative acute thrombosis, and one significant unilateral decreased vision during the postoperative follow-up.

Conclusion: LVIS stent-assisted coiling of intracranial tiny aneurysms using a compressed stent technique is safe and effective. Combined stent compression technology is beneficial to maximize the complete embolization of aneurysms and reduce aneurysm recanalization. This study expands the clinical applicability of LVIS stents.

Keywords: tiny aneurysm, endovascular treatment, coils, compression technique, LVIS stent

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INTRODUCTION

Intracranial tiny aneurysm refers to aneurysms with a largest diameter of ≤3 mm (1–3). Tiny aneurysms are being increasingly diagnosed with rapid developments in imaging techniques. Compared with aneurysms of other sizes, tiny aneurysms often present with thin aneurysmal walls (4, 5), and neurosurgical clipping is challenging. When the diameter is <3 mm, which equals the width of the aneurysmal clip blade, the clip will not effectively close the aneurysmal neck and may cause avulsion of the aneurysmal neck or parent artery (6).

Similarly, interventional embolization aneurysmal therapy also involves difficulties. During embolization, it is difficult to insert the microcatheter into the narrow aneurysm cavity, and the coil cannot be successfully bent and rotated into the aneurysm cavity. More serious is the possibility that the microcatheter or coil may pierce the aneurysm wall leading to subarachnoid hemorrhage (SAH) (2). Therefore, the very question of whether tiny aneurysms should be treated is controversial. Low-profile visualized intraluminal support (LVIS) devices are self-expanding nickel titanium (nitinol), single-wire braid, closed-cell microstents. Compared with traditional intracranial stents, such as the Enterprise, Neuroform, and Solitaire, LVIS devices have a smaller cell structure (1.0 × 0.3 mm) and higher metal coverage (up to 23%), which can effectively prevent small coils from protruding into the parent artery. LVIS devices also function in remodeling the aneurysmal neck and in flow diversion (7). When placing the LVIS device, using a compressed stent technique at the aneurysm neck can effectively increase the metal coverage and achieve dense embolization of the aneurysm cavity and reduce postoperative aneurysm recanalization (**Figure 1**). We studied patients in a single center to analyze the safety and efficacy of LVIS devices for treating tiny aneurysms using a compressed stent technique.

METHODS

Patient Selection

We retrospectively analyzed patients who were diagnosed with a tiny aneurysm by digital subtraction angiography (DSA) and who were treated with an LVIS device combined using a compressed stent technique in our hospital from July 2016 to December 2018. All aneurysms measured no more than 3 mm in size and included ruptured and unruptured aneurysms. The stent release process and medical records were reviewed to judge whether the compressed stent technique was used. Patients who did not undergo postoperative imaging follow-up were excluded. This study was approved by the Institutional Review Board of Beijing Tiantan Hospital and all patients agreed to participate and signed informed consent forms.

Data Collection and Follow-Up

Reviewing patients' medical records, we collected demographic information, such as sex, age, chief complaint, lifestyle habits, and underlying disease. We examined the imaging data to obtain the anatomical characteristics of the tiny aneurysms, such as size, shape, and location. Follow-up imaging and telephone follow-ups were performed for each patient to analyze the aneurysm embolization outcomes and patients' clinical outcomes, respectively. Postoperative follow-up imaging constituted mainly DSA and computed tomographic angiography (CTA). Embolization classification of each aneurysm was done in accordance with the O'Kelly–Marotta grading scale (D: complete occlusion; C: trace filling; B: entry remnant; A: aneurysm filling), including for immediate postoperative imaging and postoperative follow-up imaging. We followed-up each patient by telephone to determine how their initial symptoms changed and whether there were postoperative complications. Patients' final clinical outcomes were classified in accordance with the modified Rankin scale (mRS), with an mRS score of 0–1 indicating a favorable outcome.

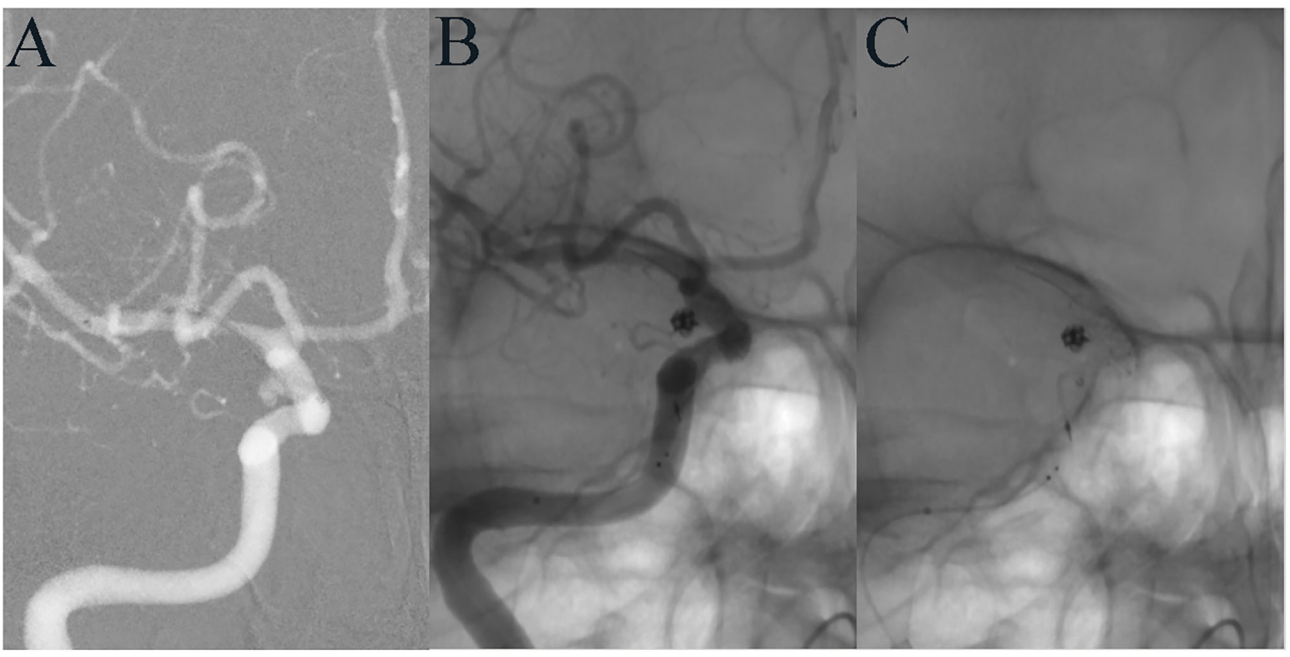

FIGURE 1 | A 35-year-old female developed mild dizziness. DSA showed a tiny aneurysm in the communicating segment of the ICA **(A)**. LVIS-assisted coil embolization was performed using the compressed stent technique, and the aneurysm was completely embolized immediately after operation **(B)**. The LVIS stent at the aneurysmal neck was densely compressed **(C)**.

Endovascular Procedure

All operations were performed under general anesthesia. The modified Seldinger technique was used to perform unilateral femoral artery puncture and to implant the arterial sheath. The parent artery was first performed with conventional three-dimensional rotatory angiography. After selecting the appropriate working position, a Headway-21 microcatheter (MicroVention, CA, USA) was implanted into the parent artery under the guidance of the microguidewire. An Echelon-10 microcatheter (Medtronic, MN, USA) was then placed into the aneurysm cavity. The LVIS device (MicroVention, CA, USA) was then delivered to the distal end of the parent artery. The first coil was partially filled to form the first ring, and the stent was then completely released. With the distal end of the stent fully adherent to the wall, we fixed the stent microcatheter to maintain tension while compressing the stent, and after maximum stent shortening with compression, the stent was slowly released. For aneurysms at bifurcations or aneurysms with important branches near the neck, the stent was released in a "lantern-like" shape after compression, meaning that the diameter of the stent was wider at the aneurysm neck. C-arm flat-detector CT was performed to observe stent apposition. Then, with the jailing technique, the first coil was filled completely, and several coils were filled in turn until the aneurysm was completely embolized and the operation was completed. All interventional procedures were performed by neurointerventionists with more than 10 years of embolization experience in our hospital.

Drug Administration

Patients with unruptured aneurysms took oral dual antiplatelet drugs for at least 5 days preoperatively, namely aspirin 100 mg per day and clopidogrel 75 mg per day. A bolus of 3,000 IU of heparin was administered intravenously after femoral arterial sheath placement. For ruptured aneurysms, if the patient was awake, 300 mg clopidogrel and 300 mg aspirin were administered orally before the procedure, without the single bolus of intravenous heparin. If the patient was unconscious and unable to take antiplatelet drugs orally, a single dose of 6 ml tirofiban (50 μg/ mL) was injected intravenously after stent release, and tirofiban was administered continuously intravenously at 6 ml/h throughout the operation. All patients received local heparinization throughout the operation as a continuous heparin saline infusion via the guiding catheter at ∼1,000 IU per hour. After discharge, patients continued to take aspirin 100 mg/day for 1 year, and clopidogrel 75 mg/day for 3 months.

RESULTS

Patients' and Aneurysm Characteristics

Forty-two tiny aneurysms in 42 patients were included in this study. The mean patient age was 52.1 ± 10.9 years (range, 28–68 years), and 15 patients were male. Eight patients presented with SAH at admission, and all were Hunt–Hess grade <II. All patients with unruptured aneurysms had mRS scores <2 at admission. Most of the aneurysms were located in the anterior circulation, with the internal carotid artery accounting for 83% (35/42). Only one aneurysm was a fusiform aneurysm (**Figure 2**); all others were saccular aneurysms. All aneurysms had a maximum diameter of no more than 3 mm and an average diameter of 2.4 ± 0.3 mm (range, 1.8–3.0 mm). Detailed patient and aneurysm characteristics are shown in **Table 1**.

Operation Outcomes and Follow-Up

Forty-two LVIS stents were used for 42 tiny aneurysms, and all stents were implanted successfully. No intraoperative aneurysm rupture occurred. Thirty-two (76.2%) tiny aneurysms were completely embolized immediately after interventional embolization, and 7 (16.7%) tiny aneurysms showed trace filling. All patients underwent imaging follow-up at least once. After an average of 8.5 months of imaging follow-up, 38 (90.5%) aneurysms showed complete embolization, three (7.1%) aneurysms showed trace filling, and only one (2.4%) aneurysm showed an entry remnant. No aneurysm recanalization occurred. Postoperative clinical follow-up was conducted for an average of 24.4 months. At the final follow-up, 24 patients showed no symptoms (mRS = 0), and 16 patients (mRS = 1) showed mild symptoms, such as occasional headache and dizziness. The rate of favorable clinical outcomes reached 95.2% (40/42). The treatment outcome details are shown in **Table 2**.

One patient was originally scheduled for simple coil embolization. After placing the first coil, the coil prolapsed into the parent artery by ∼0.5 cm; therefore, we chose to implant an LVIS device to compress the coil and stop it from falling into the parent artery completely. This patient was also the only patient with intraoperative complications. After general anesthesia, the callosomarginal artery was found to be occluded due to acute thrombosis during the implantation of the coil microcatheter. The patient underwent immediate endovascular thrombolysis treatment, and the callosomarginal artery was recanalized. After the operation, the patient presented with grade 2 muscle strength on one side of the body and speech difficulties. Head CT scan showed a large frontal parietal infarction, and the patient's mRS score was 5 when discharged (**Figure 3**). Another patient developed postoperative significant unilateral vision loss. The image of the patient 14 months after the operation showed initial stenosis of the ophthalmic artery, but the patient had not recently undergone an imaging evaluation at the time of vision loss. We considered that the LVIS stent possibly limited the ophthalmic artery blood flow (**Figure 4**).

DISCUSSION

Treatment of Tiny Aneurysms

There is currently no fixed definition of tiny aneurysm, and different terms, such as very small aneurysm and microaneurysm, appear in different studies (1, 8). There is also no consensus regarding the treatment method, and common treatment methods include craniotomy for clipping, and interventional embolization. Chalouhi et al. reported 60 tiny aneurysm patients who underwent craniotomy for clipping, with operation complications of up to 23.3%, and 91 microaneurysms that underwent interventional embolization with operation complications of 9.8% (9). In contrast, Molyneux et al. stated that tiny aneurysms were more suitable for craniotomy clipping

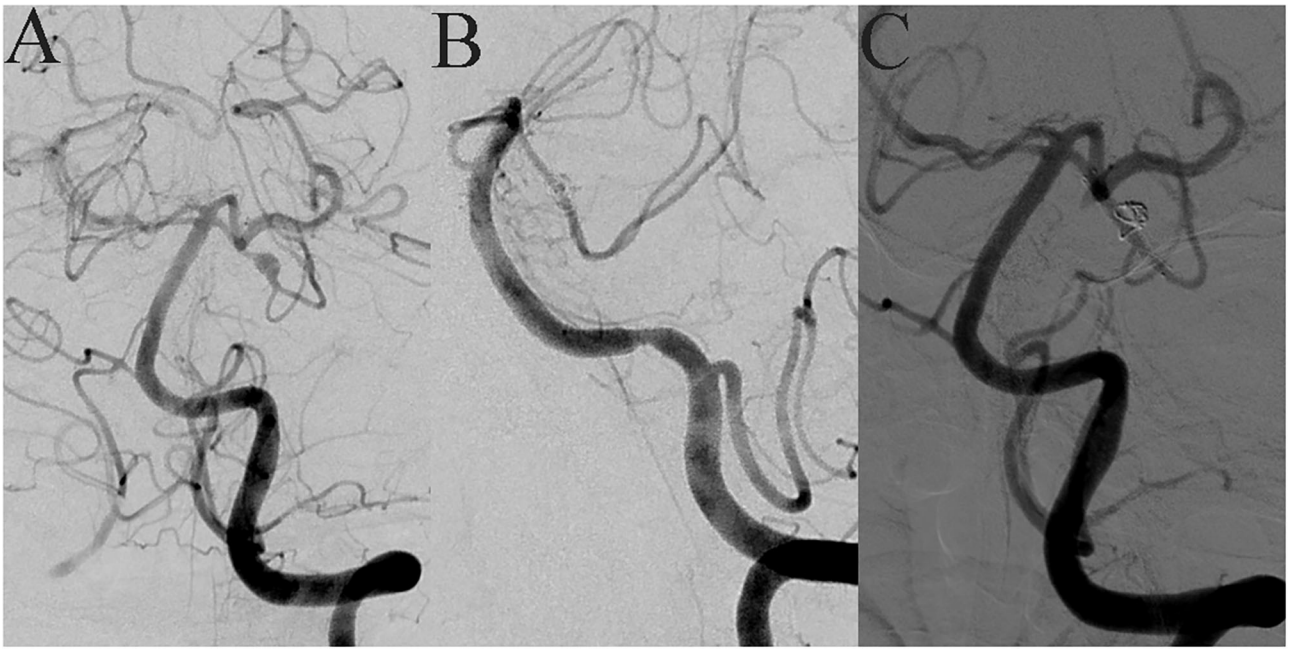

FIGURE 2 | A 42-year-old female suddenly developed severe headache with nausea and vomiting when she was 7 months' pregnant. MRA showed an intracranial tiny aneurysm, and she underwent conservative treatment. Seventeen months later, she came to our hospital for interventional embolization. DSA showed a superior cerebellar artery tiny dissecting aneurysm **(A)**. LVIS-assisted coil embolization was performed, and almost complete embolization of the aneurysm was achieved immediately after operation **(B)**. The LVIS device retained a good shape after compression release **(C)**.

considering that interventional embolization was associated with difficulties in catheterizing the aneurysm, stabilizing the microcatheter, and safely deploying coils (10). The narrow aneurysm cavity and thin aneurysm wall are associated with a high intraprocedural rupture rate (11). Some studies have reported that the intraoperative rupture rate of small aneurysms was twice or even five times that of larger aneurysms (12, 13). A meta-analysis of very small ($\leq$3 mm) intracranial aneurysms showed a higher intraprocedural rupture rate in both unruptured (5.0%) and ruptured aneurysms (10.7%), while the mortality rate due to procedural rupture was 2.4% (2). According to the International Subarachnoid Hemorrhage Test (ISHT), the 5-year rupture rate of aneurysms with a diameter $<$7 mm is $<$0.7%, while that of aneurysms located in the anterior circulation is almost 0 (14). Therefore, whether unruptured aneurysms require active intervention has aroused great controversy (15). However, according to a recent study, the rate of rupture during interventional therapy for tiny aneurysms was significantly lower, at 1% (16). With improved embolization materials, such as smaller and softer coils, steerable microcatheters, and increased embolization skill, there were no intraoperative aneurysm ruptures in any of our 42 patients. The following operation techniques may help reduce intraoperative aneurysm rupture: First, conduct reasonable modeling of the microcatheter to make it easy to enter the aneurysm cavity, and push the coil microcatheter across the aneurysmal neck and back down, to allow it to fall naturally into the arterial cavity, which can effectively prevent the microcatheter tip from acting directly on the aneurysm wall. Second, the LVIS stent combined with the compressed stent technique increases the metal coverage of the aneurysm neck and fixes the coil microcatheter for coil packing. Third, it is best to choose an ultra-soft coil and one smaller than the diameter of the aneurysm. In a word, interventional embolization for tiny aneurysms is currently considered safe and feasible, and treatment is considered necessary for ruptured aneurysms. However, for unruptured tiny aneurysms, treatment is usually necessary only under certain conditions, such as aneurysms with an irregular shape, multiple aneurysms, aneurysm growth during follow-up, a family history of SAH, or patients with severe anxiety. All treated aneurysms in our study met these operation indications.

LVIS Stents and the Compressed Stent Technique

Compared with simple coil embolization, stent-assisted coil embolization has obvious advantages. Stent-assisted coil embolization can effectively reduce coils escaping from the aneurysm cavity, increase coil packing density, and reduce aneurysm recurrence (17, 18). However, the long-term use of dual antiplatelet drugs after stenting increases the risk of aneurysm bleeding. The LVIS device is a self-expanding nickel titanium (nitinol), single-wire braid, closed-cell microstent. These devices are an intermediate choice between conventional stents and flow diverters, and the devices have the advantages of closed-cell stents, such as strong radial support, as well as the advantages of open-cell stents such as good stent–vessel wall

TABLE 1 | Patients' baseline characteristics.

Characteristic	Number
Number of patients	42
Number of aneurysms treated	42
SAH, *n* (%)	8 (19.0)
Male sex, *n* (%)	15 (35.7)
Age (years), mean ± SD	52.1 ± 10.9
Smoking, *n* (%)	6 (14.3)
Alcohol use, *n* (%)	4 (9.5)
Hypertension, *n* (%)	9 (21.4)
Hyperlipidemia, *n* (%)	5 (11.9)
Pretreatment mRS, *n* (%)	
0	14 (33.3)
1	26 (61.9)
2	2 (4.8)
Aneurysm location, *n* (%)	
ICA	35 (83.2)
AcoA	2 (4.8)
PcoA	2 (4.8)
PICA	2 (4.8)
SCA	1 (2.4)
Morphology	
Saccular and wide neck	37 (88.1)
Saccular and narrow neck	4 (9.5)
Fusiform	1 (2.4)
Size, mm, mean ± SD	2.4 ± 0.3

Data are presented as n, n (%), or mean ± standard deviation. SAH, subarachnoid hemorrhage; ICA, internal carotid artery; AcoA, anterior communicating artery; PcoA, posterior communicating artery; PICA, posterior inferior cerebellar artery; SCA, superior cerebellar artery.

TABLE 2 | Treatment outcomes and follow-up.

Results	Number
Operative time (minutes)	
Mean ± SD	91.0 ± 31.2
Postoperation immediate aneurysm occlusion, OKM, *n* (%)	
D	32 (76.2)
C	7 (16.7)
B	3 (7.1)
D + C	39 (92.9)
Aneurysm occlusion at last follow-up, OKM, *n* (%)	
D	38 (90.5)
C	3 (7.1)
B	1 (2.4)
D + C	41 (97.6)
Follow-up time (months)	8.5 ± 3.5
mRS at last follow-up, *n* (%)	
0	24 (57.1)
1	16 (38.1)
2	1 (2.4)
5	1 (2.4)
Follow-up time (months)	24.4 ± 9.2
Operation complications, *n* (%)	
Coil prolapse	1 (2.4)*
Thromboembolic events	1 (2.4)*
Neurologic deficits	1 (2.4)
Total	2 (4.8)

**Two complications occurred in one patient. Data are presented as n, n (%), or mean ± standard deviation; OKM, O'Kelly–Marotta grading scale; mRS, modified Rankin scale.*

apposition. LVIS devises also have good blood flow diversion. The LVIS stent has two radiopaque strands (the LVIS Jr has three) along its entire length as well as four proximal and distal radiopaque markers, allowing the neurointerventionist to visualize full stent release and which also provide the possibility of adopting the compressed stent technique (19, 20). Other conventional intracranial stents have markers only at the proximal and distal tines. In addition, the metal LVIS stent coverage rate is up to 23%, which is higher than the traditional Neuroform and Enterprise stents at 11 and 9%, respectively. Liu et al. reported 54 patients with small aneurysms treated with conventional stent-assisted coil embolization, namely with the Enterprise, Neuroform, and Solitaire stents, and reported that 80% of aneurysms were eventually completely embolized (21). This rate was lower than the rate of 90.5% in our study. Lee et al. reported 312 small-sized aneurysms (<10 mm) treated with different stents, in which the aneurysm recanalization rate after LVIS stenting was 6.5%; a much lower rate than with the Enterprise (18.2%) and Neuroform stents (29.6%) (22).

Using the compression technique to release the stent requires skillful operation experience. Post-stent release or partial stent release is often performed because stent compression release limits the movement of the coil microcatheter in the aneurysmal neck. First, the distal end of the stent is attached to the vessel wall for release, then stent compression is initiated when the distance from the microcatheter tip to the aneurysm neck center is 1.2–1.5 times the diameter of the parent vessel. The microcatheter is pushed and kept in maximum tension but not bent, then the microcatheter is fixed, and the stent is slowly released, which concentrates stent distribution in the aneurysm neck. Finally, the remainder of the stent is released. This approach results in better stent compression at the aneurysmal neck. If there are branched vessels near the aneurysmal neck, adding a "lantern" release technique can avoid blocking blood flow in the branches. In this study, we treated 42 tiny aneurysms with the compressed stent technique, and achieved an immediate complete embolization rate of 76.2%. In previous studies using conventional stent release techniques, Wu et al. reported an immediate postoperative embolization rate of 46.4% and Gao et al. reported a rate of 36.4% (23, 24). After an average of 8.5 months of postoperative imaging follow-up, 90.5% of the aneurysms finally achieved complete embolization, and no aneurysms were recanalized. Meanwhile, Gao et al. reported complete and near-complete embolization rates of 81.8%, and Wu et al. reported an embolization rate of 78.1%. These results show that the compressed stent technique can effectively improve the total embolization rate of aneurysms and reduce

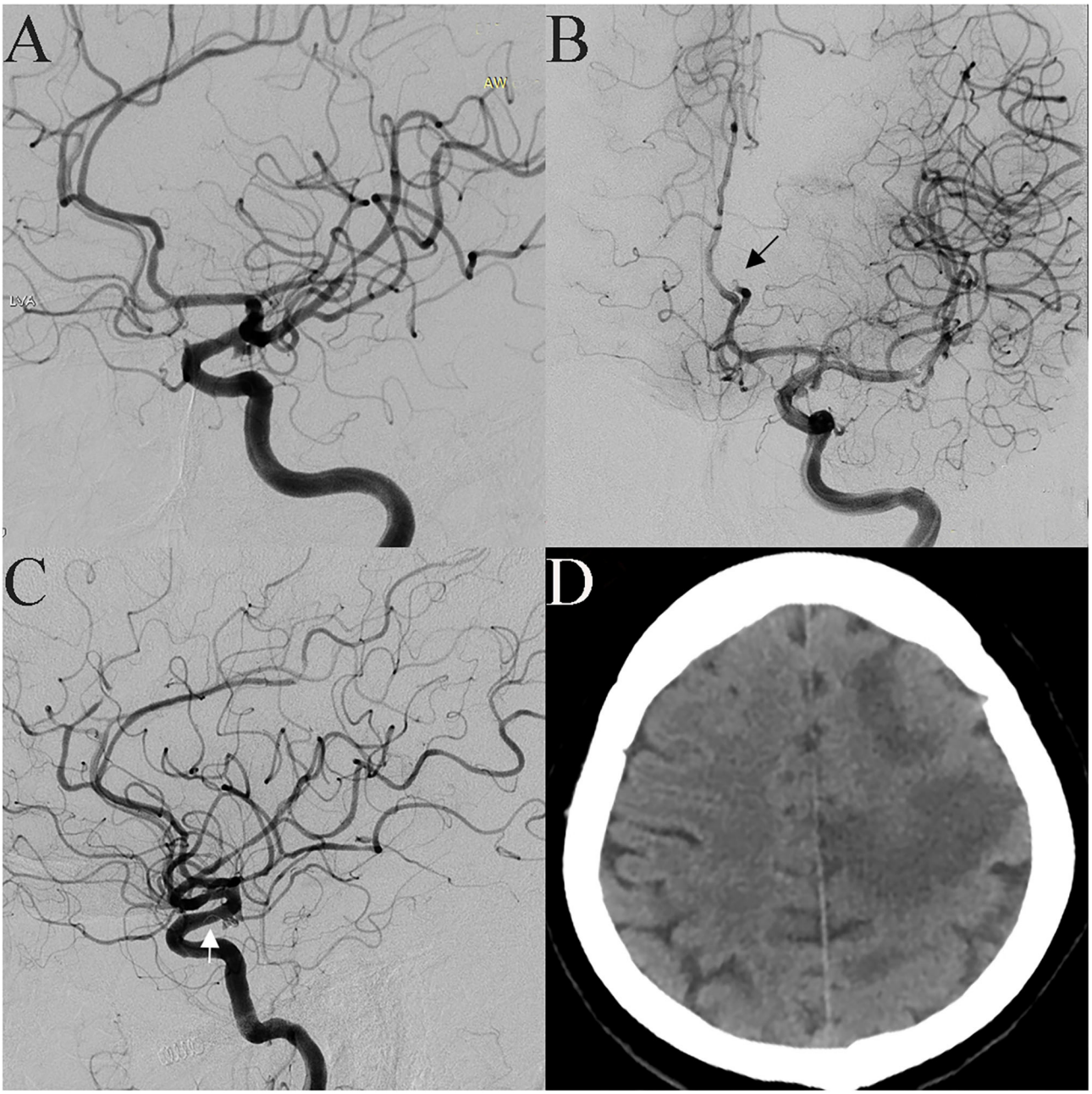

FIGURE 3 | A 53-year-old female was incidentally found have a tiny aneurysm in the communicating segment of the ICA **(A)**. Pericallosal artery occlusion was found when the microcatheter was advanced to the aneurysm cavity, and a thrombus was seen (**B**, black arrow). After intravascular thrombolysis, patency in the artery was partly restored. The coil prolapsed into the parent artery when the first coil was placed; therefore, an LVIS stent was implanted (**C**, white arrow). Postoperative CT scan showing a large infarction in the frontal parietal lobe **(D)**.

the recanalization rate. With the compressed stent technique, the LVIS metal mesh is denser and effectively prevents the coil from escaping from the stent pores, thus reducing the rate of infarction of the parent artery or terminal vessel (19). Furthermore, the compression technique increases metal coverage by the LVIS at the aneurysm neck, which not only changes the hemodynamic characteristics of the aneurysm, but also provides a good platform for intimal growth and vascular wall repair, thereby reducing aneurysm recurrence. Finally, the higher degree of metal surface area coverage at the aneurysm neck provides a more robust flow diversion effect compared with the other available stents (25). These factors likely account for the very high levels of complete and adequate aneurysm occlusion observed in the present study.

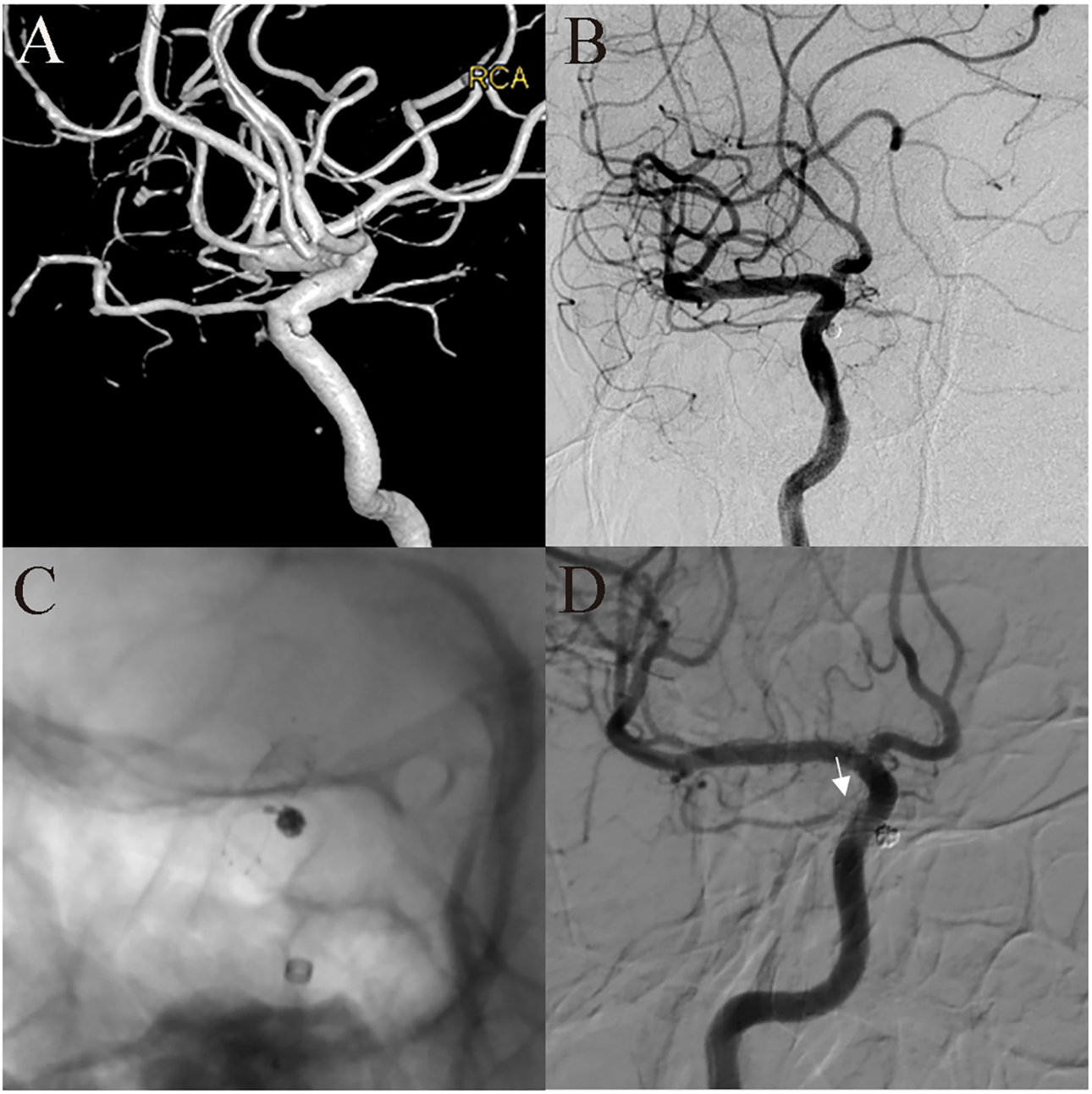

FIGURE 4 | A 52-year-old female patient with intermittent dizziness for 1 year was found to have a tiny aneurysm. DSA showed a small aneurysm in the ophthalmic segment of the ICA **(A)**, and LVIS-assisted coil embolization was performed using the compressed stent technique. Immediately after embolization, the aneurysm was completely embolized **(B)**, and the ophthalmic artery was patent. The LVIS stent was compressed at the aneurysm neck **(C)**. The 14-month follow-up images showed no recurrence of the aneurysm, but the initial segment of the ophthalmic artery was narrowed (**D**, white arrow).

Operation Complications

Thrombotic events are the most common operation complications with embolization therapy of intracranial aneurysms with LVIS devices. A meta-analysis of nine studies reported an overall operation-related complication rate of 6.5% and a thrombotic event rate of 4.9% (19). In our study, one patient developed an acute intraoperative thrombus, and despite immediate intravascular thrombolysis and recanalizing the vessel, the patient unfortunately developed severe postoperative disability. Interventional embolization of the intracranial aneurysm was performed intravascularly; however, despite careful preoperative preparation and gentle intraoperative procedures, acute endovascular thrombosis still occurred. The main causes of acute thrombosis may be related to factors such as long intraoperative operation time, intraoperative endothelial damage, insufficient anticoagulation, activation of

the coagulation system, and thrombogenicity of interventional embolization materials (26). Although dense mesh stents have many advantages over traditional stents, dense stents also increase the possibility of occlusion of branch arteries near aneurysms (27), especially when combined with the compression technique. Additionally, the LVIS device's high-profile mesh may block blood flow in the branch. After 24 months of imaging follow-up, an ophthalmic artery aneurysm patient in this study presented with ipsilateral significant vision loss. However, the patient had not undergone recent imaging. Combined with images taken immediately after embolization and at 14 months, we suspect that there may have been severe narrowing of the ophthalmic artery. Therefore, when there is a branch vessel near an aneurysm, "lantern-like" release should be adopted. If there is technical difficulty, the compression technique should be abandoned, and tension-free release should be adopted.

LIMITATIONS

This study was a retrospective, single-center study. Additionally, tiny aneurysms were less common in all aneurysms and not all patients received follow-up evaluations; therefore, we were not able to obtain a large sample size. The mean imaging follow-up time for all patients was 8.5 months, which was too short to evaluate the final complete embolization rate. Most of the aneurysms in this study were located in the internal carotid artery, which differed from the distribution of most aneurysms, and this may have resulted from neurointerventionist selection. In addition, subjective manual measurement affected the accuracy of the tiny aneurysm size.

CONCLUSIONS

LVIS-assisted coiling for intracranial tiny aneurysms combined with compressed stent release is safe and effective. Combined stent compression technology is beneficial to maximize the complete embolization of aneurysms and reduce aneurysm recanalization. This study expands the clinical applicability of LVIS stents.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Institutional Review Board of Beijing Tiantan Hospital. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

YZho collected the clinical data and wrote the manuscript. QP and XW helped collect the clinical data. YZha and JL wrote sections of the manuscript. SM and XY helped revise the manuscript. SM designed the research and handled funding and supervision. All authors read and approved the final manuscript.

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frontiers in Neurology

CLINICAL TRIAL
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Flow Diverter-Assisted Coil Embolization of Blood Blister-Like Aneurysm Using Semi-deploying Technique

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Despite many therapeutic methods were utilized to treat blood blister-like aneurysms (BBAs), the optimal treatment approach has not yet been defined. This study presents the single center experience with BBAs treated with flow diverter-assisted coiling using semi-deploying technique, and discusses the efficacy and safety of the method. The patients with subarachnoid hemorrhages (SAH) due to BBAs and treated with Pipeline Flex Embolization Device (PED) between November 2015 and February 2019 in our hospital were retrospectively reviewed. Patient demographic data, timing of treatment, angiographic details, treatment techniques, clinical outcomes and follow-up results were recorded. Ten cases (6 women and 4 men) were enrolled. The mean age of patients was 50.7 years (range 40–61 years). The aneurysm size ranged from 2 × 1.7 mm to 4.5 × 3.8 mm. Seven patients were treated with PED assisted coil embolization using semi-deploying technique, and all of the aneurysms were totally obliterated at the follow up. One patient treated with PED assisted coil embolization suffered from parenchymal hemorrhage 3 days after the treatment, and another one patient also treated with PED and coil died of severe vasospasm 10 days after the treatment. There was no reruptured cases during the follow-up. Here we showed that PED assisted coil embolization using semi-deploying technique could be a technically safe and effective treatment for BBAs.

Keywords: blood blister aneurysm, flow diversion, semi-deploying technique, coil embolization, efficacy and safety

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INTRODUCTION

Blood blister-like aneurysms (BBAs) are a rare subset of intracranial aneurysms which arise from non-branching segments of the dorsal or anterior wall of the supraclinoidal internal carotid artery (ICA) (1). BBAs account for 0.3–1.7% among all intracranial aneurysms and up to 6.6% of ruptured cerebral aneurysms (2). Histologically, BBAs behave as pseudoaneurysms and are made up of a broad base with adventitia and/or thrombus lacking both of the intima and media (3). The high rates of mortality, recurrence and poor prognosis in patients with BBAs are a testament to the unmet medical need presented by these aneurysms.

A lot of techniques have been developed to treat BBAs, such as surgical clipping, clipping after wrapping, suturing, surgical trapping, stenting with or without the assist of coils. Unfortunately, there is no optimal treatment for BBAs based on the long-term follow-up (4). Due to their wide neck, small size, and a fragile fibrous wall, BBAs are a therapeutic challenge for both surgical and endovascular treatment (5).

Endoluminal reconstruction with flow diverter appears to be a promising option for the treatment of BBAs, since it offers better mid- to long-term outcome (6). With the aim to achieve rapid aneurysm occlusion, flow diverter-assisted coiling using "semi-deploying" technique was employed to embolize BBAs at our center. This technique was found to be safe and effective, and demonstrated encouraging results in the treatment of ruptured BBAs.

METHODS

Patient Population

Data from all patients suffering from subarachnoid hemorrhage (SAH) caused by BBAs and subsequently treated with Pipeline Flex Embolization Device (PED) between November 2015 and February 2019 in our hospital were retrospectively reviewed under the approval of the local institutional review boards.

Digital subtraction angiography (DSA) was used to diagnose patients with BBAs. Based on the angiographic studies, BBAs were defined as small (<5 mm), shallow, broad-based aneurysms originating from unbranched sites on the dorsal wall of the supraclinoid ICA. We collected patient clinical data, demographic data including aneurysm characteristics, Hunt and Hess Grade, procedural details and outcomes. All enrolled patients were treated with PED.

Embolization Using Semi-deploying Technique Procedure

All patients undergoing PED therapy were administrated 300 mg of aspirin and 300 mg of clopidogrel 2 h before endovascular treatment. In hybrid operating room, all procedures were performed under general endotracheal anesthesia. Heparin was routinely administered during the procedure.

For the cases treated with PED assisted with coils using semi-deploying technique, the right and left femoral arteries were canalized by a 5-French (F) and an 8-F femoral artery short sheaths, respectively. For the cases treated with PED only, procedures were performed through an 8-F femoral artery access. Through the left 8-F femoral artery short sheath, an 8-F Mach 1 guiding catheter (Boston scientific, California, USA) was placed at the proximal ICA. 5-F Navein guiding catheter (Medtronic, California, USA) was positioned at the petrosal segment of parent ICA *via* the 8-F Mach 1 guiding catheter. Digital subtraction angiography and 3D rotational angiograms were performed to reassure the size, formation and location of the aneurysm and the diameter of the parent artery, helping select and deploy PED. A Marksman microcatheter (Medtronic, California, USA) was placed to the M2 segment of the middle cerebral artery through the Navien guiding catheter. The coiling microcatheter (Echelon 10, Medtronic, Minnesota, USA) was brought up and positioned into the aneurysm over 5F guiding catheter placed at the petrosal segment of parent ICA through the right 5F femoral artery short sheath. *Via* the Echelon 10 microcatheter 1 or 2 loops of coil were advanced into the aneurysm first. Then the PED was gently semi-deployed under fluoroscopic guidance, which means the PED was partially expanded and covered part of the aneurysm neck. The Echelon 10 microcatheter was partly jailed in the aneurysm through the wedge-shaped space between the PED and parent artery. The coil was carefully embolized within the BBA while the PED was further deployed if the coil bulged into the ICA. Following compact and complete embolization with the aneurysm, the Echelon 10 microcatheter was slowly removed and the PED was thoroughly deployed. The expansion of the PED was confirmed by fluoroscopy and Dyna CT computed tomography angiography.

Dual antiplatelet therapy (aspirin 100 mg/day and clopidogrel 75 mg/day) was started after the procedure. Four days after the procedure, thromboela-stogram (TEG) was customarily performed, by which arachidonic acid inhibition rate (AA%) and ADP inhibition rate (ADP%) were recorded. An AA% <50% and an ADP% <30% were defined as resistance to aspirin and clopidogrel, respectively. If the AA% was <50%, aspirin dose was increased up to 200 mg/d. If the ADP% was <30%, clopidogrel was dosed up to 150 mg/d or switched to ticagrelor (90 mg twice daily). If the inhibition rate was more than 90%, the risk for hemorrhage is high. The dose was reduced for the safety of patients. Three days after modifications to antiplatelet regimen, if any, TEG was reassessed. Dual antiplatelet therapy was continued for ≥6 months after the procedure.

Data Sources and Follow-Up

The information about patient age, gender, aneurysms, complications, procedure details and outcomes was collected from medical charts in our hospital. Follow-up was performed at 3, 6, and 12 months after the embolization. The modified Rankin Scale (mRS) scores were assessed on the follow-up. After the procedure and at the 6–12 months follow-up, aneurysm occlusion was elevated according to Raymond Roy Scale with DSA.

RESULTS

In the study period, 10 patients (4 males) that experienced SAH from BBAs and who were subsequently treated with PED were identified. Unenhanced cranial CT and DSA was used to diagnose patients with SAH and BBAs. The age of patients that suffered from SAH ranged from 40 to 61 years (mean 50.7 years, SD 7.1). The initial Hunt and Hess Grade was 1 in four patients, 2 in four patients, 3 in one patient and 4 in one patient (mean 1.9, SD 0.99). The mean of the number of days from occurrence of SAH to the placement of PED was 6.8 days (range from 3 to 16 days, SD 3.9). Aneurysm size ranged from 2 × 1.7 mm to 4.5 × 3.8 mm (**Table 1**).

Abbreviations: BBAs, blood blister-like aneurysms; DSA, Digital subtraction angiography; F, French; ICA, internal carotid artery; mRS, modified Rankin Scale; PED, Pipeline Flex Embolization Device; SAH, subarachnoid hemorrhages.

In all cases the procedure was technically successful. Most patients (7/10) were treated with PED assisted coil embolization using semi-deploying technique, and 3 received PED only. All the patients were treated with a single PED. Overall, the immediate angiographic results showed that 6 of 10 BBAs were totally obliterated and all these patients were treated with PED-assisted coil embolization using semi-deploying technique. The average of Raymond Roy Scale was 1.7 ± 0.95. At discharge the mean mRS Score was 1.8 ± 1.7 (**Table 2**). Patient 3 suffered from parenchymal hemorrhage 3 days after the procedure. Fortunately, the patient had mRS Score of 1 at last follow-up. Patient 5 had left lower limb deep venous thrombosis 3 days after embolization. Patient 8 developed severe vasospasm on the first day after the treatment, and died 10 days later in spite of symptomatic treatment.

Only Patient 1 who was treat with PED alone had not undergone DSA for follow-up imaging during the follow-up 6–12 months after the procedure. Among the patients with follow-up DSA, the BBAs of all patients except Patient 9 were totally obliterated. The mean Raymond Roy Scale was 1.1 ± 0.35. No permanent deficit occurred. Patient 3 and 4 complained of paroxysmal and mild headache, respectively. The mean mRS Score was 0.8 ± 1.9 including the dead case (**Table 2**).

TABLE 1 | Baseline clinical and radiographic data of patients with BBAs.

Patient	Location	Size (mm, Neck × Dome)	Hunt-Hess grade	Days to treatment
1	Left ICA	3.3 × 2.4	1	16
2	Right ICA	4.5 × 3.8	1	7
3	Left ICA	2.0 × 1.7	2	8
4	Right ICA	4.2 × 3.7	2	4
5	Left ICA	2.3 × 2.1	1	9
6	Left ICA	4.3 × 3.2	2	4
7	Right ICA	1.8 × 2.9	3	3
8	Right ICA	2.2 × 1.9	4	5
9	Right ICA	4.3 × 2.1	1	4
10	Right ICA	4.0 × 3.8	2	8

BBAs, blood blister-like aneurysms; ICA, internal carotid artery.

Typical Cases

Patient 3: The patient presented with acute and severe headache accompanied by nausea (Hunt and Hess Grade 2). A CT scan at the local hospital demonstrated SAH. Five days later, the patient was transferred to our hospital where DSA was performed, exhibiting an aneurysm in the superior segment of the clinoid process of the left ICA (**Figure 1A**). The size of the aneurysm was 2.0 × 1.7 mm (neck × dome). Eight days post-SAH, the patient underwent PED-assisted coil embolization using semi-deploying technique in our hospital. One loop of coil (1.5 × 40 mm) was placed into the BBA after the Marksman microcatheter was positioned at the M2 segment of the left middle cerebral artery. Then the PED (3.25 × 20 mm) was gently semi-deployed, and two more coils (1.5 × 20 mm) were advanced. Subsequently, the PED was fully deployed. The aneurysm was completely occluded post-treatment (**Figure 1B**). A DSA examination performed 6 months after the procedure showed patent ICA without stenosis and no signs of BBA recurrence (**Figure 1C**).

Patient 7: This patient presented with sudden onset of severe headache and vomiting (Hunt and Hess Grade 3), and a head CT scan showed SAH in suprasellar cistern and hemorrhage in lateral ventricles (**Figure 2A**). Digital subtraction angiography revealed a BBA (1.8 × 2.9 mm) of the supraclinoid right ICA (**Figure 2B**) 3 days after the occurrence of SAH. Then one-stage PED-assisted coil embolization was performed. First, the PED (3.50 × 20 mm) was gently semi-deployed, and three coils (1.5 × 40 mm, 1.0 × 40 mm, 1.5 × 40 mm) were delivered into the BBA. After complete embolization was achieved, the PED was fully deployed (**Figure 2C**). The aneurysm was completely occluded post-treatment (**Figures 2D,E**). Seven months follow-up DSA showed complete obliteration (Raymond Roy Scale 1) (**Figure 2F**).

TABLE 2 | Results of the treatment of BBAs.

Patient	PED size (mm)	Adjunctive coils	Raymond Roy scale post-treatment	Periprocedural complications	mRS score at discharge	Raymond Roy scale (6–12 months)	mRS score (6–12 months)
1	3.75 × 20	No	3	NO	0	Not available	0
2	4.0 × 18	No	3	NO	1	1	0
3	3.25 × 20	Yes	1	Parenchymal hemorrhage	3	1	1
4	4.0 × 20	Yes	1	NO	1	1	1
5	4.5 × 20	Yes	1	Lower limb deep venous thrombosis	2	1	0
6	3.75 × 18	Yes	1	NO	1	1	0
7	3.5 × 20	Yes	2	NO	2	1	0
8	3.5 × 18	Yes	1	Death	6	Death	6
9	4.0 × 20	No	3	NO	1	2	0
10	4.0 × 20	Yes	1	NO	1	1	0

BBAs, blood blister-like aneurysms; mRS, modified Rankin Scale; PED, Pipeline Flex Embolization Device.

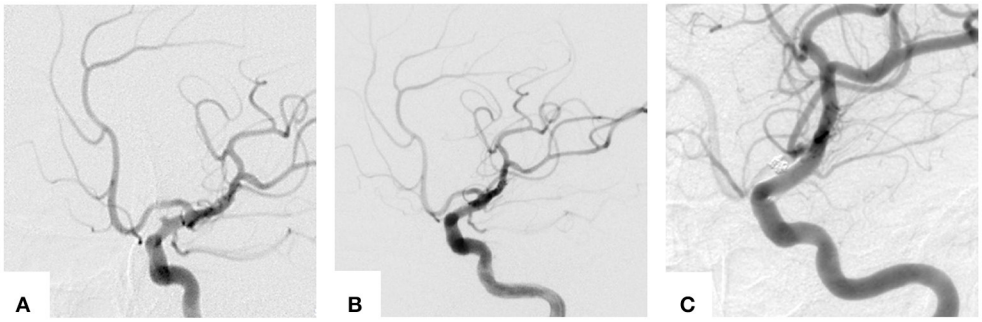

FIGURE 1 | Images of the typical cases. **(A)** Cerebral angiograms obtained immediately pre-, **(B)** post-treatment and **(C)** 10-month follow-up DSA.

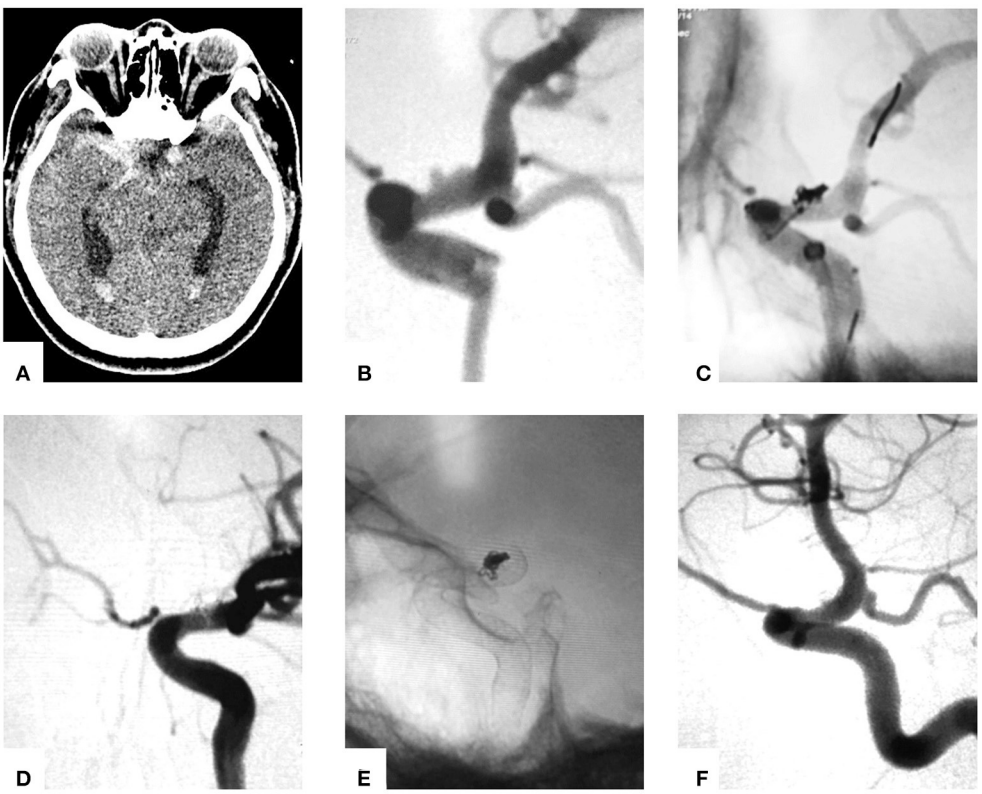

FIGURE 2 | Images of the typical cases. **(A)** CT scan showed symmetric suprasellar cistern SAH and hemorrhage in lateral ventricles. **(B)** Cerebral angiograms obtained immediately pre-embolizaton. **(C)** PED semi-deployed coiling. **(D)** and **(E)** Post-treatment DSA. **(F)** DSA follow-up 6 months after treatment.

DISCUSSION

Despite multiple therapeutic approaches (such as endovascular, microsurgical and hybrid therapy) are available to treat BBAs, satisfactory treatment of BBAs remains a challenge. Due to the rapid evolution of endovascular therapy within the last decade, embolization of BBAs may gain increasing acceptance in the future. Shah et al. systematically reviewed 36 papers involving 256 patients with BBAs treated with endovascular or surgical methods and concluded that endovascular therapy could offer lower morbidity and mortality (7).

Several endovascular approaches have been developed for treating BBAs, including direct coil embolization, multiple overlapping stents and flow diversion stents. Due to the thin and fragile characters of BBAs, most studies employing direct coil embolization of BBAs were performed with the assistance of a stent or balloon, and coiling alone was rarely reported as a sole treatment (8). Since direct coil embolization does not need antiplatelet medication it may be an appropriate choice for treatment of BBAs after the acute phase (9). The occlusion rates of ruptured BBAs treated with stent-assisted coiling were not encouraging: 33% initially post-procedure and about 70% at mid-

to long-term follow-up (6). Fang et al. retrospectively reviewed 213 BBAs treated with stent-assisted coiling and reported that 64.6% of BBAs were completely obliterated and 22.9% recurred (10). Therefore, traditional coil embolization with or without stent is not the best alternative for treating BBAs.

Hao et al. declared endovascular patch embolization as an improvement on stent-assisted coil embolization and concluded that it could be an effective treatment for BBAs to facilitate flow guidance and embolic material stabilization (8). However, the study was limited by its small sample size (11). Multiple overlapping stents may be another workable option for treating ruptured BBAs. Theoretically, overlapping stents can improve flow diversion and reconstruct the fragile neck of the BBAs, reducing the risk of rerupture and recurrence (11). In the retrospective study, Fang et al. reported that placement of ≥ 2 stents resulted in higher complete obliteration rates and lower recurrence rates (10). Song et al. used multiple overlapping stents (≥ 3) with coiling in 10 patients with ruptured BBAs, presenting that 4 of the patients required complementary treatment (12). Gaughen et al. reported that 50% (3/6) of the patients treated with overlapping stents required retreatment for recurrence or residual (13). Some clinicians question whether overlapping stents are optimal for treating BBAs. Besides the unstable rates of aneurysm obliteration, dual antiplatelet administration which is necessary for overlapping stents treatment may increase the risk of post-operative rebleeding.

Flow diversion devices have the potential to be a standard therapy for BBAs, as confirmed by multiple studies (6, 14, 15). Through their dual-center experience, Linfante et al. concluded repairing BBAs with PED may be a safe and durable option as 9 out of 10 patients with ruptured BBAs were adequately treated with a single PED (15). Zhu et al. reviewed 165 patients with BBAs, claiming that PED could be safe and effective for BBAs, and a single PED offered higher rate of good outcomes compared with overlapped PED (16). But Marcus D. Mazur thought a single flow diverter might be incomplete for ruptured BBA because of their rebleeding case after the treatment with a single flow diverter (17).

In this study, we demonstrate flow diverter-assisted coil embolization of BBAs using semi-deploying technique. First, flow diversion with PED redirects blood flow away from the BBA, thereby reducing the risk of rebleeding and recurrence. Secondly, coils within the sac of BBAs could offer mechanical support during and after deployment, reducing the possibility of stent migration or foreshortening. Thirdly, semi-deployment of PED increases the flexibility and sensibility of the coiling catheter allowing improved control during the coiling procedure, thereby achieving a compact embolization in the BBAs.

This study evaluated 10 cases of BBAs, 7 of which were embolized with PED-assisted coil embolization using semi-deploying technique, and the other 3 were embolized with PED alone. Technical success was achieved in all cases with no intraoperative accident. One patient died of severe vasospasm, which may have been due to large amount of blood loss in the subarachnoid cavity. Because of high incidence of vasospasm of ICA and middle cerebral artery, intra-arterial infusion of nimodipine was used routinely, and it is recommended that balloon angioplasty should also be considered. Also due to vasospasm of ICA, the diameter of ICA may be underestimated on DSA imaging. So the diameter of flow diverter should be larger than the measured diameter of ICA. Another patient suffered from parenchymal hemorrhage which may have been caused by sensitivity to dual antiplatelet therapy. During the follow-up, except the dead case, 6 of 7 cases treated with PED assisted coil were obliterated. It has been proven that the process of PEDs healing aneurysms occurs progressively (18). Thereby, it is possible that the remnant would be occluded during the long term follow-up.

CONCLUSION

The treatment of patients with ruptured BBAs by flow diverter-assisted coil embolization using semi-deploying technique resulted in good clinical outcomes. This therapy is emerging as a safe and effective alternative for the treatment of BBAs.

DATA AVAILABILITY STATEMENT

The original contributions generated in the study are included in the article/supplementary materials, further inquiries can be directed to the corresponding author.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Ethics Committee of Qilu Hospital of Shandong University. The patients/participants provided their written informed consent to participate in this study. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

AUTHOR CONTRIBUTIONS

PZ and YW designed the study and wrote the manuscript. WZ, TL, XT, CC, ML, and ZL collected the data and provided the interpretation of the data. GL reviewed the whole manuscript. All authors agree to be accountable for all aspects of the work, including its accuracy and integrity.

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A Hybrid Strategy for Patients With Complex Cerebral Aneurysm: STA–MCA Bypass in Combination With Endovascular Embolization

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Objective: This work aims to present our experience of patients with complex cerebral aneurysm treated with a hybrid approach: superficial temporal artery–middle cerebral artery (STA–MCA) bypass in combination with endovascular exclusion of the aneurysm.

Method: Patients with aneurysms deemed unclippable and uncoilable were included. All patients were treated with a hybrid approach. After STA–MCA bypass, the parent artery was temporarily occluded. If the intraoperative motor evoked potential (MEP) and somatosensory evoked potential (SEP) waveforms remain normal and last for 30 min, the aneurysm and te parent artery will be embolized permanently with detachable balloons or coils.

Results: A total of 20 patients with 22 aneurysms were included in this study. There were 13 women and 7 men, with an average age of 42.5 years. Intraoperative angiography showed the good patency of all the STA grafts, and neither SEP nor MEP abnormalities were detected. After the parent artery and the aneurysm were occluded, the intraoperative angiography showed an immediately successful exclusion of the aneurysm in 20 aneurysms and immediate contrast stasis in two. All patients recovered uneventfully without ischemic or hemorrhagic complication. Angiography at 6-month follow-up showed the total obliteration in 20 aneurysms. Two aneurysms showed residuals and were recoiled. All STA grafts showed a good patency, and the mean graft flow was 124.2 ml/min.

Conclusion: STA–MCA bypass in combination with endovascular exclusion is an appropriate option for patients with complex cerebral aneurysms that are not amenable to direct surgical clipping or endovascular embolization.

Keywords: cerebral complex aneurysm, hybrid surgery, superficial temporal artery-middle cerebral artery bypass, endovascular therapy, intraoperative evoked potential monitoring

INTRODUCTION

Complex cerebral aneurysms such as giant aneurysm, serpentine aneurysm, dissection aneurysm, and recurred aneurysm after embolization have always been and remain among the most difficult cerebrovascular lesions to treat, even for experienced neurovascular surgeons (1). Extracranial–intracranial (EC–IC) bypass with parent artery occlusion is one of the preferred procedures for complex aneurysms (2, 3). However, there are two debatable issues. First, the optimal bypass selection remains controversial (4–6). Besides that, the endovascular occlusion of the parent artery becomes more popular due to its less invasive nature (7).

Traditionally, the saphenous vein and the radial artery are selected as the graft for the high-flow bypass (8, 9), which has been proven as an effective and safe bypass. However, compared to the superficial temporal artery–middle cerebral artery (STA–MCA) bypass, the high-flow bypass (ECA–graft–ICA) required multiple incisions (head, neck, and arm or leg) and additional graft harvest, which made the procedure more invasive and technically difficult. STA was the first auto-graft used in EC–IC bypass and has been considered as low-flow graft. However, recent studies, including ours, have shown a significant increase in the mean flow rate of the STA graft after bypass surgery (10, 11). In Amin-Hanjani's study (12), the intraoperative cut flows of STA graft could exceed more than 100 ml/min in 16% cases, and Cherian et al. reported that 94% of the double-barrel STA–MCA bypasses had best observed flow >40 cc/min (13). More and more studies have revealed that the definition of a high-flow bypass should not be limited only to interposition grafts from cervical carotid branches (14). What is more, the concept of a flow replacement bypass does not mean replacing the entire territory of the occluded artery in virtue of the collateral flow coming from the communicating artery and/or the cortical arteries. Therefore, STA would be an efficient and simple graft for the treatment of complex aneurysm.

Here we present our experience in 20 patients with complex aneurysms treated with a hybrid approach: STA–MCA bypass in combination with endovascular exclusion of the aneurysm on the basis of preoperative multimodal imaging and intraoperative evoked potential monitoring.

PATIENTS AND METHODS

Patients

This study was approved by the Institutional Review Board of Nanfang Hospital. Twenty patients with 22 complex aneurysms underwent hybrid surgery during the period from April 2015 to January 2020 in the Department of Neurosurgery, Nanfang Hospital, Southern Medical University. Complex intracranial aneurysms include those classified as giant, those that reoccurred after embolization treatment, or those that involve arterial trunks/branches. Their ages ranged from 8 to 60 years old, with an average age of 42.5 years. Thirteen patients were female, and the other seven were male. There were 21 unruptured aneurysms and one ruptured aneurysm. Two patients had multiple aneurysms in the same ICA territory. Seven aneurysms were located on the right side and 15 on the left side. Of the 22 aneurysms, there were seven giant saccular aneurysms, seven giant serpentine aneurysms, five recurrent aneurysms after embolization, and three dissection aneurysms. Fourteen aneurysms were found to be in the cavernous segment of the internal carotid artery, three were in the supraclinoid segment of ICA, two were in the M1 segment of the MCA, two were in the inferior trunk of the MCA, and one was in the superior trunk of the MCA (**Table 1**).

Imaging and Indications for Bypass Surgery

All patients were diagnosed with digital subtraction angiography and received a balloon occlusion test (BOT). The aneurysms in these patients were considered to be surgically unclippable based on digital subtraction angiography (DSA) findings and not suitable for endovascular embolization or the patient refused to receive a pipeline device due to economic reasons. The indication for STA–MCA bypass surgery was established based upon tolerance to BOT, which has been defined as neurologically intact during the 30-min parent vessel occlusion but any inadequate venous-phase delay. The anatomy of the circle of Willis was analyzed to confirm the presence of anterior communicating artery and/or ipsilateral posterior communicating artery, which make the scheduled bypass procedure a complementary bypass due to the existence of compensation flow from the contralateral or posterior circulation. The radial artery auto-graft was the first choice for a potential rescue bypass. The ipsilateral radial artery would be taken if the Allen test revealed an adequate blood supply to the palmar arcade and hand through the ulnar artery alone.

Treatment Strategies and Surgical Techniques

The patients were treated in a hybrid operating room. The MEP and SEP were applied during the whole procedure. The targeted branches of the middle cerebral arteries were selected as recipient vessels. For ICA aneurysm, one frontal and one temporal cortical branch of the MCA were chosen as recipient arteries to get flexibility in distributing flow across separate territories. For MCA aneurysms, the exact efferent parent arteries were identified on the pre-surgical DSA with the assistance of double volume reconstruction. The projection of the target recipient arteries on the cranial bone was marked. The craniotomy was then performed based on the locations of the targeted recipient and donor vessels (STA branches). After the STA–MCA bypass was completed, intraoperative DSA was performed to verify the patency of the grafts. Then, endovascular temporary parent artery occlusion was used to observe the STA–MCA flow capacity. The evoked potentials were monitored. If the MEP or SEP waveforms decreased by 50% in amplitude compared with the baseline value, the balloon will be deflated, and in this case, a rescue bypass with radial artery graft will be performed. If the MEP and SEP waveforms remained normal for 30 min, the balloons were inflated and released to occlude the ICA (**Figure 1**). For MCA aneurysm, coils were used to embolize the aneurysm and parent artery.

TABLE 1 | Clinical characteristics of individuals with complex aneurysm treated by hybrid strategy.

No	Sex	Age	Side	Aneurysm location	Aneurysm characteristic	BOT	Venous phase delay	Circle of Willis	Pre-operative GCS	STA bypass	Emboliazaiton strategy	Complication	Graft flow	GOS at FU
1	Female	38	Right	ICA-C4	Giant, serpentine	Neg	Positive	A+P	15	Double	Balloons	None	NA	5
2	Male	49	Left	MCA-M2	Giant, serpentine	–	–	–	15	Single	Coils	None	NA	5
3	Female	48	Left	ICA-C4	BBA, recurrence	Neg	Positive	A	15	Double	Coils+balloons	None	NA	5
4	Male	49	Left	ICA-C3	Giant, serpentine	Neg	Positive	A	15	Double	Balloons	None	NA	5
5	Male	14	Left	ICA-C3	Giant, serpentine	Neg	Positive	A+P	15	Single	Balloons	None	181	5
6	Female	57	Left	ICA-C3	Giant, serpentine	Neg	Positive	A+P	15	Double	Balloons	None	73	5
7	Female	60	Right	ICA-C3	Giant, saccular	Neg	Positive	A	15	Double	Balloons	None	89	5
8*	Male	34	Left	ICA-C3	Giant, dissection	Neg	positive	A+P	15	Double	Coils+balloons	None	105	5
9	Female	22	Left	MCA-M1	Dissection, recurrence	–	–	–	15	Double	Coils	None	124	5
10	Male	8	Left	ICA-C3	Giant, serpentine	Neg	Positive	A+P	15	Double	Balloons	None	172	5
11*	Female	51	Left	ICA-C3 MCA-M1	Giant, saccular; dissection	Neg	Positive	A+P	15	Double	Coils+balloons	None	227	5
12	Male	39	Right	ICA-C3	Giant, saccular	Neg	Positive	A+P	15	Double	Balloons	None	NA	5
13	Female	55	Left	MCA-M2	Giant, recurrence	–	–	–	15	Double	Coils	None	66	5
14	Female	52	Right	ICA-C3	Giant, recurrence	Neg	Positive	A	15	Double	Balloons	None	NA	5
15	Female	56	Right	ICA-C4	Giant, saccular	Neg	Positive	P	8	Double	Balloons	None	177	3
16	Female	60	Right	ICA-C3	Giant, saccular	Neg	Positive	A	15	Double	Balloons	None	NA	5
17	Female	51	Left	ICA-C3	Giant, saccular	Neg	Positive	A+P	15	Double	Balloons	None	142	5
18	Male	35	Left	MCA-M2	Dissection, recurrence	–	–	–	15	Double	Colis	None	52	5
19	Female	50	Right	ICA-C3	Giant, saccular	Neg	Positive	A	15	Double	Balloons	None	NA	5
20	Female	22	Left	ICA-C3	Giant, serpentine	Neg	Positive	A+P	15	Double	Balloons	None	83	5

**multiple aneurysms; ICA, internal carotid artery; MCA, middle cerebral aneurysm; C3, cavernous segment; neg, negative; A, anterior communicating artery; P, posterior communicating artery; NA, not available; GOS, Glasgow outcome scale; FU, follow up.*

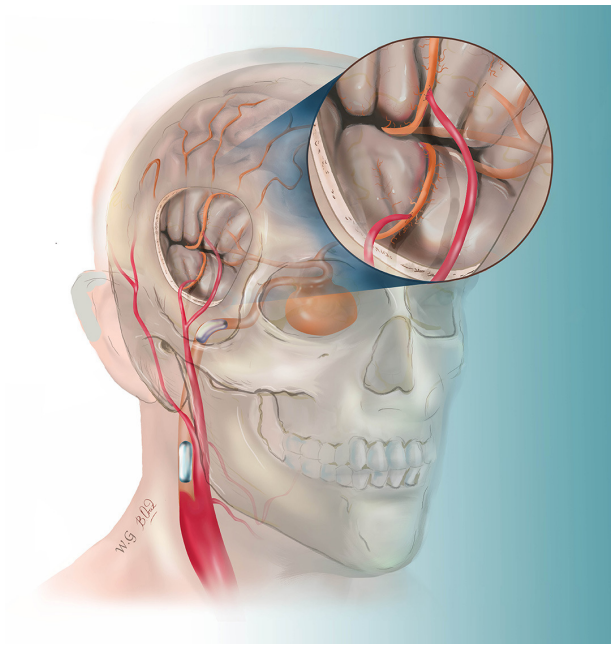

FIGURE 1 | This drawing illustrates the hybrid strategy for complex internal carotid artery (ICA) aneurysm. After double superficial temporal artery–middle cerebral artery bypass, the ICA was permanently blocked by two detachable balloons.

Post-operative management included monitoring of the patients in the intensive care unit where arterial and central venous pressures were monitored. All the patients underwent CT, MR, DSA, and CT perfusion postoperatively. The blood flow (ml/min) of STA graft was measured by duplex ultrasonography and recorded. For single bypass, the checkpoint was located at the segment where the STA passes through the skull bone. For double-barrel bypass, the checkpoint was located just at 3–5 mm proximal to the bifurcation of the frontal and parietal branches of the STA (11).

RESULT

Intraoperative angiography showed a good patency of all the 38 anastomoses (18 double-barrel anastomosis and two single anastomosis). Neither MEP nor SEP abnormality was detected. After the parent artery and the aneurysm were occluded, the intraoperative angiography showed an immediately successful exclusion of the aneurysm in 20 aneurysms and significant immediate contrast stasis in two, including one MCA aneurysm, which was loosely packed with coils to avoid acute M1 occlusion-related perforator damage. Post-operative CT demonstrated thrombosis in all the 22 aneurysms. Aneurysmal thrombosis was confirmed in all patients by MRI. MRA showed a patency in all the 38 grafts. No surgical site infection was observed after surgery. All patients recovered uneventfully, without ischemic or hemorrhagic complication. When these 20 patients were discharged from the hospital, the Glasgow Outcome Scales (GCS) were grade V in 19 and grade III in one (preoperative GCS was 8), respectively. DSA at 6-month follow-up showed a good graft patency in all the 38 bypasses. One ICA aneurysm recurred with retrograde blood supply from the posterior circulation *via* the posterior communicating artery. The remaining lumen was noted in another MCA aneurysm treated with loose packing. These two aneurysms were retreated by coils through the trans-posterior and trans-anterior communicating artery approach, respectively. The post-operative mean graft flow was 124.2 ml/min (52–227 ml/min), with a significantly dilated diameter which increased from 0.15 cm preoperatively (0.10–0.21 cm) to 0.20 cm postoperatively (0.16–0.27 cm) (**Table 2**). Representative cases are shown in **Figures 2**, **3**.

TABLE 2 | Patients, aneurysms, and treatment characteristics.

No of patients	
Female	13
Male	7
Total	20
Age, year	
Mean	42.5
Range	8-60
Aneurysm type	
Saccular	7
Dissection	3
Serpentine	7
Recurrent after stented	5
Aneurysm location	
ICA-cavernous segment	14
ICA-supraclinoid segment	3
MCA-M1 segment	2
MCA-superior trunk	1
MCA-inferior trunk	2
Bypass type	
Single STA-MCA	2
Double STA-MCA	18
Aneurysm treatment strategy	
Balloon occlusion of ICA	13
Coil embolization of aneurysm and parent artery	4
Balloon occlusion and coil embolization	3
Mortality	0
Ischemic complication	
Yes	0
No	20
Graft flow, ml/min	
Range	52–227
Mean	124.2
Aneurysm follow-up	
Cured	18
Residual and retreatment	2

DISCUSSION

Giant aneurysm, recurrent aneurysms after stent-assisted embolization, and serpentine aneurysms are rare but typical

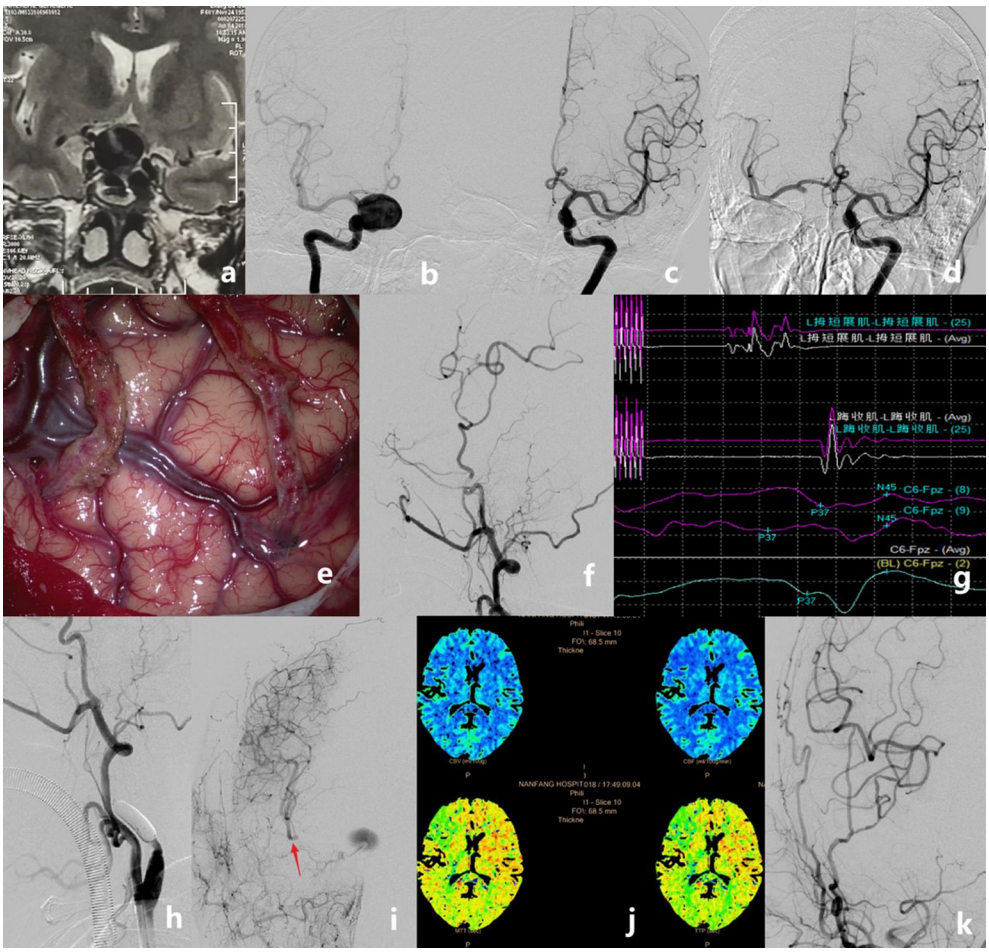

FIGURE 2 | Case example of a patient who had a giant internal carotid artery (ICA) aneurysm. MRI showed a mass with fluid void effect in the sellar region **(a)**. Pre-operative angiograms showing that the aneurysm was located at the right C4 [**(b)**, anteroposterior view]. The anterior communicating artery did not show on regular left ICA angiogram [**(c)**, anteroposterior view]. Pre-operative balloon occlusion test showing the anterior communicating artery and delayed filling of the right ICA territory [**(d)**, anteroposterior view]. Double superficial temporal artery–middle cerebral artery (STA–MCA) bypass was performed **(e)**. Intraoperative angiography showing the good patency of the anastomoses **(f)**. The intra-operative motor evoked potential and somatosensory evoked potential remained stable after temporary occlusion of the ICA for 30 min **(g)**. The ICA was occluded permanently with detachable balloons **(h)**. Controlled angiography showing the good patency of the double STA bypass and the MCA territory that was compensated very well, but the aneurysm was still stasis and fed by the anastomosic artery from the external artery **(i)**. Post-operative perfusion CT showed no ischemic area on the right hemisphere **(j)**. Digital subtraction angiography follow-up revealed the total obliteration of the aneurysms and the good patency of grafts **(k)**.

intracranial complex aneurysms (1–12, 14, 15). The primary goal of treatment is to exclude the aneurysm from the circulation and preserve the normal anatomy and function. These aneurysms have traditionally been treated with aneurysm clipping surgery, with or without thrombectomy. The perioperative morbidity and mortality rates, however, were 30–35% (16). In recent years, the development of interventional treatment, such as the pipeline embolization device (PED), has greatly improved the treatment for giant aneurysm but not for serpentine aneurysm in terms of its high risk of recurrence and technical difficulty (17). The PED is also off-label for recurrent previously stented aneurysms (18). Some patients would refuse to accept PED therapy due to its high cost, so EC–IC bypass combined with parent artery occlusion remains an effective and economic way to treat these complex aneurysms. In our study, 20 patients with 22 complex aneurysms were successfully treated with STA–MCA bypass combined with parent artery endovascular occlusion. All these patients showed a good outcome, indicating that this is an effective way to cure the aneurysm, and much less invasive because there was no need to directly expose and manipulate the complex aneurysm.

In the treatment of cerebral aneurysm that requires parent artery sacrifice, the optimal choice of bypass graft remains controversial (19). The most important issue is to determine the flow demand and assess the adequacy of potential *in situ* donors in order to get a good balance between the supply and the demand. Usually, saphenous vein (SV) or radial artery would be chosen as grafts to introduce generous blood flow from the external carotid artery to the sacrificed territory after the acute

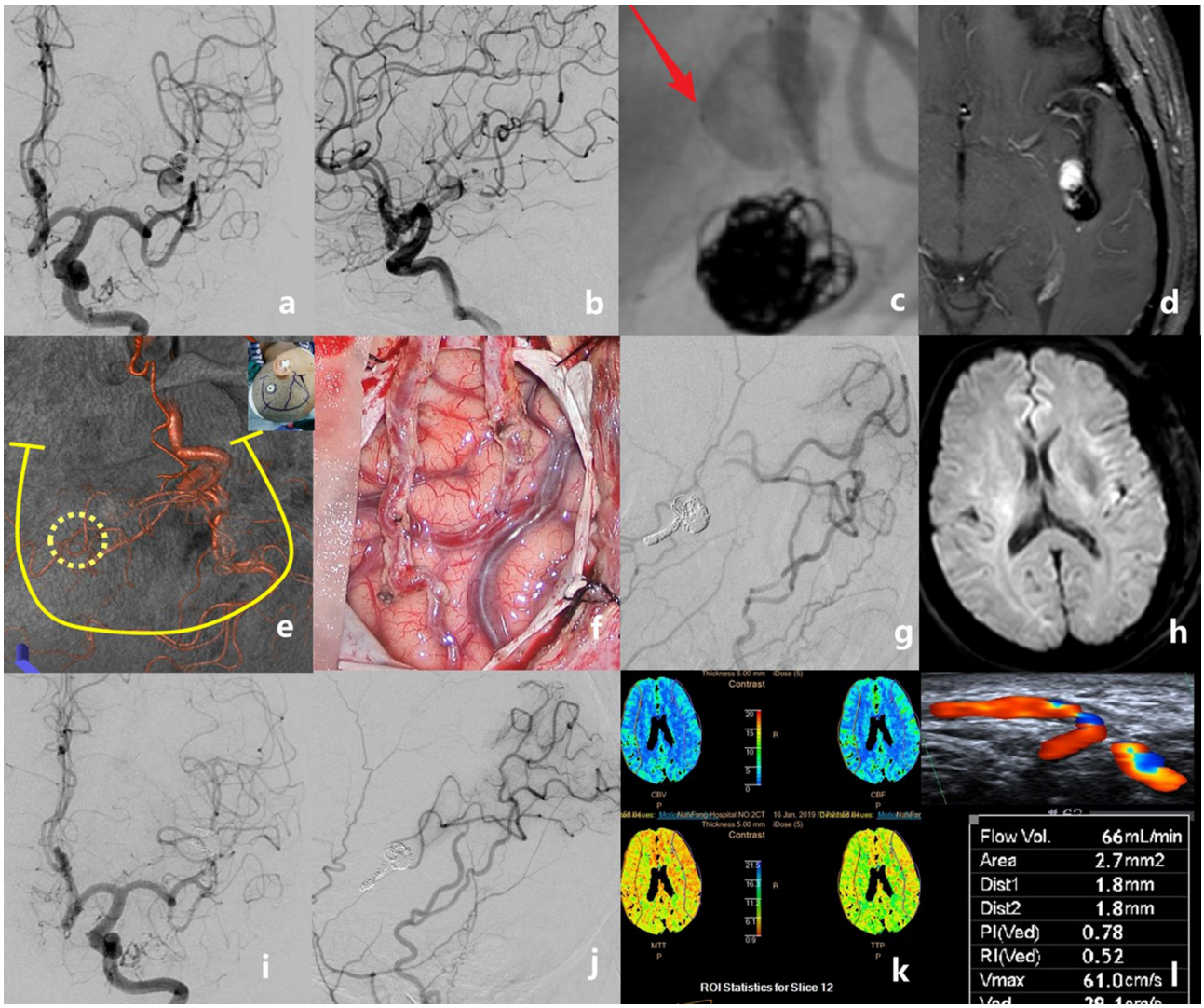

FIGURE 3 | The case of a middle-aged patient with a recurrent middle cerebral artery (MCA) aneurysm after stent-assisted coil embolization is presented. Preoperative angiograms showed that the aneurysm was located at the inferior trunk of the left MCA [**(a)**, anteroposterior view; **(b)**, lateral view]. The stent deformation-related vascular injury developed into a new dissection just proximal to the previous coiled aneurysm **(c)**. Pre-operative MRI showing the intra-aneurysmal enhancement **(d)**. Recipient and donor vessels were precisely marked on the surface of the skull, then a *U*-shaped flap with a small bone window was designed **(e)**. Double superficial temporal artery (STA)–MCA bypass was performed **(f)**. Intraoperative angiography showed the patency of anastomoses; the aneurysm and the parent artery were embolized with coils **(g)**. No new infarct was detected on the post-operative diffusion-weighted imaging **(h)**. Digital subtraction angiography follow-up at 6 months revealed the total obliteration of the aneurysm and the good patency of grafts **(i,j)**. Perfusion CT showed no ischemic area in the bypassed hemisphere **(k)**. The graft flow was 66 ml/min **(l)**.

ICA occlusion, known as high-flow bypasses. However, if an Allen test is positive, the radial artery cannot be harvested on account of poor palmer collateral circulation (20). The valves are thought to be one of the causes of SV graft failure (21). The risk of bypass graft failure at long-time follow-up was also another issue that should be considered (5–12, 14–21). By comparison, the STA can be harvested easily from the scalp during craniotomy used for the ICA and MCA aneurysm exposure so that the whole surgery is done with only one skin incision. Furthermore, the STA graft has shown a highest long-time patent rate so far. In summary, the STA would be an ideal graft for EC–IC bypass, but the STA–MCA bypass was traditionally considered as a low-flow type graft that may lead to ischemic complications in an acute ICA/MCA therapeutic occlusion. However, recent studies have found that the STA may play a more effective role in bypass surgery than previously thought. In Cherian's study (13), the maximum best observed flow (BOF) with double-barrel bypass was 120 cc/min, and 53% provided BOF ≥65 cc/min. Amin-Hanjani et al. (20) found that flow measurement in the affected vessel at baseline could predict the flow required for full replacement. For MCA aneurysms and proximal ICA aneurysms, the mean required flow was 50 ± 25 and 26 ± 18 cc/min,

respectively. In our previous study (11), the mean flow in the STA after bypass was 106.7, 112.6, 97.4, and 79.7 ml/min on post-operative day 1 and day 7 and at 3 and 6 months post-operatively. All these results indicated that an STA bypass has the potential to provide sufficient flow to allow parent artery sacrifice, especially in patients with MCA aneurysms.

However, in patients with ICA aneurysms that need ICA occlusion, the key point for this STA bypass strategy is the presence of well-developed collaterals in the circle of Willis, which can provide a collateral flow in large vessel occlusion conditions. All patients with ICA aneurysms in this study had well-developed anterior and/or posterior communicating artery as confirmed by the BOT angiogram, and in addition, the negative results of the BOT further assure the presence of good collaterals (22, 23). In our hypothesis, the STA–MCA bypass was adequate according to this collateral pattern but cannot be confirmed since the patients were under a general anesthesia during the whole hybrid procedure. Then, intraoperative monitoring of MEP and SEP was used as a real-time evaluation of the bypass function. MEPs had been widely applied in intracranial vascular surgeries in the last decades (24, 25). During parent vessel occlusion, if the flow from the STA graft and communicating arteries is insufficient, it may lead to hypo-perfusion-related infarction; MEP and SEP changes can serve as an early warning, indicating the need for changing the bypass strategy, and the temporary occlusion balloon would be deflated immediately, followed by a rescue bypass with the radial artery or SV. Fortunately, there were no intraoperative MEP or SEP changes during the temporary occlusion in our cases, confirming that the preoperative choice of STA bypass was adequate.

There are several ways to occlude the parent artery after a bypass. In earlier studies, the aneurysms and the parent artery were exposed and surgically clipped or ligated with sutures (26, 27). This procedure required more time and additional incision for ICA ligation. In Mao's study (28), the ICA occlusion was performed by placing the Selverstone clamp around the cervical ICA and gradually clipping it within 7 days. Combined surgical and endovascular treatments of complex cerebrovascular diseases in the hybrid operating room have become popular in the recent years (29–31). However, in a two-stage hybrid treatment, bypass occlusion is a potential risk due to the low-pressure gradient between the EC and the IC systems before the occlusion procedure. Meanwhile, psychological distress increases during the multiple stages of the treatment strategy. Therefore, single-session combined therapy is a better option to avoid these problems, so we introduced a combined strategy to complete the therapy in a hybrid operating theater with good surgical outcome.

This study has two limitations. First, this is a retrospective study with a limited number of patients. Further studies with a larger sample size can help to verify the efficacy and the safety of this mini-invasive hybrid strategy. Second, the patients included in this study were screened by strict preoperative imaging evaluation, which means that this hybrid strategy should be used in certain cases.

CONCLUSION

STA–MCA bypass, in combination with endovascular exclusion, is an appropriate option in patients with complex cerebral aneurysms that are not amenable to either surgical clipping or endovascular embolization.

DATA AVAILABILITY STATEMENT

The original contributions generated for the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author/s.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Institutional Review Board of Nanfang Hospital. Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin.

AUTHOR CONTRIBUTIONS

All authors listed have made a substantial, direct and intellectual contribution to the work, and approved it for publication.

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Imaging Characteristics and Endovascular Treatment of Brain Arteriovenous Malformations Mainly Fed by the Posterior Cerebral Artery

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Background: A BAVM that is mainly supplied by the posterior cerebral artery (PCA) lies deeply in the middle of the bilateral posterior hemispheres. Few studies have investigated the imaging characteristics and endovascular treatment (EVT) of brain arteriovenous malformations (BAVMs) in this area.

Methods: A retrospective study was performed for patients who were diagnosed with PCA-BAVMs from January 2015 to December 2019. The PCA-BAVMs were divided into type I and type II according to their feeding arteries. Type I PCA-BAVMs were supplied by the posterior choroidal artery (PchA) from the PCA. They could be further subdivided into type Ia and type Ib. Type II PCA-BAVMs were supplied by the temporal or occipital branch from the PCA. They could also be further subdivided into type IIa and IIb. Targeted embolization of the risk factors was the main aim of EVT.

Results: Forty-two patients were identified, with age ranging from 6 to 63 years. Twenty-four cases belonged to type I (57.1%, 24/42), including 6 Ia cases and 18 Ib cases. Eighteen cases belonged to type II (42.9%, 18/42), including 7 IIa cases and 11 IIb cases. Immediate complete or nearly complete embolization was achieved in 17 (40.5%, 17/42) cases. Partial embolization was achieved in 25 (59.5%, 25/42) cases. Two (4.8%, 2/42) patients experienced intraoperative or postoperative bleeding. The GOS scores at discharge were 3, 4, and 5 in 2 (4.8%, 2/42), 2 (4.8%, 2/42), and 38 (90.4%, 38/42) cases, respectively. There was no statistical difference between patients in type I and type II groups regarding age, BAVM rupture, SM grade, immediate extent of obliteration, and prognosis. Deep venous drainage was more common in patients of the type I group ($P < 0.001$).

Conclusions: Our classification of the PCA-BAVMs was based on the segmentation of the PCA, which is a reasonable approach and could guide the strategy of EVT. EVT is a reasonable option for the PCA-BAVMs. The main aim of EVT is to secure the weak structures. A targeted EVT aimed at the ruptured part of the BAVM can reduce the risk of early rebleeding.

Keywords: posterior cerebral artery, brain arteriovenous malformation, endovascular treatment, imaging characteristics, posterior choroidal artery

INTRODUCTION

A brain arteriovenous malformation (BAVM) is a common congenital vascular disease that belongs to the abnormal nidus between arteries and veins, which lacks an intervening capillary network and is characterized by a complex, tangled web of abnormal vessels (1, 2). Moreover, BAVMs recruit blood supply from their neighboring arteries and drain to the adjacent veins (3). BAVMs in different positions may have different characteristics (4).

A BAVM that is mainly supplied by the posterior cerebral artery (PCA) lies deeply in the middle of the bilateral posterior hemispheres and near the posterior part of the corpus callosum and the deep cerebral venous system (5). The feeding arteries of the PCA-supplied BAVMs (PCA-BAVMs) are complex, and they often drain to the deep venous system. However, few studies have investigated the angiographic characteristics and endovascular treatment (EVT) for BAVMs in this area. Therefore, in this study, we conducted a retrospective single-center investigation of the patients who were diagnosed with PCA-BAVMs.

MATERIALS AND METHODS

A retrospective study was performed for patients who were admitted to The First Hospital of Jilin University diagnosed with BAVMs mainly supplied by the PCA system from January 2015 to December 2019. This study was approved by the institutional ethics committee.

Inclusion Criteria

(1) The BAVM was located at the supplied area of the PCA, which included posterior part of the callosum, pineal region, medial posterior part of the temporal lobe, and medial part of the occipital lobe. (2) PCA was the main (if not the only) source of blood supply. (3) No previous EVT, open surgery, or radiosurgery was performed before admitting to our institution.

Classification of the PCA-BAVM

The PCA-BAVMs were divided into the following types according to their feeding arteries.

Type I: supplied by the posterior choroidal artery (PchA) from the PCA. It could be further subdivided into type Ia and type Ib. For type Ia, the PchA was the only source of arterial supply, while type Ib received additional blood supply from other sources, which included the perforating artery from the P1 segment of the PCA, the anterior choroidal artery (AchA), the anterior cerebral artery (ACA), and so on.

Type II: supplied by the temporal or occipital branch from the PCA. It could also be further subdivided into type IIa and IIb. Type IIa denoted those located at the proximal segment of the PCA and supplied by the temporal branch (including the anterior and posterior temporal arteries). While type IIb denoted those located at the distal segment of the PCA and supplied by the occipital branch of the PCA (including the lateral and medial occipital branches). Some illustrative cases are presented in **Figure 1** to expound the classification system.

Scheme and Strategy of EVT

For the EVT of BAVMs, we preferred the transarterial approach. Transvenous approach was the last resort. For aneurysms on the feeding arteries, we used the Echelon (Medtronic, Irvine, California, USA) microcatheter for coiling. To obliterate the BAVM or aneurysm near the BAVM, we used Marathon (Medtronic, Irvine, California, USA) microcatheter to cast Onyx. To avoid Onyx reflux, the proximal feeding artery could be partially coiled, creating the so-called pressure cooker effect.

The specific strategy adopted for a ruptured BAVM was determined by the ruptured or bleeding structure. For a ruptured aneurysm on the feeding artery, simple coiling or stent-assisted coiling was preferred. When the aneurysm was near the BAVM, parent artery occlusion (PAO) was preferred. For a ruptured intranidal aneurysm, the EVT was targeting the BAVM compartment harboring the ruptured intranidal aneurysm. If there were no clear risk factors, the aim of EVT was reducing the blood flow of the ruptured BAVM (6). For an unruptured BAVM, identification and management of the weak structures, such as aneurysm on the feeding artery or dilated structure in the BAVM, were of utmost importance. If no weak structures were identified or the venous drainage was patent, a wait-and-see regimen would be adopted. For the patients with obstructed venous drainage, we would like to embolize the BAVM nidus to reduce venous volume load.

After EVT of the risk factors, if the venous drainage was patent, a wait-and-see regimen could be adopted. Otherwise, another session of EVT, open surgery, or radiosurgery would be recommended to the patient.

Follow-Up and Evaluation of Outcome

The extent of obliteration was classified into complete/nearly complete obliteration and partial obliteration. Complete or nearly complete obliteration was defined as invisible or near-invisible nidus and venous drainage. Partial obliteration was defined as decrease in size but still visible. Complications, further treatment, and Glasgow Outcome Scale (GOS) score at discharge and follow-up were also recorded.

Statistical Analysis

GraphPad Software (LLC, San Diego, USA) was used to perform statistical analysis. Continuous variables were expressed as the mean ± standard deviation. The Chi-square or Fisher's exact test was used to analyze count or categorical data. $P < 0.05$ was considered with statistical significance.

RESULTS

General Information

Forty-two patients were identified, with age ranging from 6 to 63 years (mean 31.5 ± 14.7 years). Fifteen patients were males (35.7%, 15/42). The BAVMs were unruptured in 8 (19.0%, 8/42) patients, of whom five were admitted for headache and three were admitted for epilepsy. The remaining 34 (81.0%, 34/42) patients presented with intracranial bleeding, including two patients with subarachnoid hemorrhage (SAH), two patients with SAH and intracerebral hematoma (IH), nine patients with IH, 16 patients

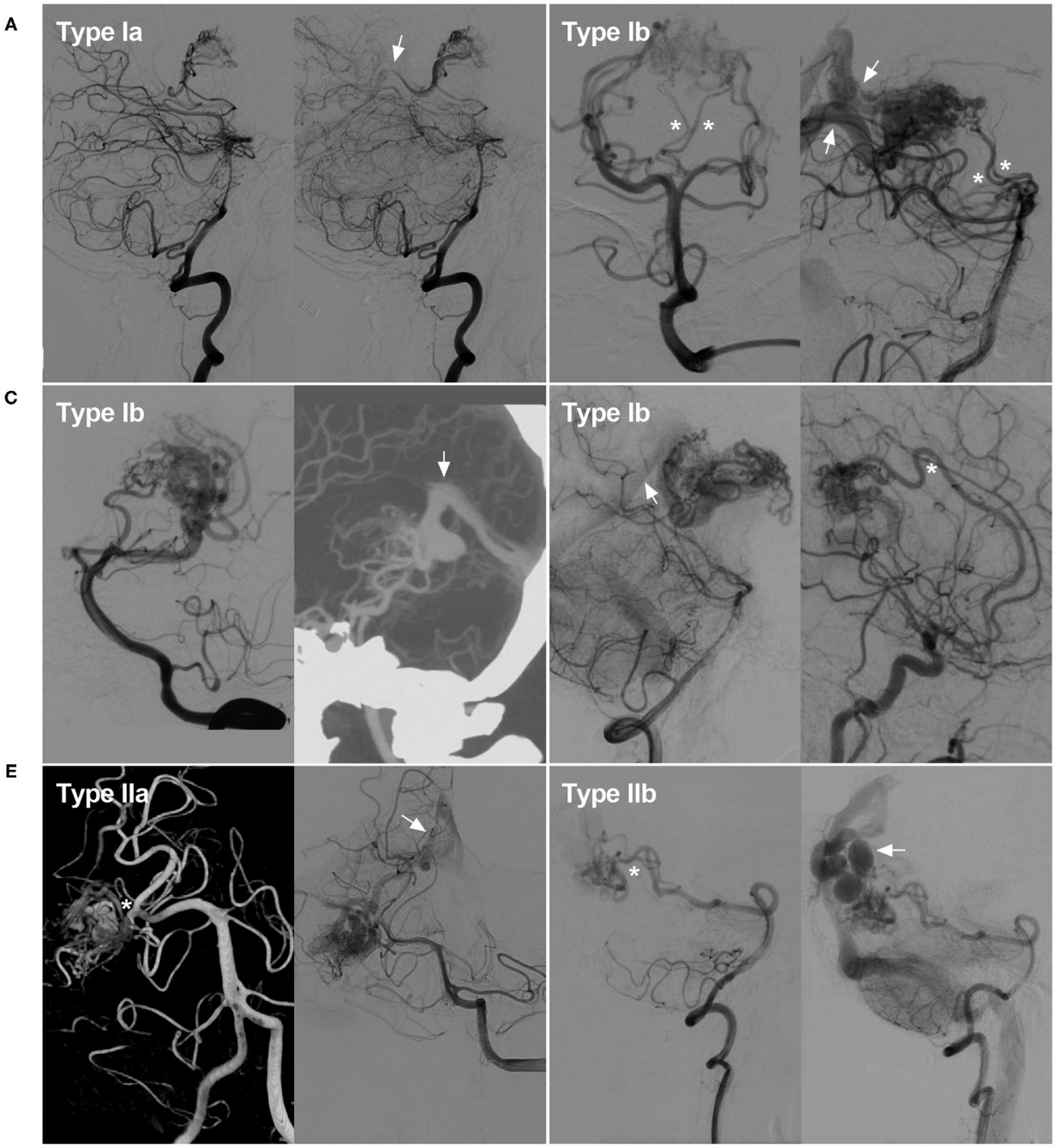

FIGURE 1 | Classification of the PCA-BAVMs. **(A)** Angiogram of the VA in lateral view shows a Type Ia BAVM supplied by the PchA from the PCA only and drained to the deep venous system (arrow). **(B)** Angiogram of the VA in anteroposterior (left) and lateral (right) views shows a type Ib BAVM supplied by the PchA (asterisk) and the proximal perforating branches of the PCA (asterisks). Multiple deep venous drainage (arrows) can be observed. **(C)** Angiogram of the VA in lateral (left) view shows a type Ib BAVM supplied by the PchA and the lateral and medial occipital branches of the PCA. Computed tomography angiography (right) in maximum intensity projection shows the BAVM drains through the deep venous system (arrow). **(D)** Angiogram of the VA (left) and internal carotid artery (right) in lateral view shows a type Ib BAVM supplied by the PchA and ACA (asterisk). Deep venous drainage (arrow) can be observed. **(E)** Angiogram of the VA shows a Type IIa BAVM supplied by the temporal branch (asterisk) of the PCA and drained to the deep venous system (arrow). **(F)** Angiogram of the VA shows a Type IIb BAVM supplied by the medial occipital branch (asterisk) and drained through the cortical veins (arrow). ACA, anterior cerebral artery; BAVM, brain arteriovenous malformation; PCA, posterior cerebral artery; PchA, posterior choroidal artery; VA, vertebral artery.

TABLE 1 | Clinical data of the patients.

Age (years)	Mean	31.5 ± 14.7
	Range	6–63
Female/Male	15/27	
Presentation	Unruptured	8 (19.0%, 8/42)
	Ruptured	34 (81.0%, 34/42)
Hunt-Hess*	I	26
	II	7
	III	1
Nidus Size (cm)	Mean	4.0 ± 1.8
	Range	0.8–9
Spetzler-Martin grade	1	5 (11.9%, 5/42)
	2	14 (33.3%, 14/42)
	3	13 (31.0%, 13/42)
	4	10 (23.8%, 10/42)
Classification	Type I	24 (57.1%, 24/42)
	Type II	18 (42.9%, 18/42)
Associated aneurysm	4 (9.5%, 4/42)	
Venous drainage	Superficial vein drainage	13 (31.0%, 13/42)
	Deep vein drainage	26 (61.9%, 26/42)
	Both	3 (7.1%, 3/42)

**Hunt-Hess grade for ruptured cases.*

with intraventricular hemorrhage (IVH), and five patients with IH + IVH. For the ruptured cases, the Hunt-Hess grades were I, II, and III in 26, 7, and 1 patient, respectively.

Imaging Characteristics

Classification of PCA-BAVMs

Twenty-four cases belonged to type I (57.1%, 24/42), including 6 Ia cases and 18 Ib cases. Eighteen cases belonged to type II (42.9%, 18/42), including 7 IIa cases and 11 IIb cases.

Sizes and Spetzler-Martin (SM) Grades of the BAVMs

The maximum size of BAVMs ranged from 0.8 to 9 cm (4.0 ± 1.8 cm). Five cases belonged to SM grade 1 (11.9%, 5/42), 14 cases belonged to grade 2 (33.3%, 14/42), 13 cases belonged to grade 3 (31.0%, 13/42), and 10 cases belonged to grade 4 (23.8%, 10/42). Four (9.5%, 4/42) cases were identified with feeding artery or intranidal aneurysms.

Venous Drainage

Thirteen cases had superficial venous drainage (31.0%, 13/42), 26 cases had deep venous drainage (61.9%, 26/42), and 3 cases (7.1%, 3/42) had both superficial and deep venous drainage.

The clinical and imaging data of the patients are summarized in **Table 1**.

EVT

Onyx embolization of the BAVMs through the PCA was performed in 33 (78.6%, 33/42) cases, of which two cases used the pressure cooker technique. Onyx embolization of the BAVMs through the ACA was performed in 7 (16.6%, 7/42) cases, of which one case used the pressure cooker technique. Onyx embolization of the BAVMs through the ACA + PCA was performed in 2 (4.8%, 2/42) cases.

Four cases with feeding artery or intranidal aneurysms underwent Onyx embolization of the aneurysms. Some typical cases of EVT are shown in **Figures 2–9**.

Immediate complete or nearly complete embolization was achieved in 17 (40.5%, 17/42) cases. Partial embolization was achieved in 25 (59.5%, 25/42) cases. Two (4.8%, 2/42) patients experienced intraoperative or postoperative bleeding, all of whom were appropriately managed and experienced satisfactory recovery. **Figure 7** illustrates a patient who experienced postoperative bleeding.

The GOS scores at discharge were 3, 4, and 5 in 2 (4.8%, 2/42), 2 (4.8%, 2/42), and 38 (90.4%, 38/42) cases, respectively.

Follow-Up

Two patients were lost to follow-up. The follow-up period of the remaining 40 patients ranged from 3 to 115 (36.4 ± 23.8) months. Ten patients underwent further radiosurgery or EVT. The GOS scores at the latest follow-up were five and four in 39 patients (97.5%, 39/40) and one patient (2.5%, 1/40), respectively. As many patients refused further angiographic investigation, complete obliteration of the BAVMs was demonstrated in only 17 patients.

Statistical Analysis

There was no statistical difference between patients in type I and type II groups regarding age, BAVM rupture, SM grade, immediate extent of obliteration, and prognosis (**Table 2**). Deep venous drainage was more common in patients of the type I group ($P < 0.001$) (**Table 3**).

DISCUSSION

BAVMs can occur at any part of the brain. A BAVM mainly supplied by the PCA may involve the PchA at the proximal end of the PCA and/or the temporal and occipital branches at the distal end of the PCA. These branches often supply the corpus callosum. The PchA often participates in the choroidal artery system of the posterior ventricle of the brain and can anastomose with the ACA to form a callosal circle (7–10). A case of BAVM mainly supplied by the PchA is illustrated in **Figure 4**.

Therefore, the blood supply of the PCA-BAVMs is complex. PCA-BAVMs at different locations have different feeding arteries. This study found that a PCA-BAVM supplied by the proximal segment of the PCA was more commonly supplied by the PchA, while a PCA-BAVM supplied by the distal segment of the PCA was mainly supplied by the temporal and occipital branches. Because a BAVM could hijack the feeding artery to the greatest extent, the ends of the ACA can also be involved. As the PCA is close to the deep venous system of Galen, a PCA-BAVM often has deep venous drainage. Among the 42 cases in this study, 29 cases (69%) had deep venous drainage (**Table 1**).

Surgical resection, EVT, and adjuvant radiotherapy are available treatments for BAVMs. In recent years, EVT has also been used as the main approach for BAVMs, especially for

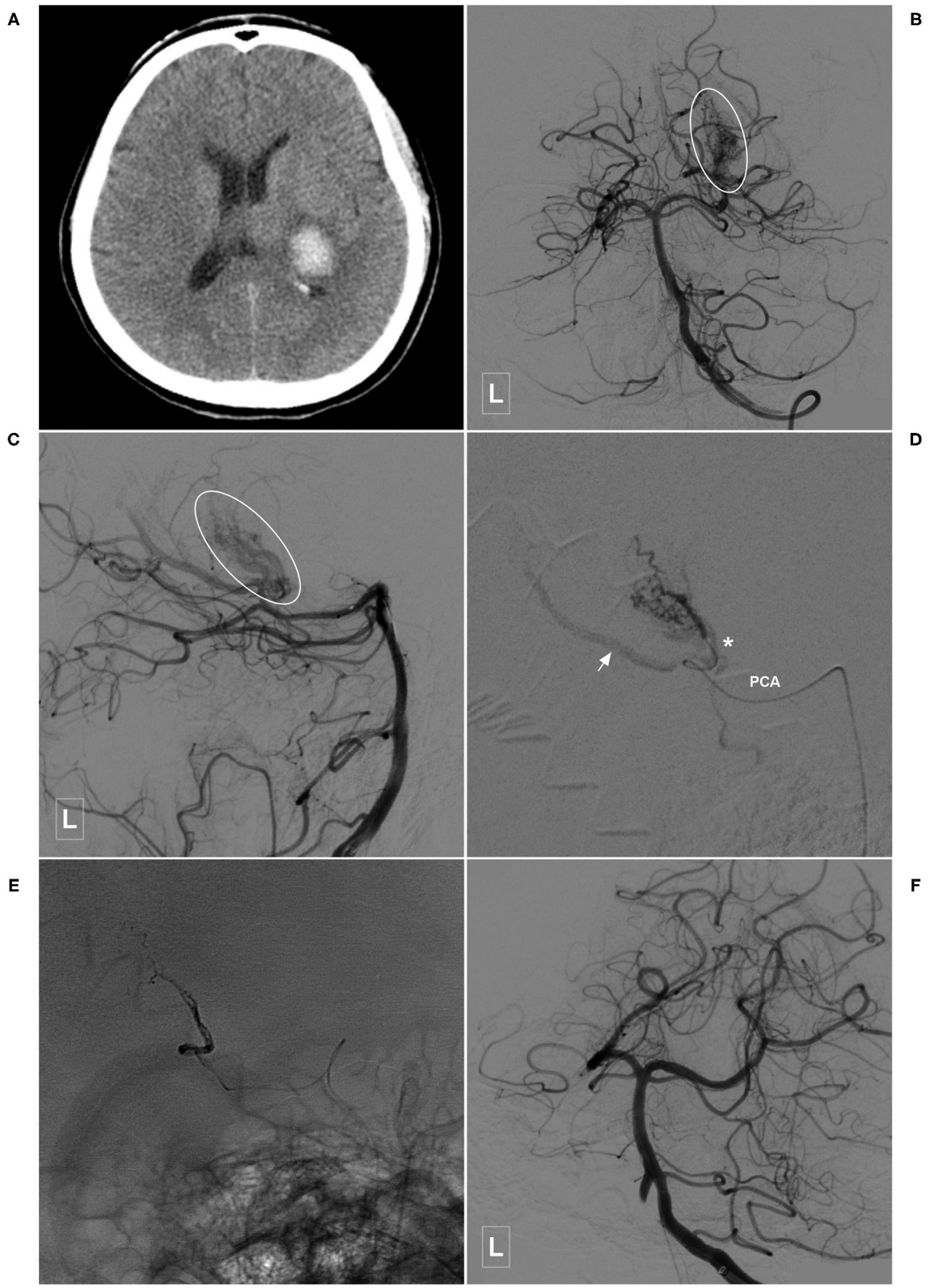

FIGURE 2 | Illustrative case of a Type Ia PCA-BAVM. **(A)** Computed tomography shows hemorrhage at the left thalamus with ventricular extension. **(B,C)** Angiogram of the left VA in the anteroposterior **(B)** and lateral **(C)** views shows a Type Ia PCA-BAVM (encircled area) solely supplied by the PchA. **(D)** Super-selective angiogram of the BAVM. Arrow denotes the draining vein and the asterisk denotes the lateral PchA. **(E)** X-ray of the cranium after embolization shows Onyx casting. **(F)** Angiogram of the left VA shows complete embolization of the BAVM. BAVM, brain arteriovenous malformation; PCA, posterior cerebral artery; PchA, posterior choroidal artery; VA, vertebral artery.

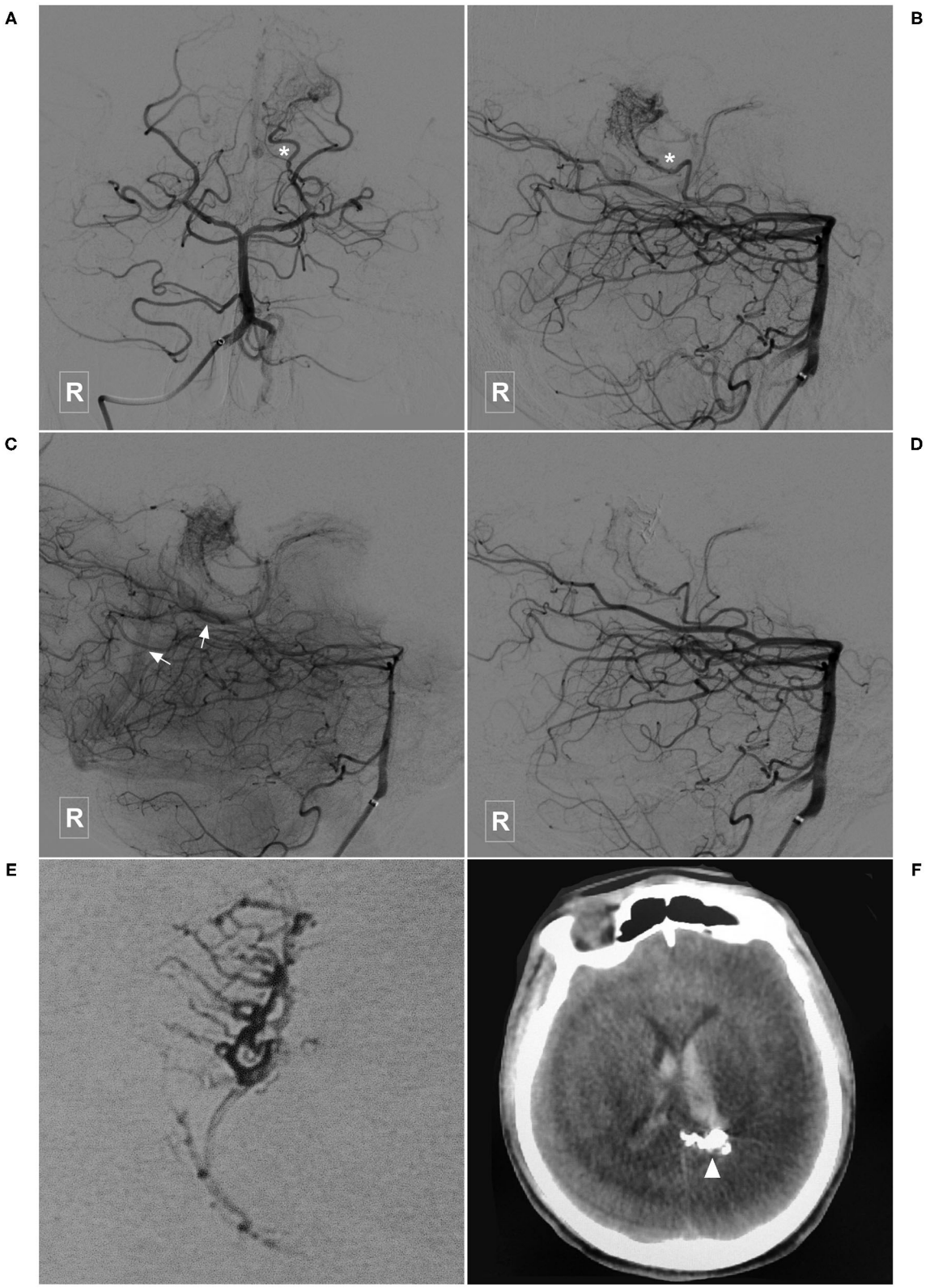

FIGURE 3 | Illustrative case of a Type Ia PCA-BAVM. **(A,B)** Angiogram of the right VA in the anteroposterior **(A)** and lateral **(B)** views shows a BAVM supplied by the lateral PchA (asterisk). **(C)** Angiogram of the left VA in lateral view at venous phase shows that the BAVM drains to the deep venous system (arrow). **(D)** Angiogram of the left VA after embolization shows the complete obliteration of the BAVM. **(E)** X-ray of the cranium shows the Onyx casting in the BAVM. **(F)** Postoperative computed tomography shows Onyx (arrowhead) and intraventricular hemorrhage. BAVM, brain arteriovenous malformation; PchA, posterior choroidal artery; VA, vertebral artery.

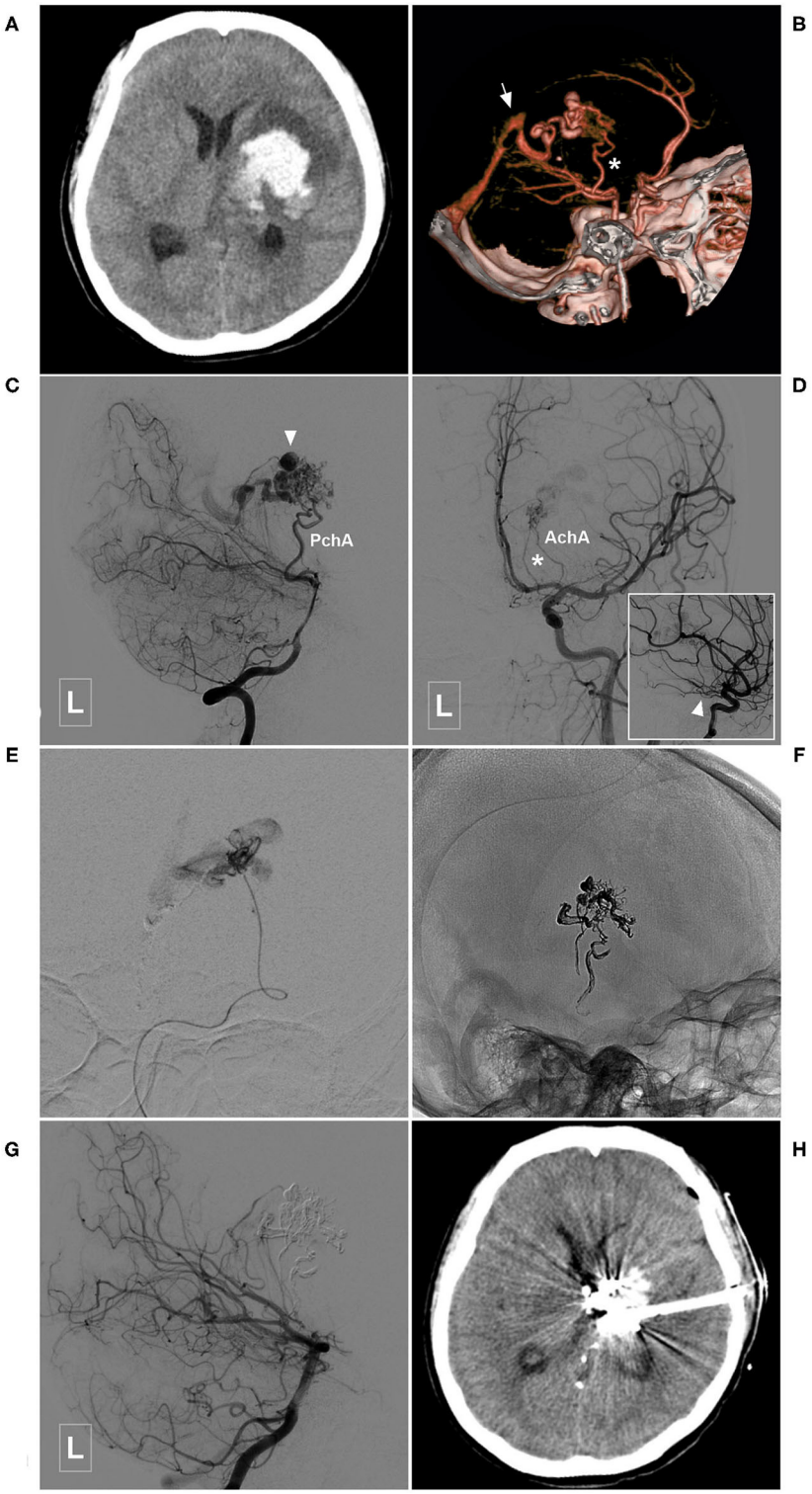

FIGURE 4 | Illustrative case of the Type Ia PCA-BAVM with intranidal aneurysm. **(A)** CT shows hemorrhage at the left thalamus and basal ganglia. **(B)** CT angiography reveals a BAVM fed by the left PchA (asterisk) and drained to the deep venous system (arrow). **(C)** Angiogram of the left VA in lateral view shows that the BAVM is supplied by the PchA and an intranidal aneurysm (arrowhead) is also noted. **(D)** Angiogram of the left internal carotid artery in anteroposterior view shows the left AchA (asterisk) also provides some blood supply to the BAVM. Arrowhead in the square denotes the proximal segment of the AchA. **(E)** Super-selective angiogram of the BAVM. **(F)** X-ray of the cranium after Onyx casting. **(G)** Angiogram of the left VA in lateral view shows complete obliteration of the BAVM. **(H)** CT shows that the hematoma is drained out after embolization of the BAVM. BAVM, brain arteriovenous malformation; CT, computerized tomography; AchA, anterior choroidal artery; PchA, posterior choroidal artery; VA, vertebral artery.

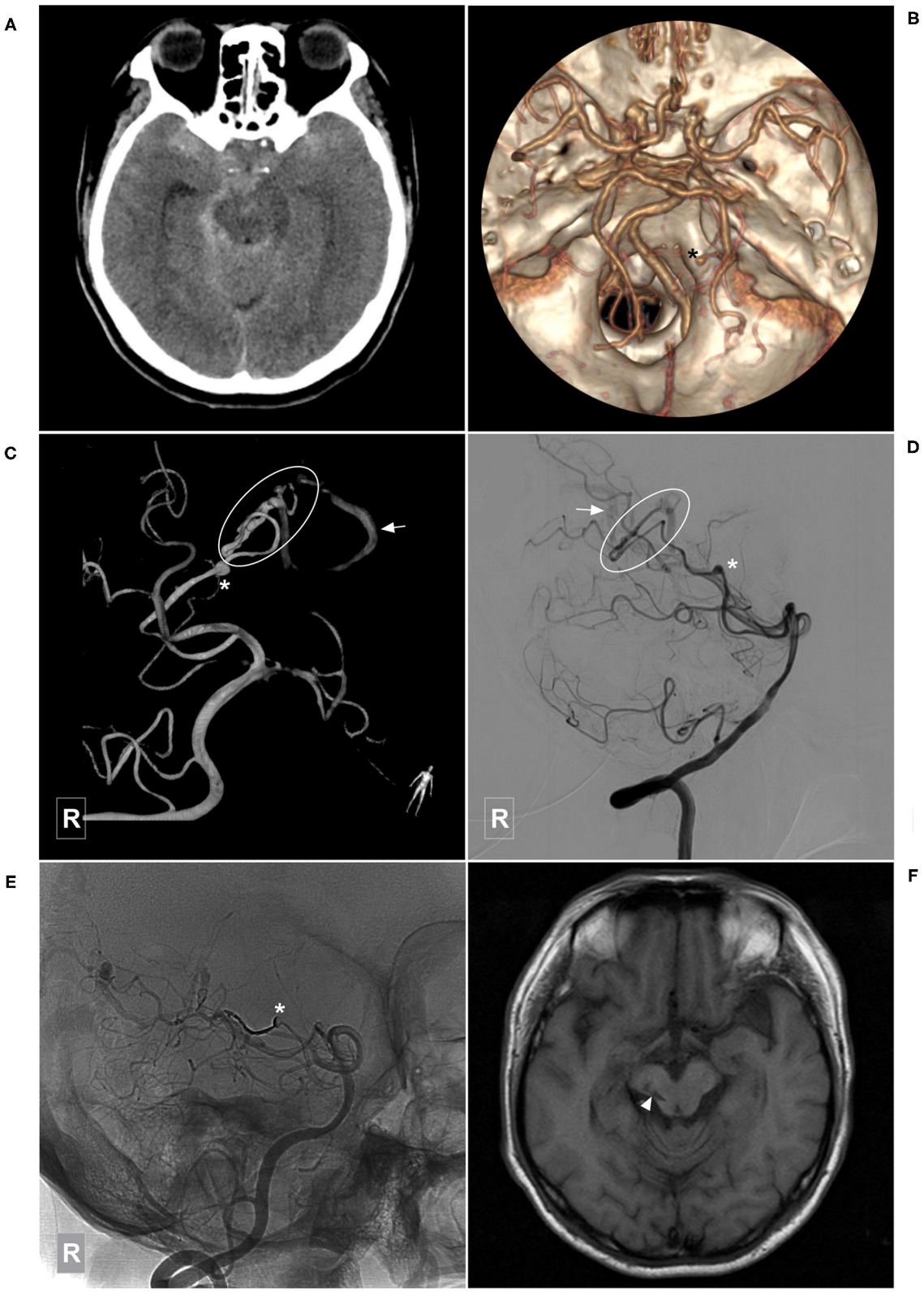

FIGURE 5 | Illustrative case of a Type Ia PCA-BAVM with flow-related aneurysm. **(A)** CT shows diffuse subarachnoid hemorrhage. **(B)** CT angiography shows an aneurysm (asterisk) originated from the right lateral PchA. **(C,D)** Angiogram of the right VA in 3D **(C)** and lateral **(D)** views shows a BAVM (encircled area) supplied by the lateral PchA. Arrow denotes the superficial draining vein and asterisk denotes the aneurysm. **(E)** Unsubtracted angiogram of the right VA shows obliteration of the aneurysm (asterisk) and partial obliteration of the BAVM. **(F)** Magnetic resonance imaging at 3-month follow-up shows an old infarction focus (arrowhead) at the midbrain. BAVM, brain arteriovenous malformation; CT, computerized tomography; PchA, posterior choroidal artery; VA, vertebral artery.

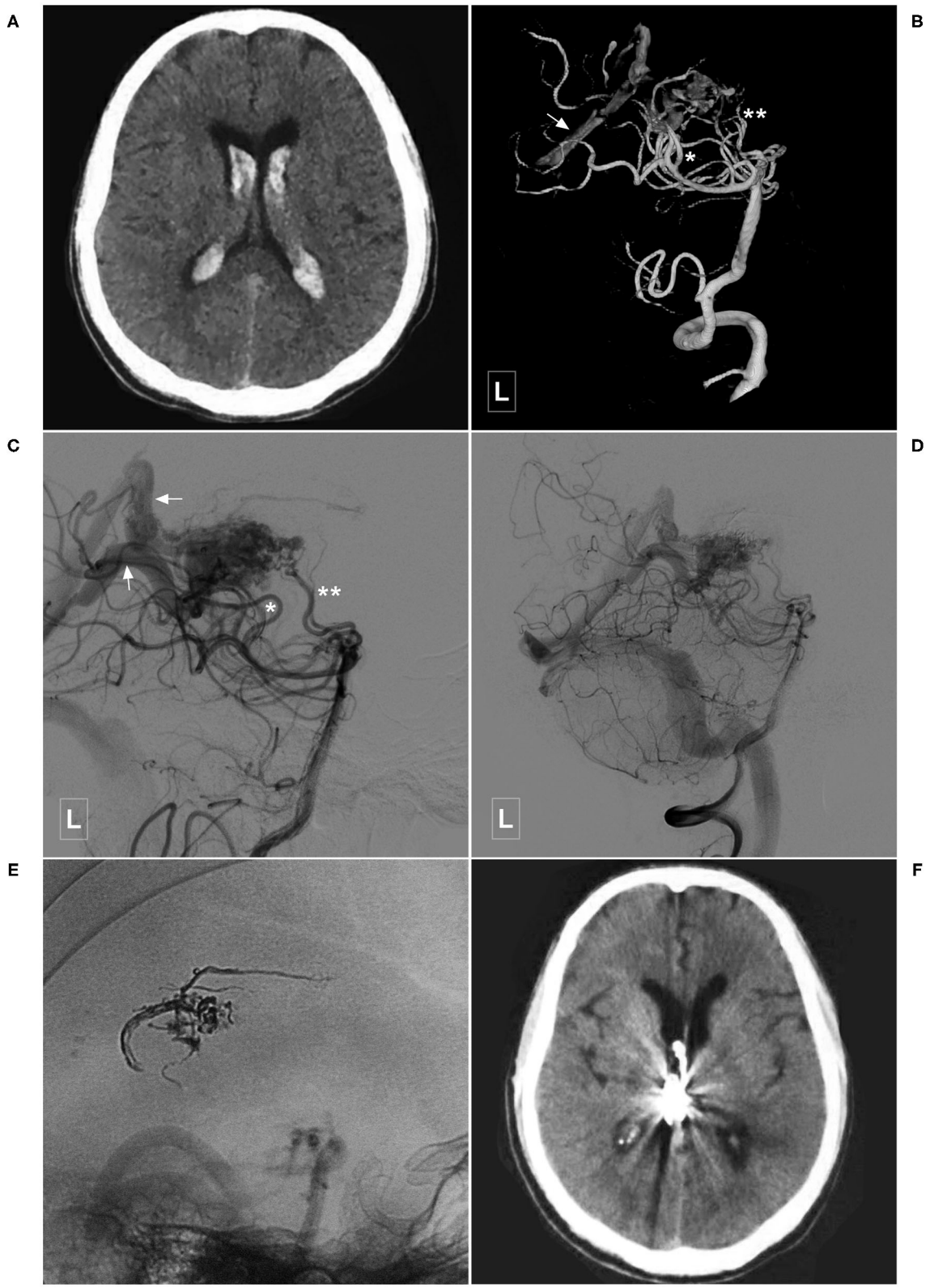

FIGURE 6 | Illustrative case of a Type Ib PCA-BAVM. **(A)** CT shows intraventricular hemorrhage. **(B,C)** Angiogram of the left VA in 3D **(B)** and lateral **(C)** views shows a BAVM supplied by the lateral PchA (single asterisk), and the perforating artery (double asterisks) of the PCA and drained through the deep veins (arrow). **(D,E)** Angiogram of the left VA shows that the BAVM is partially embolized. **(E)** X-ray of the cranium shows the casting Onyx. **(F)**, Follow-up CT shows the intraventricular hemorrhage has resolved. BAVM, brain arteriovenous malformation; CT, computed tomography; PCA, posterior cerebral artery; PchA, posterior choroidal artery; VA, vertebral artery.

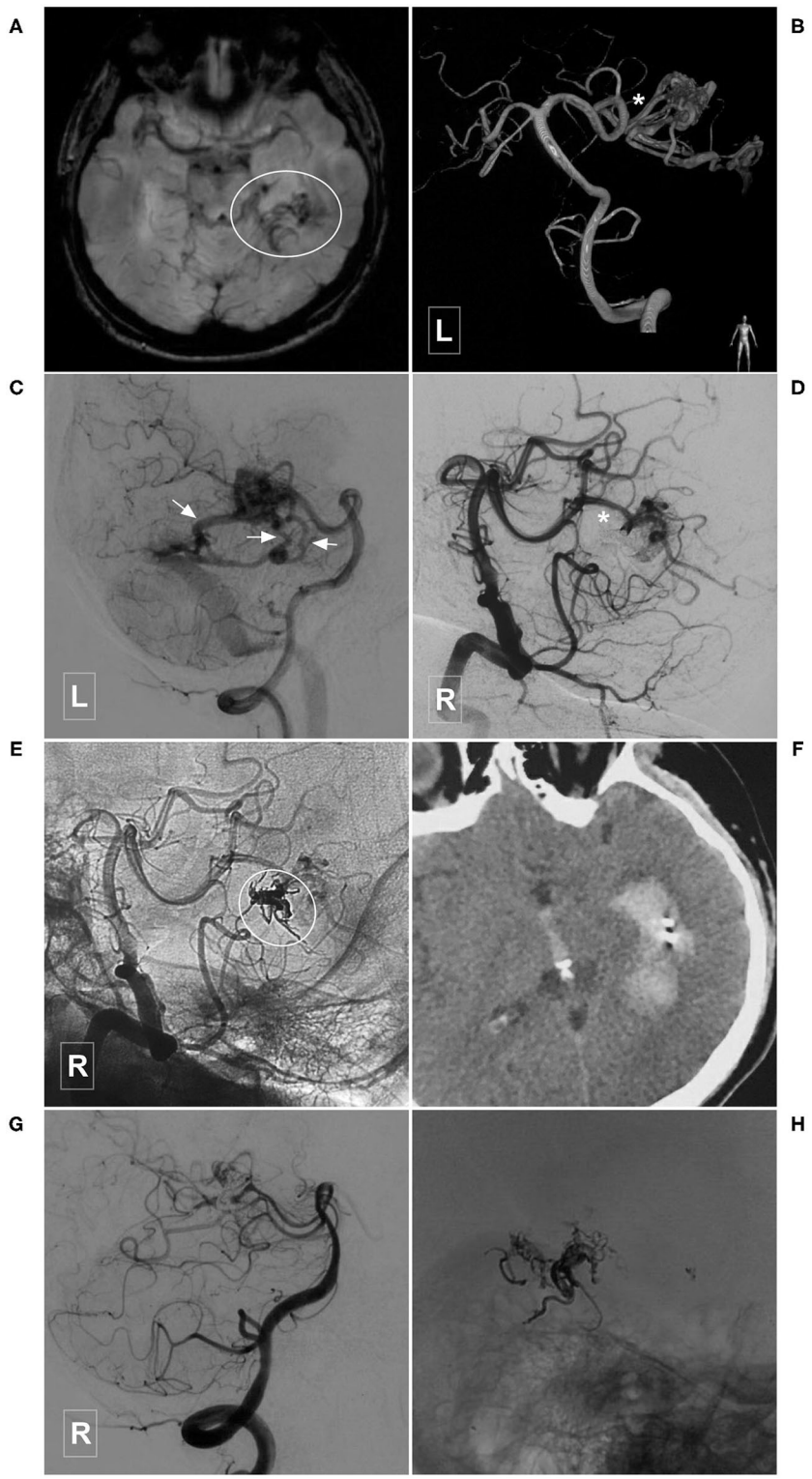

FIGURE 7 | Illustrative case of a Type IIa PCA-BAVM. **(A)**, Magnetic resonance imaging shows flow-voids at the medial temporal lobe (encircled area). **(B)** Angiogram of the left VA in 3D view reveals a BAVM supplied by the temporal branch (asterisk) of the PCA. **(C)** Angiogram of the left VA in lateral view shows that the BAVM drains through multiple superficial veins (arrow). **(D,E)** Subtracted **(D)** and unsubtracted **(E)** angiogram of the right VA shows that the BAVM is partially embolized (encircled area) via the temporal branch (asterisk) of the PCA. **(F)** Computed tomography shows left intraventricular hemorrhage 4 h after the embolization. **(G)**, Follow-up angiogram of the right VA 3 months later shows nearly complete embolization of the BAVM. **(H)**, X-ray of the cranium shows the casting Onyx. BAVM, brain arteriovenous malformation; PCA, posterior cerebral artery; VA, vertebral artery.

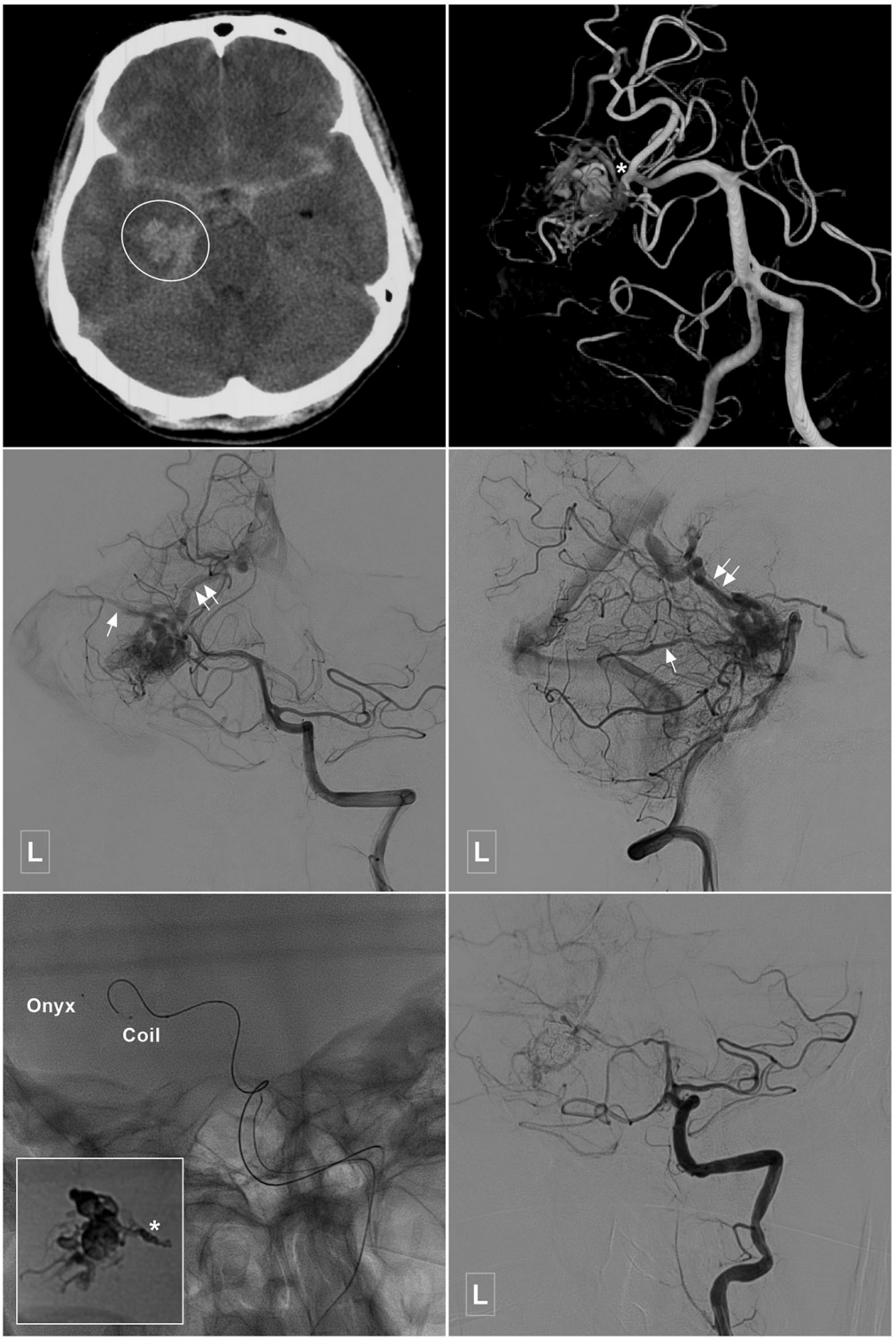

FIGURE 8 | Illustrative case of a Type IIa PCA-BAVM with intranidal aneurysm. **(A)** Computed tomography shows diffuse subarachnoid hemorrhage and a hematoma (encircled area) in the right medial temporal lobe. **(B)** 3D angiogram of the VA shows a BAVM supplied by the temporal branch (asterisk) of the right PCA. An intranidal aneurysm can be seen in the nidus. **(C,D)** Angiogram of the left VA in anteroposterior **(C)** and lateral **(D)** views shows that the BAVM drains both to the superficial (single asterisk) and deep (double asterisks) veins. **(E)** X-ray of the cranium shows the embolization process of the BAVM. One proximal microcatheter is used to release the coils to establish the "pressure cooker" effect. Another distal microcatheter is used to cast the Onyx. Enlarged picture in the square shows the coils (asterisk) and Onyx. **(F)** Angiogram of the left VA shows that the BAVM is completely embolized. BAVM, brain arteriovenous malformation; PCA, posterior cerebral artery; VA, vertebral artery.

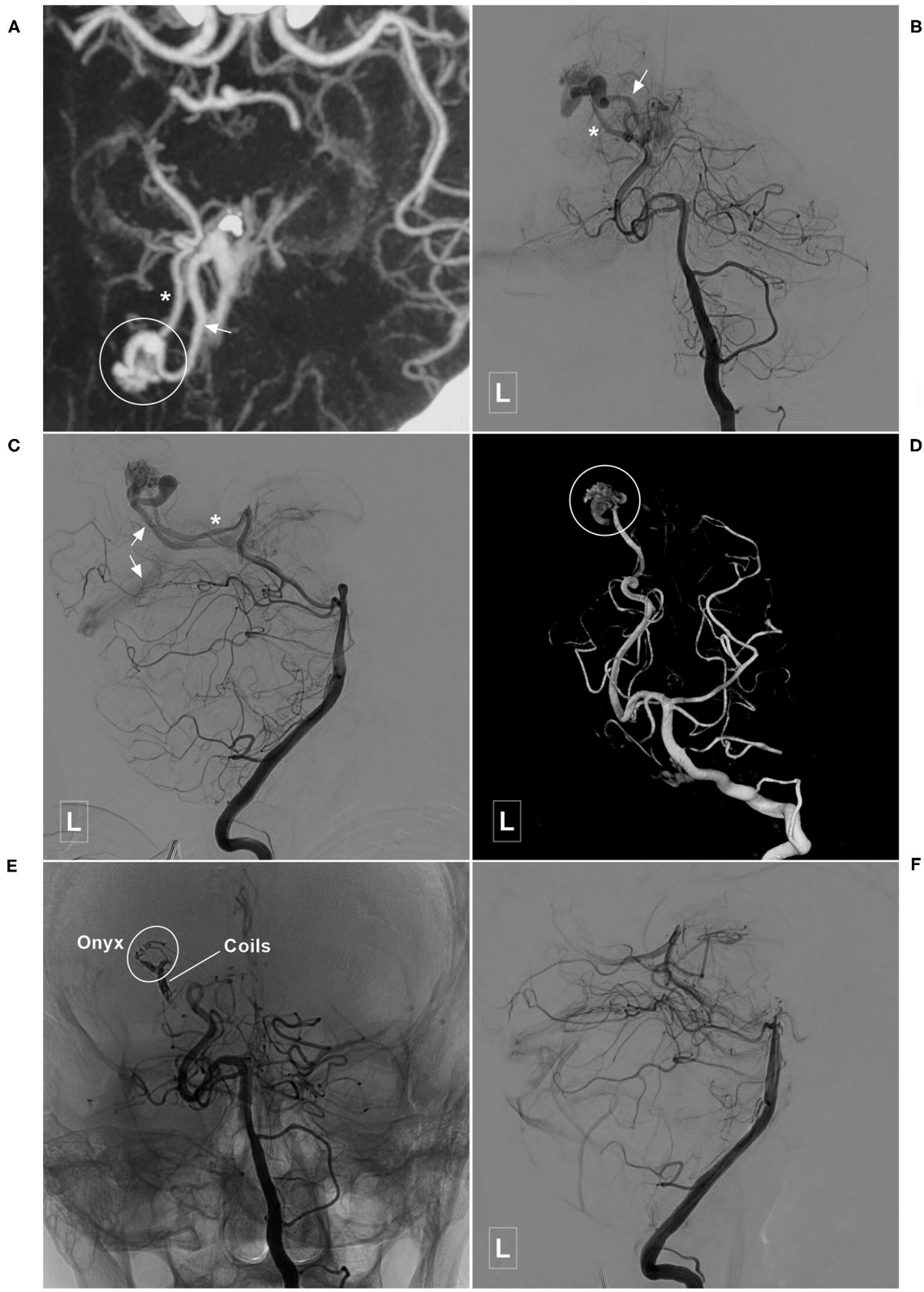

FIGURE 9 | Illustrative case of a Type IIb PCA-BAVM. **(A)** Maximum intensity projection image shows a BAVM (encircled area) supplied by an artery (asterisk) from the occipital branch of the PCA and drained to the deep veins (encircled area). **(B–D)** Angiogram of the left VA in the anteroposterior **(B)**, lateral **(C)**, and 3D **(D)** views shows the feeding artery (asterisk) and deep draining vein (arrow) of the BAVM nidus (encircled area). **(E)** Angiogram of the left VA shows that coils are released proximally to establish a "pressure cooker" effect. Then, the Onyx (encircled area) is Casted. **(F)** Angiogram of the left VA shows that the BAVM is completely embolized. BAVM, brain arteriovenous malformation; PCA, posterior cerebral artery; VA, vertebral artery.

TABLE 2 | Statistical analysis of the clinical data between type I and Type II PCA-BAVMs.

	Type I (18 cases)	Type II(24 cases)	*P*-value
Age	32.3 ± 11.9	30.9 ± 16.7	0.7699
Rupture before admission	15	19	>0.9999
Higher SM grade (≥3)	13	10	0.0653
Complete or nearly complete obliteration	5	12	0.2079
Good prognosis (GOS = 5) at discharge	15	23	0.2972

GOS, Glasgow Outcome Scale; PCA-BAVM, posterior cerebral artery-brain arteriovenous malformation; SM, Spetzler-Martin.

TABLE 3 | Pattern of venous drainage in type I and type II PCA-BAVMs.

	Superficial venous drainage alone	Concurrent with deep venous drainage	*P*-value
I	1 (4.2%)	23 (95.8%)	<0.001
II	12 (66.7%)	6 (33.3%)	

PCA-BAVM, posterior cerebral artery-brain arteriovenous malformation.

the ruptured ones (11–13). The main aim of EVT is securing the weak structures. A targeted EVT aimed at the ruptured part of the nidus can reduce the risk of early rebleeding (6). As illustrated in **Figure 5**, embolization of the aneurysm is in priority.

For BAVMs, the SM grading system is most popular for predicting surgical outcome. It categorizes the BAVMs into five grades based on size, existence of deep venous drainage, and eloquence of location (14). In 2010, a supplementary novel Lawton–Young grading system was proposed to predict the treatment outcomes of BAVMs, which is a better predictor of neurological outcome after BAVMs surgery and supplemented the SM system greatly (15).

To our knowledge, no previous study has specifically studied the angioarchitecture of PCA-BAVMs. Therefore, in this study, we classified the PCA-BAVMs into two types according to the blood supply and location. This classification is based on the segmentation of the PCA, which is a reasonable approach. Different types of PCA-BAVMs have different arterial supply, which directly determines the strategy of EVT.

In this study, 42 cases with PCA-BAVMs were analyzed. There were some differences between type I and type II PCA-BAVMs. Type I PCA-BAVMs are mainly supplied by the PchA, the treatment of which was mostly via the PchA. Because the PchA is small, the microcatheter tip can be wedged into a type I PCA-BAVM, with little reflux of liquid embolic material during EVT (**Figures 2**–**4**). The type II BAVMs are mainly supplied by the temporal and occipital branches of the PCA. During EVT, the liquid embolic material can easily reflux into the PCA trunk. The "pressure cooker" technique proved to be a useful measure (**Figures 8**, **9**). For cases with additional blood supply from the ACA, further EVT through the ACA can also be tried if EVT through the PCA is difficult or not satisfactory (**Figure 6**).

EVT is a reasonable option for the PCA-BAVMs. In this study, 97.5% (39/40) of the patients achieved a GOS score of 5 at the last follow-up. Only 2 (4.8%, 2/42) patients experienced intraoperative or postoperative bleeding. Intraoperative bleeding might be caused by the acute increase of intravascular pressure during Onyx casting. In case of intraoperative bleeding, continuous casting of Onyx till obliteration of the bleeding site is the best option. The cause of postoperative bleeding is complex, including early venous occlusion or arterial rupture during microcatheter retrieval. The patient illustrated in **Figure 7** was admitted with an unruptured PCA-BAVM. The intraoperative process was unremarkable. The draining veins were patent after embolization. However, the patient experienced sudden onset of headache 4 h after EVT. Head CT revealed IVH. We speculated that the postoperative bleeding might be caused by increased pressure in the vessels near the embolized nidus due to blood flow redistribution.

In addition, we also compared the angiographic and clinical characteristics between the patients with type I and type II PCA-BAVMs. No statistical significance was noted between the two groups in age, rupture before admission, SM grade, extent of obliteration, and prognosis. Type I PCA-BAVMs were prone to have deep venous drainage (**Tables 2**, **3**). Type Ia PCA-BAVMs are the easiest type to treat due to the single blood supply. However, it becomes more difficult to treat for type Ib PCA-BAVMs due to the multiple sources of feeding arteries. Type II PCA-BAVMs are supplied by the distal branches of the PCA and EVT is relatively easy. However, care should be taken during EVT to prevent the liquid embolic material reflux into the proximal PCA trunk. Therefore, our classification of PCA-BAVMs based on the feeding arteries can effectively guide the EVT.

LIMITATIONS

This is a retrospective study with limited sample size, and the conclusion in this study should be cautiously interpreted. The rate of angiographic follow-up in this study is low, which makes it difficult to evaluate the long-term efficacy of EVT. As EVT was given priority for the management of BAVMs in our center, comparison with other treatments could not be performed in this study.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the ethics committee of The First Hospital of

Jilin University. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

AUTHOR CONTRIBUTIONS

JY: contributed to the conception and design of the manuscript and critically revised the manuscript. KH and CL: wrote the manuscript. CL and HS: collected the medical records of the patients. All authors approved the final version of this manuscript.

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Standard vs. Modified Antiplatelet Therapy Based on Thromboelastography With Platelet Mapping for Preventing Bleeding Events in Patients Undergoing Stent-Assisted Coil for a Ruptured Intracranial Aneurysm

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Background and Purpose: Stent-assisted coiling (SAC) of intracranial aneurysms is usually treated with antiplatelet therapy to reduce the risk of postoperative ischemic events. However, using the same antiplatelet therapy for all patients may increase the risk of bleeding in patients with aneurysmal subarachnoid hemorrhage (aSAH). Thromboelastography-platelet mapping (TEG-PM) measures platelet function, which reflects the effect of antiplatelet drugs. This study aimed to evaluate the benefits of individualized antiplatelet regimens based on TEG-PM parameters for patients with aSAH who underwent SAC.

Methods: We retrospectively included patients with aSAH who treated with SAC during the period from June 2012 to December 2019. Patients were divided into two groups: patients whose antiplatelet therapy adjusted by TEG-PM parameters after surgery (adjustment group) and patients who were treated with standard dual antiplatelet therapy without TEG-PM test (control group). The occurrence of major/minor bleeding events, major/minor thromboembolic events, and favorable outcome (modified Rankin scale <3) were compared in both groups during hospitalization.

Results: Of 188 aSAH patients considered for this study, 145 met the criteria for inclusion and were included in the analysis (93 patients in the adjustment group and 52 patients in the control group). The risks of minor bleeding events (1.1 vs. 9.6%, $p = 0.02$) were significantly lower in patients in the adjustment group. However, there was no significant difference in the rate of major bleeding events at discharge between adjustment and control groups ($p = 0.35$). The rates of thromboembolic events and favorable outcome were similar in both groups (22.6 vs. 28.8%, $p = 0.42$, 95.7 vs. 96.2%, $p = 1.00$). Furthermore, the minor thromboembolic events rate was significantly lower in the patients treated with treatment plan C ($p = 0.02$ for treatment plan C vs. treatment A, $p = 0.03$ for treatment plan C vs. treatment plan B). However, there was no significant

difference in the rate of other mentioned above complications and favorable outcomes among patients treated with different antiplatelet regimens.

Conclusions: Individualized antiplatelet therapy based on TEG-PM parameters might positively impact the bleeding risk of aSAH patients, without increasing the risk for clinically relevant thromboembolic events.

Keywords: aneurysmal subarachnoid hemorrhage, thromboelastography, platelet function, stent-assisted coiling, antiplatelet therapy

INTRODUCTION

Stent treatment technology has emerged as a viable and preferable method for wide-necked, complex-shaped, and dissecting intracranial aneurysms (1). However, compared with coil embolization, stent-assisted coiling (SAC) of intracranial aneurysms has a higher incidence of perioperative complications and mortality (2, 3). Dual antiplatelet therapy (100 mg of aspirin and 75 mg of clopidogrel daily) has been wildly used to decrease the incidence of thromboembolic events in intracranial aneurysms treated with stents (4–6). Nevertheless, dual antiplatelet therapy also increased the likelihood of postoperative bleeding events (7). Especially for patients with aneurysmal subarachnoid hemorrhage (aSAH), once intracranial hemorrhage occurs, the prognosis will be severely deteriorated.

Thromboelastography-platelet mapping (TEG-PM) is a measure derived from thromboelastography (TEG) for detecting platelet function in the form of platelet inhibition rate, which can indirectly reflect the platelet aggregation function and can benefit to prevent and reduce thromboembolic events after embolization. Therefore, it is widely used in most hospitals around the world to evaluate the efficacy of dual antiplatelet agents before SAC for intracranial aneurysm (8). Current research have focused on the relationship between TEG-PM parameters and thromboembolic or bleeding events after SAC (9–12). Some studies (11–14) suggested that the parameter of TEG-PM could be identified as parameters for tailor-individualized antiplatelet treatment designed to reduce ischemic events and bleeding. However, there is little consensus regarding how to adjust the antiplatelet regiment according to TEG-PM parameters. The benefits of individualized antiplatelet therapy have not been well-investigated.

The purpose of this study is to explore whether the tailor reduction of the dose of antiplatelet drugs based on TEG-PM parameters can reduce the incidence of bleeding events after SAC without increasing the rate of thromboembolic events and whether it will affect the prognosis of patients.

METHODS

This study was a single-institution retrospective study conducted at The First Affiliated Hospital of Chongqing Medical University. The STROBE statement on cohort studies guided study design and manuscript organization. We retrospectively recruited patients with aSAH who underwent SAC between June 2012 and December 2019. Patients who were treated with an antiplatelet regimen based on TEG-PM parameters due to SAC treatment were included into an "adjustment" group. A "control" group consisting of aSAH patients who underwent SAC without TEG-PM test during the period from June 2012 to January 2015 was added to the final analysis (**Figure 1**). A further subgroup analysis was performed within the adjustment group, comparing patients with different antiplatelet therapy. The baseline demographic information, including age, sex, Hunt-Hess grades, modified Rankin scale (mRS) score, procedure time, cerebrovascular risk factors (smoking and drinking history, diabetes, hypertension), aneurysm characteristics (location, size), multiple aneurysms, stent types, and platelet count were recorded. The initial clinical condition of the patients was graded by Hunt-Hess grade, and we only included 1–3 grades into the analysis. This study was approved by the institutional review board of The Frist Affiliated Hospital of Chongqing Medical University, in accordance with the Declaration of Helsinki. Due to the retrospective nature of the study, informed consent was waived.

Inclusion/Exclusion Criteria

Inclusion criteria were as follows: (1) Patients (ages $\geq$18 years) with aSAH were treated with SAC were included; (2) have complete perioperative-related imaging and laboratory data; and (3) Initial Hunt-Hess grades were grades I–III. Exclusion criteria included the following: (1) treatment with anticoagulants, thrombolytic agents, and other antiplatelet drugs before admission; (2) severe cardiovascular disease or cerebral ischemic stroke; (3) severe hepatic or renal dysfunction, malignant disease, chronic inflammatory disease, significant coagulopathy, or an infectious condition at study entry; (4) combined with other cerebral diseases; and (5) recurrent aneurysm which is treated with coils only or stent.

Management Protocol

A standardized protocol was strictly followed in all cases. All cases were treated according to the standardized aSAH treatment protocol (15) consisting of absolute bed rest until endovascular treatment, strict blood pressure control, intravenous administration of hemostatic agents and nimodipine, and regular assessment of clinical status. All patients were treated with 300 mg of aspirin and 300 mg of clopidogrel at least 2 h before the procedure. The endovascular procedure was performed under general anesthesia, and a bolus of heparin was administered using 3,000 IU, then 1,000 IU every hour. The Enterprise (Codman Neurovascular), Solitaire AB neurovascular remodeling device (eV3, Inc.),

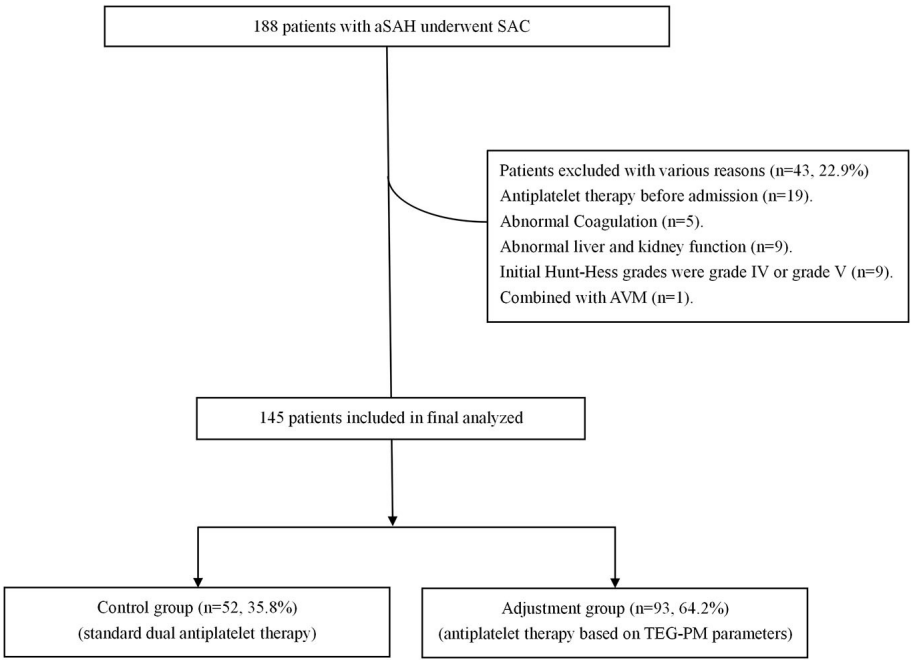

FIGURE 1 | Abbreviated flowchart for patients included in this study based on the inclusion and exclusion criteria. aSAH, aneurysmal subarachnoid hemorrhage; SAC, stent-assisted coiling; AVM, arteriovenous malformations.

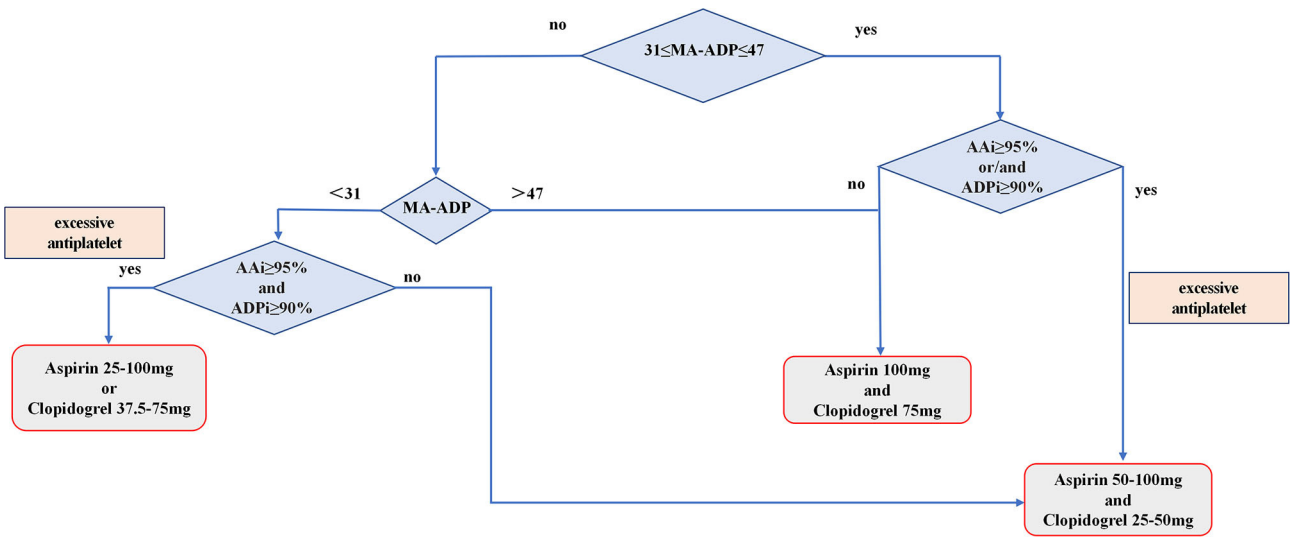

FIGURE 2 | Flowchart showing the process of patients receive individualize antiplatelet therapy based on TEG-PM parameters.

LVIS (MicroVention Terumo, Tustin, California, USA), and LEO stents (Balt, Montmorency, France) stents were used to treat aneurysms. All patients discontinued heparin on day 3 postoperatively, and patients in the adjustment group would be treated with the antiplatelet regimen based on TEG-PM parameters. Patients in the control group would be treated with standard dual antiplatelet therapy (aspirin 100 mg and clopidogrel 75 mg).

Laboratory Examination

Patients in the adjustment group were drawn blood samples for TEG and TEG-PM testing on the 3rd day after surgery draws blood. Blood samples (3–4 ml) were drawn from a single clean puncture of a forearm vein and collected in a 4-ml test tube (Becton-Dickinson) containing lithium heparin.

The platelet inhibition was tested using a TEG-PM analyzer (Haemoscope, Model 5000). Adenosine diphosphate (ADP)

agonists and arachidonic acid (AA) were added to measure the platelet inhibition of the P2Y12 receptor and cyclooxygenase pathways. Inhibition rate (%) is equal to (AA- or ADP-induced clot strength-fibrin clot strength)/(thrombin-induced clot strength-fibrin clot strength) × 100% (16). The percentage of platelet inhibition in response to ADP (ADPi) and MA-ADP (ADP-induced clot strength) were used to measure the response to clopidogrel. The percentage of platelet inhibition in response to AA (AAi) was used to measure aspirin's response.

The following TEG parameters were recorded: the time from the start of the sample until amplitude of clot formation reaches 2 mm (*R*, min); the time elapsed from *R* until 20-mm amplitude is achieved (*K*, min); the time to reach maximum speed of initial clot formation (α angle, deg); maximum clot strength (MA, mm); percent of clot lysis 30 min after MA (EPL); and percent of amplitude decay 30 min after MA (LY30).

Antiplatelet Regimen

Patients in the control group were treated with standard dual antiplatelet after surgery due to the TEG-PM test has not been applied in our department between June 2012 and January 2015. Patients in the adjustment group were treated with an antiplatelet regimen adjusted according to TEG-PM parameters on the 3rd day after surgery. The specific process of individualized antiplatelet therapy is shown in **Figure 2** which includes three antiplatelet treatment options, as follows: (1) When MA-ADP <31, if AAi ≥ 95% and ADPi ≥ 90%, choose treatment plan A (aspirin, 25–100 mg or clopidogrel, 37.5–75 mg), otherwise use treatment plan C (aspirin, 50–100 mg and clopidogrel 25–50 mg); (2) When 31 ≤ MA-ADP ≤47, if AAi ≥ 95%, and/or ADPi ≥ 90%, use treatment plan C (aspirin, 50–100 mg and clopidogrel 25–50 mg); otherwise, use treatment plan B (aspirin, 100 mg and clopidogrel, 75 mg); (3) When MA-ADP > 47, use treatment plan B (aspirin, 100 mg and clopidogrel, 75 mg); and (4) If the patient's treatment plan is A or C, the specific antiplatelet drug dose is based on the value of AAi, ADPi, and MA-ADP values. The higher the value of AAi and ADPi, the lower the dose of antiplatelet drugs. The lower the value of MA-ADP, the lower the dose of antiplatelet drugs. During hospitalization, if patients have symptoms of bleeding or ischemia, the dose of antiplatelet drugs should be increased or decreased according to the signs. All patients in the adjustment group adjusted antiplatelet therapy based on TEG-PM parameters again when they were discharged from the hospital and 6 weeks after discharge. If the patient has no symptoms of bleeding or ischemia, the adjusted antiplatelet drug regimen will be maintained until 6 months. The total duration of antiplatelet therapy for patients in this study was 6 months.

Complications and Outcomes

Trained neurosurgeon reviewed all follow-up CT/MRI scans during the period of antiplatelet therapy (4 days after surgery to the time of discharge) for any clinical information about the occurrence of cerebral infarctions and new intracranial bleedings. Minor bleeding was defined as any extracranial bleeding (gastrointestinal hemorrhage, ecchymosis, epistaxis, and hematuria) documented during antiplatelet therapy that does not cause clinical deterioration. Major bleeding was defined as any new hemorrhage that led to clinical deterioration. Accordingly, a minor thromboembolic event was defined as new asymptomatic cerebral infarction in the stent vessel area, which was diagnosed by diffusion-weighted imaging (DWI). Major thromboembolic events included newly developed transient ischemic attack (TIA) or symptomatic ischemic infarctions. We followed up with patients in the adjustment group via hospital medical records or telephone interviews in July 2020, and the median follow-up time was 11 (7, 19) months. Functional outcome was evaluated at discharge and at least 6 months after discharge. Due to the large time span of patients in the control group and the adjustment group, this study only followed up patients in the adjustment group. Favorable functional outcome was defined as mRS < 3.

TABLE 1 | Baseline characteristics of the patients in the adjustment and control groups.

Variable (No. %)	Adjustment ($n = 93$)	Control ($n = 52$)	p-values
Age (mean ± *SD*, years)	53 ± 11	54 ± 10	0.77
Female sex	61 (65.6)	38 (73.1)	0.45
Hunt-Hess grade			0.24
Grade I	15 (16.1)	6 (11.5)	
Grade II	74 (79.6)	40 (76.9)	
Grade III	4 (4.3)	6 (11.5)	
Procedure time (IQR, min)	120 (95–140)	120 (102–160)	0.87
Medical history			
Hypertension	41 (44.1)	23 (44.2)	1.00
Diabetes mellitus	9 (9.7)	3 (5.8)	0.53
Smoking	24 (25.8)	14 (26.9)	1.00
Drinking	15 (16.1)	8 (15.4)	1.00
Anterior circulation aneurysm	81 (87.1)	46 (88.5)	1.00
Aneurysm size ≥10 mm	14 (15.1)	6 (11.5)	0.62
Multiple aneurysms	24 (25.8)	7 (13.5)	0.09
Stent types			0.14
Enterprise	52 (55.9)	24 (46.2)	
LVIS	8 (8.6)	4 (7.7)	
Solitaire AB	30 (32.3)	17 (32.7)	
LEO	3 (3.2)	7 (13.5)	
PLT[a] [k/μl (Med, IQR)]	196 (165–236)	216 (169–277)	0.08

SD, standard deviation; PLT, platelet; Med, median; IQR, interquartile range.
[a] *Postprocedure.*

Statistical Analysis

Data are presented as mean SD or expressed in terms of frequency and percentage. Categorical variables were analyzed using the Chi-square test or, if applicable, with the Fisher exact test. Continuous variables were analyzed using the Student's *t*-test for normally distributed and the Mann–Whitney *U*-test for non-normally distributed data. $p < 0.05$ was considered statistically significant. The statistical analysis was performed by SPSS 23.0 software (SPSS Inc., Chicago, Illinois, USA).

TABLE 2 | Baseline characteristics of the patients who underwent SAC with individualized antiplatelet therapy.

Variable (No. %)	Treatment plan A	Treatment plan B	Treatment plan C	*p*-values		
	ASA, 25–100 mg or CLOP, 37.5–75 mg	ASA, 100 mg and CLOP, 75 mg	ASA, 50–100 mg and CLOP, 25–50 mg	A vs. B	A vs. C	C vs. B
Number of patients	49 (52.7)	28 (30.1)	16 (17.2)			
Age (mean ± *SD*, years)	52 ± 11	57 ± 12	51 ± 11	0.07	0.68	0.10
Female sex	15 (30.6)	8 (28.6)	9 (56.3)	1.00	0.08	0.10
Hunt-Hess grade				0.89	1.00	1.00
Grade I	9 (18.4)	4 (14.3)	2 (12.5)			
Grade II	38 (77.6)	23 (82.1)	13 (81.3)			
Grade III	2 (4.1)	1 (3.6)	1 (6.3)			
Procedure time (IQR, min)	125 (100-140)	120 (91-143)	120 (96-157)	0.45	0.51	0.83
Medical history						
Hypertension	19 (38.8)	17 (60.7)	5 (31.3)	0.09	0.73	0.11
Diabetes mellitus	2 (4.1)	5 (17.9)	2 (12.5)	0.09	0.25	1.00
Smoking	11 (22.4)	6 (21.4)	7 (43.8)	1.00	0.11	0.17
Drinking	7 (14.3)	4 (14.3)	4 (25.0)	1.00	0.44	0.43
Anterior circulation aneurysm	44 (89.8)	22 (78.6)	15 (93.8)	0.19	1.00	0.39
Aneurysm size ≥10 mm	10 (20.4)	4 (14.3)	0	0.55	0.05	0.28
Multiple aneurysms	9 (18.4)	8 (28.6)	7 (43.8)	0.39	0.05	0.34
Stent types				0.81	0.43	0.13
Enterprise	26 (53.1)	18 (64.3)	8 (50.0)			
LVIS	5 (10.2)	3 (10.7)	0			
Solitaire AB	16 (32.7)	6 (21.4)	8 (50.0)			
LEO	2 (4.1)	1 (3.9)	0			
Post-procedure laboratory test						
PLT [k/μl (Med, IQR)]	196 (164–232)	193 (168–230)	205 (159–269)	0.88	0.72	0.75
R [min (Med, IQR)]	5.6 (4.7–6.2)	5.6 (5.0–6.7)	4.8 (4.2–5.7)	0.88	0.21	0.34
K [min (Med, IQR)]	1.3 (1.2–1.6)	1.3 (1.2–1.5)	1.2 (1.0–1.3)	0.91	0.17	0.39
α-Angle [deg (Med, IQR)]	70.6 (67.0–72.9)	69.9 (67.7–71.9)	73.2 (67.9–74.5)	0.53	0.13	0.11
MA [mm (Med, IQR)]	67.8 (64.9–71.0)	67.6 (63.4–70.8)	68.7 (64.4–71.2)	0.98	0.72	0.34
EPL [% (Med, IQR)]	0.9 (0.2–1.8)	1.0 (0.1–3.3)	0.8 (0.1–3.9)	0.88	0.82	0.75
LY30 [% (Med, IQR)]	0.8 (0.1–1.7)	0.5 (0.1–3.0)	0.7 (0.1–2.2)	0.55	0.94	0.58

SAC, stent-assisted coiling; SD, standard deviation; vs., versus; PLT, platelet; Med, median; IQR, interquartile range; R, reaction time to clot formation; K, clotting time until 20-mm amplitude is achieved; α-Angle, time to reach maximum speed of initial clot formation; MA, maximum amplitude; EPL, percent of clot lysis 30 min after MA; LY30, percent of amplitude decay 30 min after MA.

RESULTS

Population

Of 188 aSAH patients enrolled for this study, 145 endovascularly treated individuals (77.5%) met the inclusion criteria and were included in the final analysis (see **Figure 1**). The mean age of these patients at admission was 54 ± 11 years. The majority (99, 68.3%) were females. One hundred and seventy-six stents were placed in patients. **Table 1** shows the baseline characteristics of both adjustment and control groups. There are no statistically significant differences between the groups for age, sex, procedure time, Hunt-Hess grade, medical history, aneurysm location and size, multiple aneurysms, platelet count, and stent types (see **Table 1**).

There was also no statistical difference in baseline characteristics between patients with different antiplatelet treatment plans in the adjustment group (see **Table 2**). Six (6.5%) patients were lost to follow-up in the adjustment group. The proportion of different antiplatelet treatment plan in the adjustment group is as follows: treatment plan A (49, 52.7%, aspirin, 25–100 mg or clopidogrel, 37.5–75 mg); treatment plan B (28, 30.1%, aspirin, 100 mg and clopidogrel, 75 mg); and treatment plan C (16, 17.2%, aspirin 50–100 mg and clopidogrel, 25–50 mg).

Antiplatelet Therapy and Bleeding Events

The adjustment group had a significantly decreased incidence of minor bleeding events compared with the control group (1.1 vs. 9.6%, $p = 0.02$). But there was no significant difference in the rate of major bleeding events at discharge between adjustment and control groups ($p = 0.35$, see **Table 3**). One patient in the adjustment group experienced gastrointestinal bleeding 11 days after surgery. After adjusting the antiplatelet

regimen to aspirin 100 mg, the patient did not show any bleeding symptoms during hospitalization. There were six bleeding patients in the control group, including intracranial hemorrhage (1, 1.9%), gastrointestinal bleeding (1, 1.9%), hematuria (2, 3.8%), and ecchymosis (2, 3.8%). After symptomatic treatment, the bleeding symptoms disappeared and the patient with intracranial hemorrhage did not develop neurological deficits. Telephone follow-up found that four patients in the adjustment group had intracranial hemorrhage due to improper blood pressure control, all of which occurred after being transferred to a local hospital for treatment. The rate of minor/major bleeding events at discharge and major bleeding events during follow-up was compared among the patients with a different treatment plan within the adjustment group, and we find no significant difference among them (see **Table 4**).

Antiplatelet Therapy and Thromboembolic Events

There was no significant difference in the rate of minor/major thromboembolic events at discharge between adjustment and control groups ($p = 0.41$ for minor, $p = 1.00$ for major, see **Table 3**). One patient in the adjustment group developed TIA during antiplatelet therapy. After adjusting the patient's antiplatelet regimen from aspirin 100 mg to aspirin 100 mg and clopidogrel 75 mg, the ischemic symptoms did not recur. No patients in the control group developed major thromboembolic events. The rate of minor/major thromboembolic events at discharge and major thromboembolic events during follow-up was compared among the patients with a different treatment plan within the adjustment group, and we find that the minor thromboembolic events rate was significantly lower in the patients treated with treatment plan C ($p = 0.02$ for treatment plan C vs. treatment A, $p = 0.03$ for treatment plan C vs. treatment plan B, see **Table 4**).

Antiplatelet Therapy and Outcome

The rate of favorable outcomes at discharge in the adjustment group was not statistically different from that in the control group ($p = 1.00$ at discharge, see **Table 3**). Furthermore, we find that there is no significant difference in the rate of favorable outcomes at discharge or least 6 months after discharge among patients with a different antiplatelet treatment plan within the adjustment group ($p = 0.13$, $p = 0.55$ for treatment plan A vs. treatment B, $p = 1.00$, $p = 1.00$ for treatment plan A vs. treatment C, $p = 0.29$, $p = 0.52$ for treatment plan C vs. treatment B, see **Table 4**).

DISCUSSION

In this retrospective cohort study, we analyzed the benefits and risks associated with the tailor reduction of the dose of antiplatelet drugs based on TEG-PM parameters in patients with aSAH after SAC. In addition, we find that the individualized antiplatelet therapy based on TEG-PM parameters could reduce the bleeding risks of patients with aSAH after SAC without increasing the rates of thromboembolic events and unfavorable outcomes.

TABLE 3 | Complications and favorable outcomes in patients between adjustment and control groups.

Variable (No. %)	Adjustment ($n = 93$)	Control ($n = 52$)	p-values
Bleeding events			
Minor at discharge	1 (1.1)	5 (9.6)	0.02
Major at discharge	0	1 (1.9)	0.35
Thromboembolic events			
Minor at discharge	20 (21.5)	15 (28.8)	0.41
Major at discharge	1 (1.1)	0	1.00
Favorable outcomes			
mRS <3 at discharge	89 (95.7)	50 (96.2)	1.00

mRS, modified Rankin scale.

TEG-PM Parameters and Antiplatelet Therapy

Current studies show that ADPi, AAi, and MA-ADP values can predict the risk of ischemic events after SAC of intracranial aneurysms. Lower ADPi, AAi, and higher MA-ADP values and thromboembolic events after SAC of intracranial aneurysms are related. On the other hand, a higher ADPi value can predict bleeding events after SAC of intracranial aneurysms (9, 12, 13). However, the definition of TEG-PM parameter safety ranges is different in different studies. The results of the study by Ge et al. showed that the safe range of ADPi in patients after SAC of intracranial aneurysms is 29.45–55.4%, and the safe range of MA-ADP is <46.15, and they suggest that ADPi < 29.45% or MA-ADP > 46.15 need aggressive antiplatelet therapy (10). According to Wang et al. study, MA-ADP > 49.95 mm is the best cut-off value for predicting ischemic events after SAC of intracranial aneurysms (9). Moreover, many studies on percutaneous coronary intervention (PCI) was defined AAl < 50% and ADPi < 30% as resistance to aspirin and clopidogrel, respectively, and showed that resistance to aspirin and clopidogrel is associated with the high thromboembolic risk of the patients after PCI (17–20). However, thromboembolic events are undoubtedly multifactorial, and increasing the dose of antiplatelet drugs for patients with aSAH due to the "resistance" is more likely to increase the risk of bleeding after endovascular treatment. In this study, given that there is no consensus on the definition of the safety range of TEG-PM parameters, and the definition of resistance is affected by multiple factors, we tailored to reduce the dose of antiplatelet drugs for patients with excessive antiplatelet indicated by the TEG-PM parameters.

Individualized Antiplatelet Therapy Impact on Complications and Outcome

Previous large-scale cardiovascular prospective clinical studies (ANTARCTIC, ARCTIC, GRAVITAS) (21–23) have shown that individualized antiplatelet therapy which was based on the results of VerifyNow platelet function testing cannot reduce cardiovascular mortality and long-term ischemia in patients after PCI. However, given the characteristics of shorter use time of antiplatelet drugs in neuro-interventional therapy and a higher risk of postoperative bleeding in

TABLE 4 | Complications and favorable outcomes in patients who underwent SAC with individualized antiplatelet therapy.

Variable (No. %)	Treatment plan A	Treatment plan B	Treatment plan C	*P*-values		
	ASA, 25–100 mg or CLOP, 37.5–75 mg	ASA, 100 mg and CLOP, 75 mg	ASA 50–100 mg and CLOP, 25–50 mg	A vs. B	A vs. C	C vs. B
Number of patients	49 (52.7)	28 (30.1)	16 (17.2)			
Bleeding events						
Minor at discharge	0	1 (3.5)	0	0.36	-	1.00
Major at discharge	0	0	0	-	-	-
Major during follow-up	1 (2.0)	2 (7.1)	1 (6.3)	0.55	0.43	1.00
Thromboembolic events						
Minor at discharge	13 (26.5)	7 (25.0)	0	1.00	0.02	0.03
Major at discharge	1 (2.0)	0	0	1.00	1.00	-
Major during follow-up	0	0	0	-	-	-
Favorable outcomes						
mRS < 3 at discharge	48 (2.0)	25 (89.3)	16 (100)	0.13	1.00	0.29
mRS < 3 at least 6 months[a]	42 (97.7)	26 (92.9)	16 (100)	0.55	1.00	0.52

SAC, stent-assisted coiling; vs, versus; mRS, modified Rankin scale; ASA, aspirin; CLOP, clopidogrel.
[a] *87 patients were followed up at least 6 months after discharge.*

patients with ruptured aneurysms, TEG-PM parameters are used for adjusting antiplatelet drugs to reduce complications after SAC of intracranial aneurysms deserves further study. Some studies suggested that patients who underwent SAC of intracranial aneurysms have been associated with perioperative ICH, and some studies (24–26) indicate that P2Y12 receptor over-inhibition may play a role. The Japanese Registry of Neuroendovascular Therapy (JR-NET) which was a nationwide survey from January 2005 to December 2009 found that there was a significant decreased rate of ischemic complications (4.2–2.1%) but a significantly increased rate of intracranial hemorrhagic complications (2.1–5.3%), as well as a significantly increased rate in death or severe disability (1.5–2.1%) for those patients who receive endovascular treatment with antiplatelet therapy (27). Congruently, Darkwah et al. also reported that there was an increased risk for major bleeding events in aneurysmal subarachnoid hemorrhage patients with dual antiplatelet therapy, as compared with aspirin monotherapy (7). In our study, the adjustment group's bleeding rate was significantly lower than that of the control group which consistent with the findings of Darkwah et al. Only one patient in the adjustment group had a bleeding event (gastrointestinal bleeding) on the 11th day after surgery whose AAi was 12.4%, ADPi was 69.5%, and MA-ADP value was 35.4. Although this TEG-PM parameter does not indicate excessive antiplatelet, bleeding events still occurred. The cause of bleeding events may be that TEG parameters can only represent the patient's platelet function during a period, suggesting that TEG-PM needs to be reviewed in time to assess changes in platelet function. McTaggart et al. (28) also use TEG-PM parameters to tailor dual-antiplatelet therapy in patients undergoing treatment of intracranial aneurysms with the Pipeline embolization device and followed up for 1 year. They found that none of the 31 patients had bleeding events. However, since the study by McTaggart et al. is a descriptive observational study and the sample size is small, further research is needed to use TEG-PM as a tool to identify the subset of patients who are at highest risk for bleeding events.

On the other hand, increasing the dose of antiplatelet drugs to reduce the risk of thromboembolic in patients with SAC of intracranial aneurysms needs to be further studied. Although McTaggart et al. (28) changed the clopidogrel hypo-responders' antiplatelet regimen, the thromboembolic risk for patients who underwent pipeline embolization did not eliminate. In their study, clopidogrel hypo-responders were either reloaded with clopidogrel 600 mg before the procedure or changed over to prasugrel before the procedure or the next day using the IIb/IIIa antagonist Integrilin as an effective antiplatelet bridge. Our study showed that despite the reduced dose of antiplatelet drugs, the incidence of minor/major thromboembolic events in the adjustment group was not higher than in the control group. Furthermore, the incidence of minor ischemic events in patients with treatment plan C was also significantly lower than that of patients with treatment plan A or B. The results mentioned above suggest that the preventive effect of increasing antiplatelet drugs on minor/major thromboembolic events needs further study. The results of Price et al. (29) showed that increasing the dose of antiplatelet drugs in patients with platelet hyperresponsiveness after PCI failed to reduce postoperative cardiogenic mortality and the incidence of non-fatal myocardial infarction or stent thrombosis which also support this view.

Besides, the incidence of TIA in the adjustment group of this study (1.1%; 1/93) and the incidence of minor thromboembolic events (21.5%; 20/93) were lower than the reported incidence in the literature [1.9% (30) for TIA, 43% (31) for minor thromboembolic events], which also showed that targeting to reduce the doses of antiplatelet drugs in patients with high bleeding risk did not lead to an increase in the incidence of ischemic events.

Finally, there is no significant difference between adjustment and control groups with regard to favorable outcomes at

discharge. This finding is in line with several previous publications reporting thromboembolic events are not an important risk factor for poor prognosis in aSAH patients treated with SAC of intracranial aneurysms (32, 33). Therefore, the primary goal of individualized antiplatelet therapy based on TEG-PM parameters after SAC of intracranial aneurysms should be to identify people at high risk of bleeding and reduce the dose of antiplatelet drugs to reduce the risk of bleeding.

CONCLUSION

Individualized antiplatelet therapy based on TEG-PM parameters might positively impact the bleeding risk of aSAH patients, without increasing the risk for clinically relevant thromboembolic events. However, our data underline the need for a prospective randomized trial for a definite safety range of TEG-PM parameters in individuals with aSAH.

LIMITATIONS

There are some limitations to our study. First, we included only the patients whose initial Hunt-Hess grades were grades I–III. Therefore, our results and conclusions on the benefits of individualized antiplatelet therapy based on TEG-PM parameters after SAC of intracranial aneurysms cannot be generalized on aSAH patients whose initial Hunt-Hess grades were grades IV–V. Second, the dynamic of ADPi, AAi, and MA-ADP values during follow-up was lacking due to our retrospective design. Moreover, 6.5% of patients in the adjustment group were lost to follow-up, and it cannot be excluded that some of them could have been dead for cerebrovascular events. Last, this was a retrospective study with a small sample size, so further studies are required to support our findings.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the institutional review board of The First Affiliated Hospital of Chongqing Medical University. The ethics committee waived the requirement of written informed consent for participation.

AUTHOR CONTRIBUTIONS

YL: conception, collection of data, interpretation of data, and drafting the work. XZ, ZG, JZ, RX, and ZH: collection of data and interpretation of data. XS: conception and revising the work critically for important intellectual content. All authors contributed to the article and approved the submitted version.

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Endovascular Treatment of Ruptured Wide-Necked Anterior Communicating Artery Aneurysms Using a Low-Profile Visualized Intraluminal Support (LVIS) Device

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Objective: To evaluate the safety and efficacy of low-profile visualized intraluminal support (LVIS) stent-assisted coiling for the treatment of ruptured wide-necked anterior communicating artery (ACoA) aneurysms.

Methods: The clinical and angiographic data of 31 acutely ruptured wide-necked ACoA aneurysms treated with LVIS stent-assisted coiling between January 2014 and December 2018 were retrospectively reviewed.

Results: All stents were successfully deployed. The immediate angiographic results were modified Raymond-Roy class I in 27 cases, modified Raymond-Roy class II in 2 cases, and modified Raymond-Roy class IIIa in 2 cases. Intraoperative thrombosis and postoperative aneurysmal rebleeding occurred in one case each. Two patients (6.5%) who were admitted due to poor clinical grade conditions died during hospital admission as a result of initial bleeding. Angiographic follow-up (mean: 12.9 months) was performed for 26 patients, the results of which demonstrated that 25 aneurysms were completely occluded and one was class II. The last clinical follow-up (mean: 25.3 months) outcomes demonstrated that 27 patients had favorable clinical outcomes and two had poor clinical outcomes.

Conclusion: LVIS stent-assisted coiling for ruptured wide-necked ACoA aneurysms was safe and effective, with a relatively low rate of perioperative complications and a high rate of complete occlusion at follow-up.

Keywords: intracranial aneurysm, ruptured, anterior communicating artery, LVIS stents, safety, wide-necked aneurysms

INTRODUCTION

The anterior communicating artery (ACoA) is one of the most common sites of ruptured intracranial aneurysms (RIAs) (1, 2). Endovascular treatment has become an important approach to manage these lesions (3–7). However, endovascular coiling of ruptured wide-necked ACoA aneurysms is still technically challenging because of the small vessel diameter, very small size,

and accompanying hematoma. Our previous studies have shown that stent-assisted coiling achieved favorable outcomes in the treatment of ruptured wide-necked ACoA aneurysms (8, 9). Nevertheless, compared with a non-braided stent, whether the low-profile visualized intraluminal support (LVIS) device (MicroVention, Tustin, CA, USA), which is unsuitable for the Y-stent technique due to a small mesh, can be fully opened in the small-diameter vessel of the anterior communicating complex, and whether it can provide good protection to incorporating vessels is not well-reported. Therefore, we herein present a patient cohort with ruptured wide-necked ACoA aneurysms treated with LVIS stent-assisted coiling, in which we evaluated the safety and efficacy of this strategy.

MATERIALS AND METHODS

The local Institutional Review Board approved the present study protocol. The requirement for written informed consent was waived due to the retrospective nature of the study.

Patient Population and Selection

Between January 2014 and December 2018, 328 patients with 328 ruptured ACoA aneurysms were admitted to our institution. We excluded (a) aneurysms treated more than 3 days after the initial rupture; (b) aneurysms with traumatic, infectious, pseudo, fusiform, dissecting, and blood blister-like properties; (c) aneurysms treated by surgical clipping; and (d) those combined with other severe cerebral diseases (Arteriovenous Malformation, moyamoya, Dural arteriovenous fistulae, Carotid-Cavernous Fistula, tumor) that also required treatment. Finally, 31 patients with 31 ruptured wide-necked ACoA saccular aneurysms treated with LVIS stent-assisted coiling, and 241 ruptured ACoA aneurysms treated with other therapies, including 12 cases with laser-cut stent-assisted coiling, 34 with balloon-assisted coiling, and 195 with simple coiling, were included.

Endovascular Procedure

All procedures were performed with the patients under general anesthesia. A 6F guiding catheter was introduced through the femoral artery and placed in the distal internal carotid artery. Three-dimensional (3D) reconstructions of rotational digital subtraction angiography (DSA) were performed to obtain the morphology and size of the aneurysm and parent artery. Optimal working projections were obtained for coil packing and stent delivery after adequate assessment of the aneurysm size and dome projection, as well as the angle between the A1 and A2 segments and the tortuosity of the involved vasculature. The stent microcatheter (Headway 21; MicroVention, Tustin, California, USA) was delivered to the contralateral A2 or ipsilateral A2 segment of the anterior cerebral artery for stent deployment as appropriate. The Echelon-10 (Covidien/ev3; Irvine, California, USA) or Headway 17 (MicroVention, Tustin, California, USA) was navigated into the aneurysm sac. After the first coil was introduced, the stent was deployed and completely covered the aneurysm neck using the semi-jailing technique to ensure that the stent could be fully opened and apposed well across the aneurysm neck. The aneurysm was packed with more coils until aneurysm obliteration was considered adequate. For the cases scheduled for coiling only, bailout stenting was used to compress the coil into the aneurysm sac when the coil protruded into the parent artery.

Antiplatelet and Anticoagulation Therapy

Throughout the procedure, systemic heparinization was performed for all patients with an activated clotting time of 2–3 times that of the baseline. A loading dose of aspirin (300 mg) and clopidogrel (300 mg) was administered rectally immediately after the operator decided to deploy a stent. Glycoprotein IIb/IIIa inhibitor (tirofiban; Grand Pharma, Wuhan, China) was administered (5 μg/kg for 3 min) intravenously before stent deployment and was maintained at a rate of 0.075 μg/kg/min until 6 h after the loading dose of aspirin and clopidogrel. In the postoperative period, all patients continued to receive aspirin (100 mg daily) and clopidogrel (75 mg daily) for 6 weeks, followed by 100 mg of aspirin daily alone indefinitely.

Clinical and Angiographic Evaluation

All surviving patients were followed up through clinical evaluation or telephone interview at 3, 6, and 12 months, and once a year thereafter. The clinical outcomes at discharge and follow-up were evaluated using the modified Rankin Scale (mRS). Favorable clinical outcomes were defined as an mRS score of 0–2, and poor clinical outcomes were defined as an mRS score of 3–6.

The immediate embolization results and angiographic follow-up results were evaluated according to the modified Raymond-Roy classification. Postoperative angiographic follow-up was recommended for all surviving patients, including 3-month magnetic resonance angiography (MRA), 6-month DSA, and MRA or DSA yearly thereafter (10).

RESULTS

Patient Enrollment and Baseline Characteristics

Of the 31 patients, 12 (38.7%) were men and 19 (61.3%) were women. The patients' age ranged between 35 and 85 years (mean: 55.9 years). There were 19 (61.3%) aneurysms with superior projection, eight (25.8%) with inferior projection, three (9.7%) with anterior projection, and one (3.2%) with complex projection. Dysplasia of one A1 segment was encountered in nine (29.0%) patients. The aneurysm neck involved the ipsilateral A2 in 13 (41.9%) cases, the contralateral A1 in seven (22.6%), and bilateral A2 in 11 (35.5%).

Immediate Embolization Results and Peri-Procedure Complications

All LVIS stents were successfully implanted for the 31 ruptured wide-necked ACoA aneurysms (illustrative case shown in **Figure 1**). No stent displacement or migration occurred during the procedures. Bailout stenting was performed in two cases (6.5%). Immediate embolization results demonstrated that modified Raymond-Roy class I was achieved in 27 (87.1%) cases, modified Raymond class II in 2 (6.5%), and modified Raymond class IIIa in 2 cases (6.5%). T-configuration stent deployment was performed in two (6.5%) cases for bilateral A2 protection

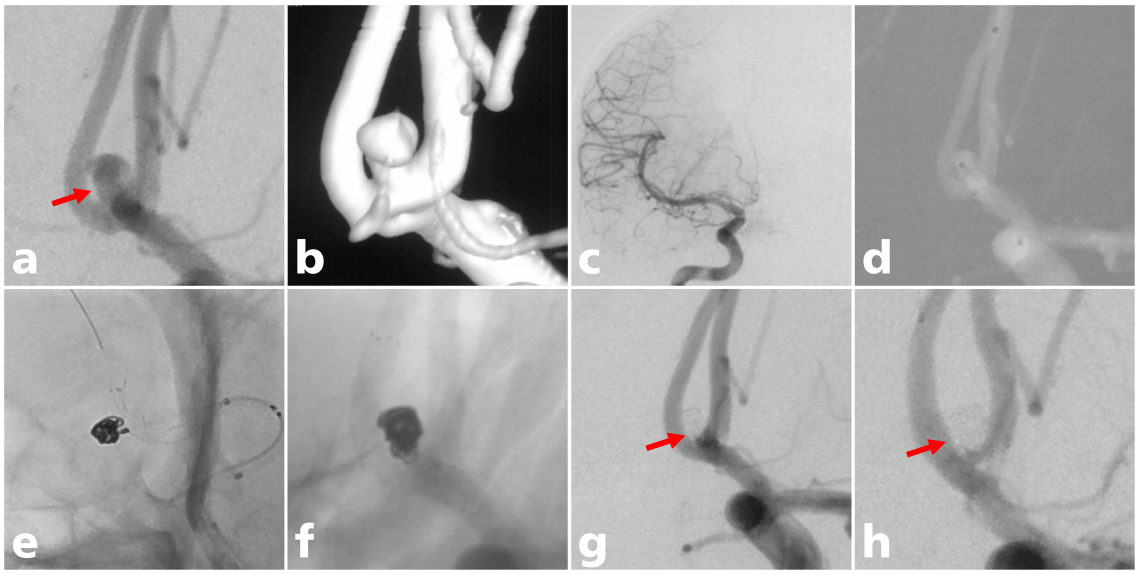

FIGURE 1 | A 38-year-old man with an ACoA aneurysm treated with LVIS stent-assisted coiling. **(a)** A wide-necked ACoA aneurysm in which the aneurysm neck mostly involved the ACoA (solid arrow); **(b)** three-dimensional reconstruction of the aneurysm; **(c)** aplasia of the right A1 segment; **(d)** the microcatheter was delivered into the aneurysm sac to place the coils; **(e)** the stent microcatheter was exchanged to the contralateral A2 segment for stent deployment; **(f)** the LVIS stent (3.5 mm × 15 mm) was successfully deployed using the semi-jailing technique; **(g)** complete occlusion was achieved under final view (solid arrow); **(h)** complete occlusion (modified Raymond-Roy class I) of the aneurysm at 12-month angiographic follow-up (solid arrow).

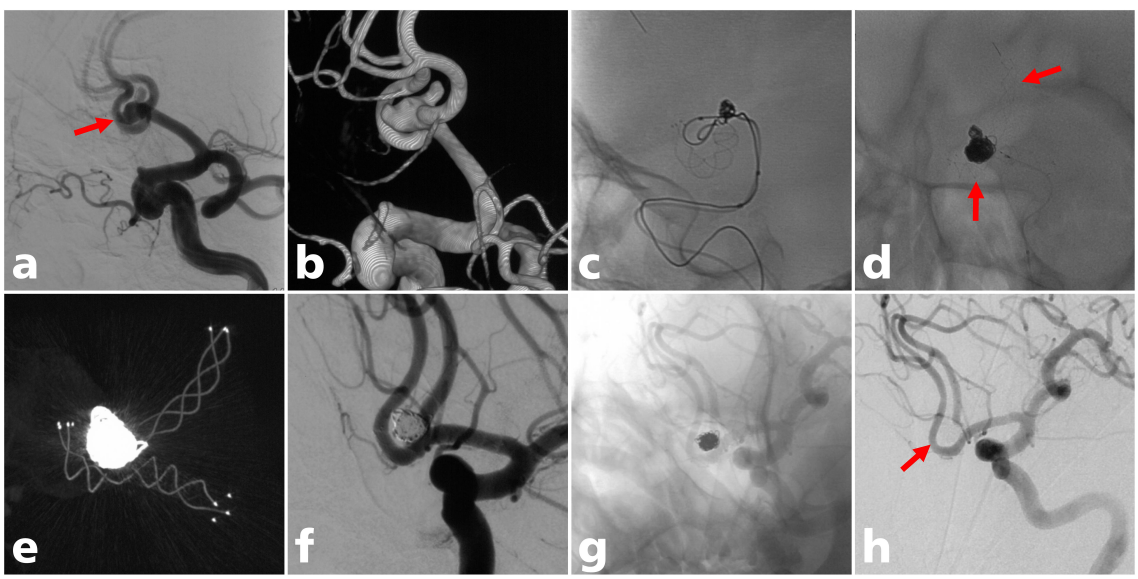

FIGURE 2 | A 60-year-old man with an ACoA aneurysm treated with LVIS stent-assisted coiling with a T configuration. **(a)** Angiogram showed a wide-neck ACoA aneurysm (solid arrow); **(b)** three-dimensional reconstruction of the aneurysm; **(c)** the LVIS stent (3.5 mm × 20 mm) was successfully deployed crossing the ACoA to the contralateral A2 segment; **(d)** the LVIS Jr stent (3.5 mm × 18 mm) was successfully deployed from the ipsilateral A2 to the A1 segment in a T configuration (solid arrow); **(e)** postoperative CT reconstruction showed that the two stents were complete opened **(f)** partial occlusion (modified Raymond-Roy class IIIa) was achieved under final view; **(g,h)** complete occlusion (modified Raymond-Roy class I) of the aneurysm at last angiographic follow-up (solid arrow).

(illustrative case shown in **Figure 2**). The stent was positioned across the ACoA from A1 to the contralateral A2 segment in 18 (58.1%) patients and to the ipsilateral A2 segment in 11 (35.5%) patients.

Intraoperative thrombosis was observed in one patient. When more coils were placed into the aneurysm sac to achieve greater aneurysm packing, one coil protruded into the parent artery and acute thrombosis occurred around the

coil loop. A loading dose (10 μg/kg for 3 min) of tirofiban was immediately administered proximal to the thrombus intra-arterially through the microcatheter; this allowed the operator to confirm that the blood flow was restored, and a maintenance dose of tirofiban (0.075 μg/kg/min) was subsequently administered intravenously for 6 h. Next, a Headway 21 microcatheter was navigated across the ACoA to the contralateral A2 segment, and as a bailout technique, an LVIS stent (3.5 mm × 15 mm) was deployed, covering the aneurysm neck to press the coil into the aneurysm sac. Fortunately, the thrombus disappeared quickly, and no neurological deficit occurred in this patient after the endovascular procedure. Postoperative aneurysmal rebleeding occurred in one patient; in this patient, the LVIS stent was deployed successfully and no complications were observed during the entire endovascular procedure. Immediate embolization results demonstrated that modified Raymond-Roy class I was achieved. However, the patient suffered cerebral hernia 1 day after the endovascular procedure. The computed tomography scan showed an increased hematoma in the right frontal lobe, and aneurysmal rebleeding was suspected. Decompressive craniotomy, right frontal lobe hematoma evacuation, and ACoA aneurysm wrapping were performed. The patient was dependent on an mRS score of 3 at discharge and recovered well with an mRS score of 1 at the last clinical follow-up.

Clinical Outcomes

At discharge, 26 (83.9%) patients were independent, with an mRS score of 0–2, three (9.7%) patients were dependent on an mRS score of 3–5, and two (6.5%) patients died due to severe cerebral vasospasm. The results of the last clinical follow-up (mean: 25.3 months) showed that 27 patients (93.1%) had favorable clinical outcomes, while the remaining two (6.9%) had poor clinical outcomes.

Angiographic Follow-Up Results

Angiographic follow-up (mean: 12.9 months) was performed for 26 patients, and the results indicated that 25 (96.1%, 25/26) aneurysms were completely occluded and one (3.9%, 1/26) was stable. No in-stent stenosis or parent artery occlusion were observed.

Outcomes for Other Therapies

With regard to the three other therapies, laser-cut stent-assisted coiling achieved modified Raymond-Roy class I in 10 (83.3%), while two (16.7%) developed perioperative complications, including one intraoperative rupture and one intraoperative thrombosis. In addition, 9/10 (90%) patients showed complete long-term occlusion, 34 patients had accepted balloon-assisted coiling, and 26 (76.5%) patients achieved immediate complete occlusion. Two patients developed perioperative complications. Of the 20 patients who underwent long-term follow-up, 17 achieved complete occlusion. Simple coiling was administered to 195 patients, resulting in 137 (70.3%) immediate complete occlusions and 12 complications. Long-term imaging follow-up showed 112 (79.4%) occlusions in 141 patients (**Table 1**).

DISCUSSION

This study is the first report of LVIS stent-assisted coiling for acutely ruptured wide-necked ACoA aneurysms. The results demonstrate procedure-related morbidity and mortality of 6.5% and 0, respectively, and 93.1% of the patients had favorable clinical outcomes at follow-up. The complete occlusion rate immediately after the procedure was 87.1%, which increased to 96.1% at the last angiographic follow-up. These results suggest that LVIS stent-assisted coiling for acutely ruptured wide-necked ACoA aneurysms could result in favorable clinical and angiographic outcomes, with a relatively low rate of procedure-related complications.

Stent-assisted coiling for intracranial wide-necked aneurysms has been well-documented. Stenting strategies, including the crossing technique, stenting after coiling (11), semi-jailing (12), Y-configuration (13), and T-configuration (14), vary according to the branch vessels involved in the aneurysm neck. As for ACoA, whether the contralateral A1 is dysplastic is an important factor to be considered when establishing the strategy for positioning the stent (15). For patients with dysplasia or no contralateral A1 segment, the stent was generally positioned crossing the ACoA from one A1 segment to the contralateral A2 segment to protect the patency of the ACoA and branch vessels. For patients without dysplasia of the contralateral A1 segment and in those without contralateral A2 involvement, the stent was regularly positioned from the ipsilateral A2 to the A1 segment. For patients in whom the bilateral A2 segment was involved in the aneurysm neck, the repeated "pull-push" technique was used to make the stent partially protruding into the aneurysm to provide better protection to the involved vessels. The LVIS stent has a small mesh (<1 mm), especially when placed into a small-diameter vessel; thus, a second stent deployment with Y-configuration crossing the small mesh was difficult, as was complete opening and good apposition to the vessel wall. Therefore, the Y-configuration technique is considered unsuitable for LVIS stents. However, for patients with an extremely wide aneurysm neck, it may be necessary to use the T-configuration technique to implant a stent with smaller outer diameters, such as a LVIS Junior stent (LVIS Jr), in the other vessel.

The ACoA complex often involves small-diameter vessels and a sharp angle between the A1 and A2 segments. One concern following stenting in such vessels is the risk of incomplete stent expansion, which is a common cause of periprocedural thromboembolic complications (16). Earlier studies have demonstrated that the LVIS stent has a higher likelihood of incomplete stent expansion in the tortuous parent arteries or the acute angle between the parent and daughter artery due to its low radical force (16, 17). Cho et al. reported five cases (18.5%, 5/27) of segmentally incomplete stent expansion where the LVIS stent was deployed from the distal internal carotid artery to the cavernous internal carotid artery (17). However, no incomplete stent expansion or stent migration events were observed in the present study, which may be due to greater operator experience. More importantly, the internal carotid artery was fixed within the rigid bone structure from the petrous segment to the paraclinoid segment, which is a limitation for

TABLE 1 | Results of different methods used for the treatment of ruptured ACoA aneurysms.

	LVIS stent-assisted coiling	Laser-cut stent-assisted coiling	Balloon-assisted coiling	Simple coiling
Number of patients	31	12	34	195
Immediate complete occlusion rate	27/31 (87.1%)	10/12 (83.3%)	26/34 (76.5%)	137/195 (70.3%)
Perioperative complication rate	2/31 (6.5%)	2/12 (16.7%)*[1]	2/34 (5.9%)*[2]	12/195 (6.2%) *[3]
Long-term occlusion rate	25/26 (96.1%)	9/10 (90%)	17/20 (85.0%)	112/141(79.4%)

*[1] *One case of intraoperative rupture and one case of intraoperative thrombosis.*

*[2] *One case of postoperative aneurysmal rebleeding and one case of intraoperative thrombosis.*

*[3] *Eight cases of intraoperative thrombosis, three cases of intraoperative aneurysm rupture, and one case of postoperative aneurysmal rebleeding.*

stent deployment. In contrast, the ACoA is relatively free within the subarachnoid space, and stent placement can significantly change the angle between efferent and afferent vessels, which facilitates complete opening of the stent and better apposition to the vessel wall (18). All of the stents in our study were released successfully before the packing was complete. In addition, a cone-beam CT scan was used to ensure that the stent was fully opened and well-apposed.

The periprocedural complication rates of ACoA aneurysms treated with non-LVIS stent-assisted coiling range from 0 to 34.6% (9, 19–22). Fan et al. reported 63 patients with ruptured ACoA aneurysms who underwent laser-cutting stent-assisted coiling, and found that the rates of intraprocedural aneurysm rupture and thrombus formation were 9.5% (6/63) and 15.9% (10/63), respectively (19). Similarly, Yang et al. retrospectively reviewed 45 cases of ruptured ACoA aneurysms treated with non-LVIS stent-assisted coiling, and the results revealed that the rates of ischemic complications and intraoperative rupture were 17.8% (8/45) and 8.9% (4/45), respectively (20). Our previous study, with 27 cases of ruptured wide-necked ACoA aneurysms treated with Enterprise stent-assisted coiling, demonstrated a procedure-related complication rate of 7.4% (2/27) (9). However, LVIS stents have also been reported to have a high perioperative thromboembolic complication rate due to their high metal coverage, which ranges from 3.5 to 4.9% (16, 23, 24). A recent meta-analysis suggested that the most common periprocedural complications of LVIS stents for the treatment of intracranial aneurysms were thromboembolisms and in-stent thrombosis (23). Similarly, Mokin et al. compared the differences between Enterprise stents, Neuroform stents, and LVIS stents in the treatment of intracranial aneurysms, and found that procedure-related complications were higher in the LVIS stents than in the Enterprise and Neuroform stent (24). Although there has been no direct comparison of different types of stents, the results of our study, with a procedure-related complication rate of 6.5%, seem favorable. The lower complication rate may be related to the braided characteristic; the LVIS stent can fully expand at the neck of the aneurysm to protect the neck and vessels. Furthermore, the use of cone-beam CT can help make an accurate judgment about whether the LVIS stent has effectually opened and incorporated vessels. This will significantly reduce complications of thromboembolism. With a small mesh (<1 mm), LVIS can effectively prevent coils from protruding into the vessel; this enables the selection of a smaller coil to make the procedure safer and significantly reduces the probability of aneurysm perforation.

Stenting in ruptured intracranial aneurysms remains controversial because of the need for antiplatelet medication, which carries the risk of theoretically elevating aneurysm rebleeding and surgery-related hemorrhage for patients requiring surgery. The endosaccular flow disruption device [WEB (Woven EndoBridge), LUNA AES (LUNA Aneurysm Embolization System), MED (Medina Embolic Device), and Contour (Contour Neurovascular System)] were designed to target the aneurysm neck and block the blood flow into the aneurysm, thus promoting intratumoral thrombosis and neo-endothelialization at the aneurysm neck (25). Theoretically, an endosaccular flow disruption device is an ideal treatment option for ruptured intracranial aneurysms because antiplatelet medication is not required. Of these endosaccular flow disruption devices, the WEB is the most widely used in clinical practice, while the other three devices are rarely reported for the treatment of ruptured intracranial aneurysms (26). To date, no studies have specifically evaluated the safety and efficacy of WEB for the treatment of ruptured ACoA aneurysms. A systematic review by van Rooij et al. showed that for patients with ruptured intracranial aneurysms treated with WEB, the procedure-related complication rate ranged from 0 to 27.3%, the thromboembolic complication rate ranged from 9.4 to 21%, the procedure-related mortality ranged from 1.0 to 12.1%, and the follow-up aneurysm occlusion rate ranged from 33.3 to 73.0% (27). Some clinicians initiate antiplatelet medication for patients with ruptured intracranial aneurysms treated with WEB given the high incidence of thromboembolic complications. Nevertheless, the dose and duration of antiplatelet therapy varies widely in different studies (27). Moreover, there remain concerns that the WEB devices can protrude into the parent artery in some more complex cases, and carry the risk of thromboembolic events; this requires the use of salvage stent placement to stabilize the WEB into the aneurysm sac (28). Indeed, a retrospective study reported by Maurer et al. (29) showed that the incidence of protrusion of WEB into the parent artery was 4%. Overall, the safety and long-term efficacy of WEB in the treatment of ruptured intracranial aneurysms still need to be further assessed.

The pCONus is a new neck remodeling device designed for bifurcated wide-necked aneurysms. Drug-coated stents designed to have a tissue organization effect on the outer aneurysmal

side of the stent and an antithrombotic effect on the inner stent blood-facing side might be a promising device to treat ruptured intracranial aneurysms. Daisuke et al. conducted an *in vitro* experiment on a drug-containing stent capable of controlled release of basic fibroblast growth factor and argatroban to treat rabbit cerebral aneurysms. The results showed that the majority of the aneurysm cavity was occupied by loose connective tissues in the drug-coated stent group, whereas extensive massive hematomas were observed in the drug-free stent group. Moreover, the drug-coated stents had a relatively low rate of in-stent thrombosis (30). However, the feasibility and safety of drug-coated stents for the treatment of human intracranial aneurysms still needs to be further explored.

The retrospective design has several limitations. First, the lack of a control group is likely the major limitation of the study. Second, this case series had a small sample size and all patients were from only one institution, which may have resulted in selection bias. Third, the self-adjudication of clinical and angiographic outcomes is bias that is inherent to this type of study. However, this is the first study to report the safety and efficacy of LVIS stent-assisted coiling for the treatment of acutely ruptured wide-necked ACoA aneurysms. Our findings may provide an alternative treatment option for ruptured wide-necked ACoA aneurysms.

CONCLUSIONS

The LVIS stent-assisted technique is a feasible, safe, and promising option for the treatment of acutely ruptured wide-necked ACoA aneurysms. Further follow-up is needed to adequately assess the long-term efficacy of this strategy.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

Ethical review and approval was not required for the study on human participants in accordance with the local legislation and institutional requirements. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

QH, BH, YX, and JL participated in the design of this study. GX, PL, and FX drafted the manuscript. PL and FX performed statistical analysis. GX carried out the collected important background information. YF and QL carried out literature search. QH modified the manuscript. All authors read and approved the final manuscript.

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Imaging Identification and Prognosis of the Distal Internal Carotid Artery With Near and Complete Occlusion After Recanalization

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Background and Purpose: Previous studies have mainly focused on treatment strategies and clinical outcomes for internal carotid artery near occlusion (ICANO) and internal carotid artery complete occlusion (ICACO). However, reports on the morphological changes of distal internal carotid artery (ICA) after recanalization are scarce. This study aimed at illustrating identifying features, assessing prognosis of the distal ICA after recanalization, and exploring best practices for treatment for ICANO and ICACO.

Materials and Methods: We retrospectively studied the clinical characteristics of 57 patients with ICANO or ICACO who underwent surgical recanalization. The clinical data, angiographic morphology, technical successful rate, perioperative complications, and the lumen changes of distal ICA before and after successful recanalization were analyzed.

Results: Fifty-two patients who achieved successfully recanalization were studied. Based on the postoperative lumen diameter changes in the distal ICA, 19 cases were classified as distal-dilatation and the remaining 33 as distal-narrowness. Patients in the distal-narrowness group mostly had ICACO (21.1 vs. 54.5%) and were men (68.4 vs. 93.9%). In the distal-narrowness group, the lumen of the distal ICA recovered to normal in 32 of the 33 patients during the follow-up period. Of the 32 patients reviewed, the ICA of 28 patients dilated back to normal after 1 week of surgery; the ICA of remaining patients 4 dilated 2 weeks postoperatively.

Conclusions: Narrowness of the distal ICA after hybrid recanalization was more prevalent in male patients with ICACO. Homogeneous stenosis of the whole course of the distal ICA is a low-perfusion narrowness which does not require intervention and will spontaneously recover after successful recanalization with an increase in the forward flow.

Keywords: hybrid recanalization, internal carotid artery, near occlusion, occlusion, low-perfusion narrowness

INTRODUCTION

Near occlusion of internal carotid artery (ICANO), also known as pseudo-occlusion, subtotal occlusion, string sign of the internal carotid artery (ICA), describes a phenomenon of an obvious reduction of the artery diameter beyond the stenotic lesion in an ICA with severe stenosis (1, 2). It represents a critical stenotic state before ICA severe stenosis progresses to complete occlusion (ICACO). Follow-up in the drug-treated group showed that about 40% of near occlusion of the ICA progressed to total occlusion within 12 months (3, 4). Therefore, the diameters decrease and even collapse of distal lumens can be discovered in both ICANO and ICACO.

Drug therapy is still the preferred treatment in treating carotid ICANO and ICACO, but ischemic symptoms refractory to medical therapy are an indication for revascularization (5–7). Both carotid endarterectomy (CEA) and endovascular intervention (EI) with a proximal embolic protection device have achieved satisfactory results for ICANO (8). As for ICACO, hybrid surgery is a feasible and effective surgical method, which combined CEA, immediate intraoperative angiography, and EI in a hybrid operating suite (7, 9). Recent studies have reported that compared with EI, hybrid surgery has a higher success rate of recanalization and less complication for ICACO (5, 6, 10). In clinical practice, we discovered that two changes existed in the distal ICA after surgical or hybrid recanalization: distal-dilatation and distal-narrowness. In this study, we retrospectively analyzed the angiographic characteristics, illustrated identifying features of the two lesions, and we investigated the postoperative short-term change in the diameter of the distal ICA to explore best practices for treatment of ICANO and ICACO.

MATERIALS AND METHODS

Patients and Materials

We retrospectively studied the medical records of patients with symptomatic ICANO or chronic ICACO treated at our institution between December 2015 and April 2020. ICANO is diagnosed if patients meet the following criteria: (1) delayed imaging of the ICA compared with that of the external carotid artery (ECA); (2) contrast agent filled the intracranial branches of the ICA via collateral circulation, usually via the ophthalmic artery; (3) obviously reduced diameter of the ICA (2). Chronic ICACO was defined as total occlusion of the ICA for at least 4 weeks seen on an angiogram (11).

We reviewed demographic characteristics, such as age, sex, history of disease (hypertension, diabetes mellitus, diabetes, and ischemic heart disease), smoking status and alcohol drinking status. The detail about symptomatology (transient ischemic attack, stroke), treatment modalities and perioperative complications were collected. And the level of total cholesterol, homocysteine (hCY), low density lipoprotein (LDL), and high density lipoprotein (HDL) were recorded.

We classified the post-recanalization findings of the ICA beyond the stenotic lesion into distal-dilatation (**Figure 1B**) and distal-narrowness groups (**Figure 1D**). Referring to the study of Rothwell et al. (12), the former was defined as the cases with an ICA/common carotid artery (CCA) ratio of $\geq$0.42 and the latter with a ratio <0.42. Patients who performed a deployment of stents due to intraoperative carotid segment dissection were outside the scope of the study, but included the calculation of the technical success rate. The morphological changes in the distal ICA lumen were followed up with computed tomographic angiography (CTA), magnetic resonance angiography (MRA), or digital subtraction angiography (DSA).

The study was approved by the hospital's ethics committee. Informed consent was obtained from all patients.

Surgical or Hybrid Treatment

All patients daily received dual-antiplatelet medication (aspirin 100 mg and clopidogrel 75 mg) for at least 3 days before the procedure. The procedure was performed in a hybrid operating room and general anesthesia was administered in all patients. An incision was made in the anterior border of the sternocleidomastoid muscle. After the patient was fully heparinized with 125 IU of heparin per kg of body weight intravenously, carotid bifurcation was exposed and then isolated by sequentially cross-clamping the internal, external, and common carotid arteries. The artery is opened and the plaque removed. A mechanical thrombectomy was cautiously attempted with a 4F Fogarty embolectomy balloon catheter, especially in ICACO cases. The ICA was subsequently sutured. Next, a immediate intraoperative carotid angiography was performed via a right femoral puncture using the Seldinger technique. If forward flow of the ICA recovered, we sutured the wound. If not, a 6F catheter was used to access the proximal occlusion site. Then a 0.014-inch microguidewire and a microcatheter cross the occlusion under the guidance of the roadmap. A balloon-mounted stent angioplasty was performed in the distal ICA, usually in the petrous/cavernous segment. No stent was implanted in carotid segment, unless intraoperative maneuvers caused carotid segment dissection.

Statistical Analysis

Normally distributed quantitative data was expressed as the mean $\pm$ standard deviation, and was analyzed by the Student's *t*-test. Non-normally distributed quantitative data was expressed as the median and interquartile range, and was analyzed by the Mann-Whitney *U* test. The qualitative data was expressed as percentage, and was analyzed using the chi-square test or the Fisher exact test. Logistic regression was used to evaluate effect of relevant risk factors on distal-narrowness after recanalization. A $P < 0.05$ was considered significant. SPSS software was used for data analysis.

RESULTS

Among the 57 patients with ICANO or ICACO who received hybrid treatment, a total of 53 achieved successful recanalization.

Abbreviations: ICANO, internal carotid artery near occlusion; ICACO, internal carotid artery complete occlusion; ICA, internal carotid artery; CEA, carotid endarterectomy; EI, endovascular intervention; CCA, common carotid artery; CTA, computed tomographic angiography; DSA, digital subtraction angiography; CHS, cerebral hyperperfusion syndrome; TIA, transient ischemic attack.

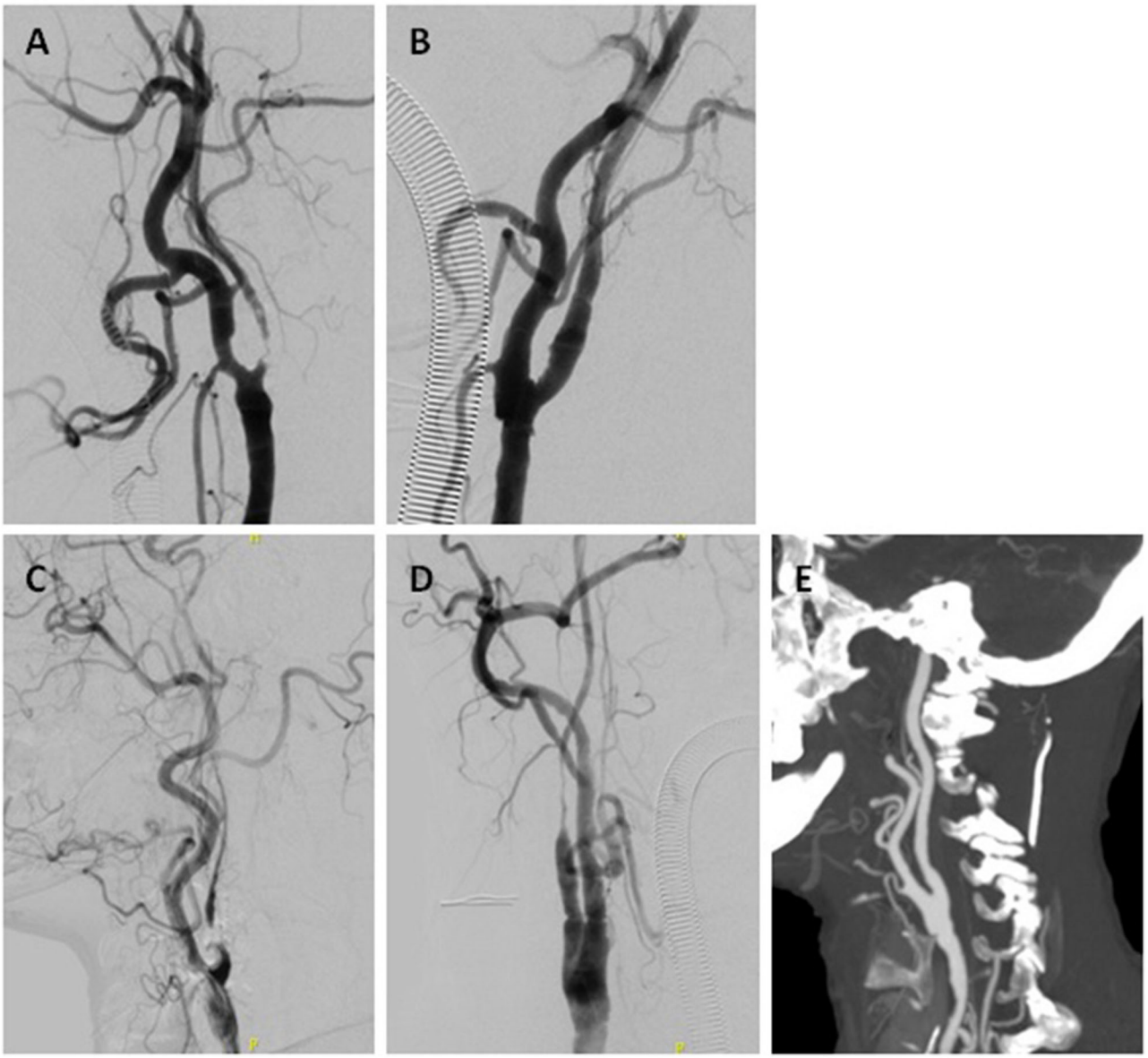

FIGURE 1 | Two cases of ICANO with hybrid recanalization. Case-1 **(A,B)** A 66-year-old woman complaining of TIA 2 months was hospitalized. **(A)** Digital subtraction angiogram (DSA) before the hybrid surgery revealed a left ICANO. **(B)** Immediate angiogram of the left ICA after recanalization showed distal-dilatation. CASE-2 **(C–E)** A 71-year-old man complaining of glossolalia and left limbs weakness 20 days was hospitalized. **(C)** Preoperative DSA revealed a right ICANO. **(D)** Immediate angiogram of right ICA after recanalization showed distal-narrowness. **(E)** Computed tomography angiogram (CTA) performed 1 week postoperatively showed dilated right ICA.

Among these successful cases, a patient who performed a deployment of stents due to intraoperative carotid segment dissection was excluded from this study. The clinical characteristics, procedure, and perioperative complications of the patients in these two lesions are summarized in **Table 1**. The distal-dilatation and distal-narrowness groups consisted of 19 and 33 patients, respectively. The mean age of the patients was 63.74 $\pm$ 7.53 years in the distal-dilatation group and 62.21 $\pm$ 6.64 years in the distal-narrowness group ($P = 0.45$). Patients in the distal-narrowness group were more likely to have ICACO (21.1% for distal-dilatation vs. 54.5% for distal-narrowness group; $P = 0.02$) and were males (68.4% for distal-dilatation vs. 93.9% for distal-narrowness group; $P = 0.04$).

There were no significant differences in terms of symptom, duration from initial symptom, hypertension, diabetes mellitus, ischemic heart disease, smoking history, status of alcohol drinking, serum total cholesterol, hCY, LDL, HDL level, procedure and perioperative complications between the two groups. In perioperative period, two patients showed an increase in the myocardial enzyme. One ICANO patient

TABLE 1 | Patient characteristics, procedure and perioperative complication.

	Distal-dilatation	Distal-narrowness	*P*-value (<0.05)
No. patients	19	33	
Patient characteristics			
Age	63.74 ± 7.53	62.21 ± 6.64	0.45
Sex male	14 (68.4%)	30 (93.9%)	0.04
Symptom			0.08
TIA	11 (57.9%)	11 (33.3%)	
Stroke	8 (42.1%)	22 (57.7%)	
Duration from initial symptom to recanalization, median (IQR), month	2 (1–2)	3 (1–10.5)	0.07
ICACO	4 (21.1%)	18 (54.5%)	0.02
Hypertension	16 (84.2%)	25 (75.8%)	0.73
Diabetes mellitus	5 (26.3%)	13 (39.4%)	0.34
Ischemic heart disease	3 (15.8%)	4 (12.1%)	0.70
History of smoking	9 (47.4%)	12 (36.4%)	0.44
Total cholesterol (mmol/L)	3.49 ± 0.80	3.49 ± 0.90	1.00
hCY (μmol/L)	15.06 ± 6.23	15.07 ± 6.19	1.00
LDL (mmol/L)	1.90 ± 0.75	2.04 ± 0.70	0.50
HDL (mmol/L)	1.12 ± 0.25	1.02 ± 0.22	0.16
Procedure			
Mechanical thrombectomy	2 (10.5%)	6 (18.2%)	0.74
Balloon and stent angioplasty in the petrous/cavernous segment	4 (21.1%)	9 (27.3%)	0.87
Perioperative complication			
Cardiovascular events	0	2 (6.1%)	0.53
CHS	1 (5.3%)	0	0.37
Intracranial hematoma	1 (5.3%)	0	0.37

TIA, transient ischemic attack; IQR, indicates interquartile range; ICACO, internal carotid artery complete occlusion; hCY, homocysteine; LDL, low density lipoprotein; HDL, high density lipoprotein; CHS, cerebral hyperperfusion syndrome.

with distal-dilatation experienced an perioperative intracranial hematoma due to cerebral hyperperfusion syndrome (CHS), and recovered conservatively.

In the distal-narrowness group, lumen of the distal ICA dilated to normal in 32 of the 33 patients in the follow-up period about 1–2 weeks (**Figures 1**, **2**). However, one case (3.03%) still showed distal-narrowness 1 month later.

The logistic regression analysis revealed that factors significantly associated with distal-narrowness were ICACO and male (odds ratio 5.30, 95% confidence interval: 1.26–22.29, $P = 0.02$; odds ratio 8.83, 95% confidence interval: 1.33–58.81, $P = 0.02$, **Table 2**).

DISCUSSION

Carotid atherosclerotic stenosis is a common disease and is closely related to ischemic cerebrovascular events. Internal carotid artery near occlusion (ICANO), also known as pseudo-occlusion, subtotal occlusion or string sign of ICA, describes a phenomenon of an obvious reduction of the artery diameter beyond the stenotic lesion in an ICA with severe stenosis (1, 2). On angiograms, the distal ICA becomes narrow or even collapsed. A major collapse of the ICA described as the "string sign," "slim sign," "small distal ICA," or "post-stenotic narrowing," (13–15) represents the critical state before internal carotid artery stenosis progresses to total occlusion. Ultimately, 40% of the near occlusion of ICA progress to total occlusion within 12 months (3, 4). The present definition of chronic ICACO is controversial. The minimum time for chronic total occlusion of the ICA should be at least 4 weeks and possibly even more than 3 months (11). Hybrid surgery is a newly-developing treatment which combines CEA, immediate intraoperative angiography, and EI (9). In a hybrid operation, we can get intraoperative angiograms after CEA, and instantly decide whether to perform mechanical thrombectomy and/or endovascular angioplasty, which raises the success rate of recanalization and is especially suitable for the treatment of ICACO. Li et al. (6) reported that hybrid surgery have a higher success rate of recanalization than EI in patients with ICACO (88.2 vs. 53.3%; $P = 0.05$). Our success rate for cases with ICACO is 85.19% (23/27), and that for cases with ICANO is 96.77% (30/31). Therefore, hybrid surgery is effective for recanalization of patients with ICANO and ICACO.

On intraoperative angiograms after successful recanalization, we discover that the distal ICA beyond a critical stenosis shows two states: (1) distal ICA with an approximate normal diameter; and (2) distal ICA with homogeneous narrowness. It is difficult to confirm normal diameter of ICA, but the lower limit of normal ICA/CCA ratio is 0.42 by studying angiograms of carotid arteries with 0–49% stenosis (12). Therefore, we define the cases with an ICA/CCA ratio of $\geq$0.42 as distal-dilatation corresponding to the former state and the ones with an ICA/CCA ratio of $<$0.42 as distal-narrowness corresponding to the latter state. Among our 52 patients with successful recanalization, 19 (36.5%) cases were distal-dilatation and 33 (63.5%) cases were distal-narrowness.

Early carotid atherosclerosis only causes slight stenosis, with a normal diameter of the distal ICA. As the stenosis progressively becomes more severe and exceeds a critical degree, a further deterioration in stenosis will result in a decrease of forward flow, and the diameter of the ICA beyond the stenosis progressively begins to decrease. By sacrificing the diameter, the distal ICA makes wall shear stress recover a baseline of 15∼20 dyn/cm^2, which not only provides effective support in stabilizing blood vessel wall, but also maintains adequate perfusion. When blood vessels have a chronically low wall shear stress for a long time, vascular remodeling will happen by accumulation and differentiation of the intimal cell (16). Irace et al. (17) also reported that intima-media thickening is significantly associated with low wall shear stress. Meanwhile, reduction of shear stress can alter the endothelial production of bioactive molecules related to vascular tone, which may achieve through regulating the expression of gene (18). As a result, the blood vessel wall incrassates, the lumen becomes narrow, and the distal ICA takes a longer time to reverse the vascular remodeling after recanalization. Therefore, ICACO is more likely to be distal-narrowness because of a longer period of distal ICA flow impairment than ICANO.

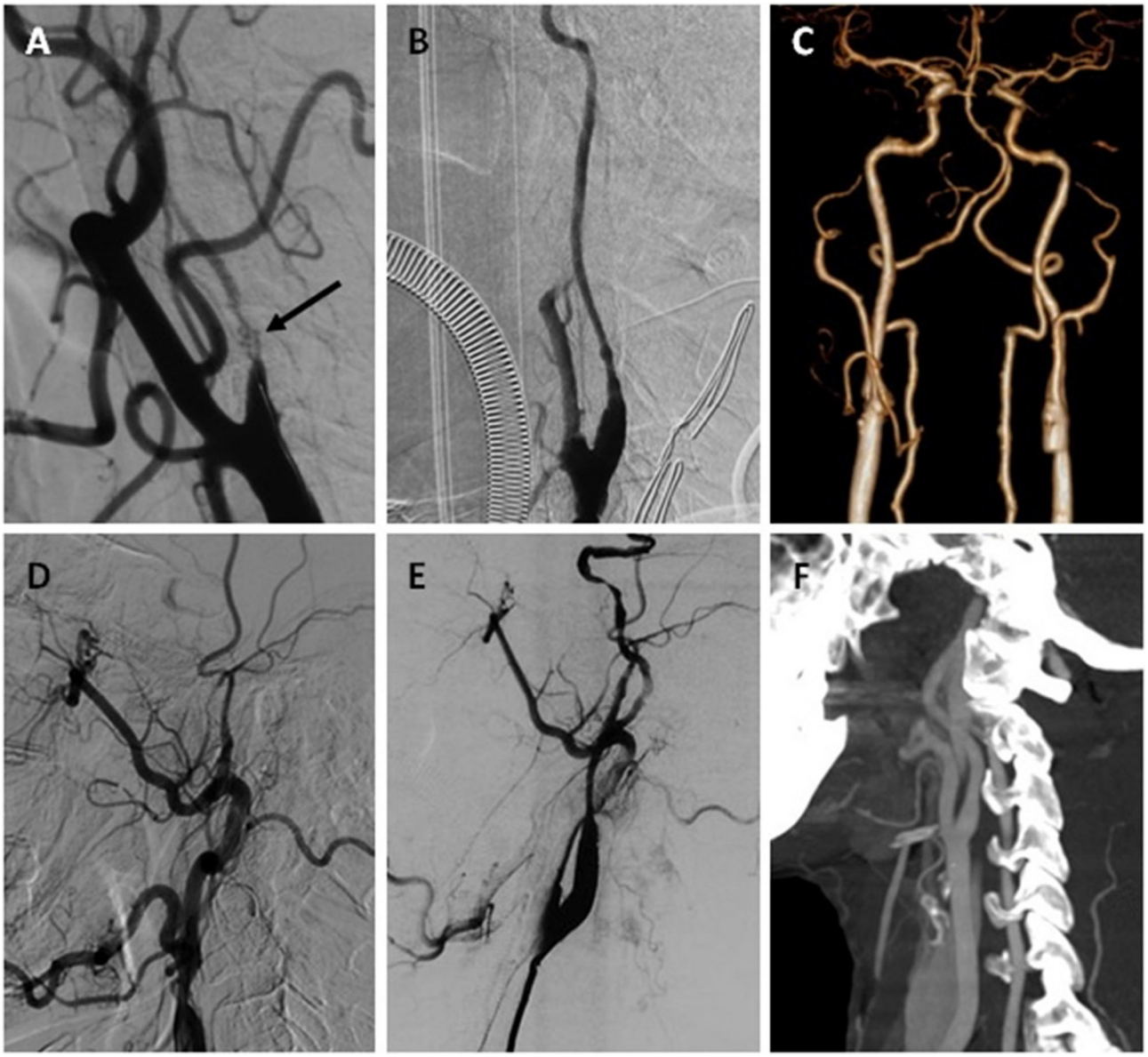

FIGURE 2 | One ICANO and one ICACO with hybrid recanalization. Case-3 **(A–C)** A 56-year-old man complaining about TIA 2 years was hospitalized. **(A)** DSA before the hybrid surgery revealed a left ICANO with total occlusion and recanalization, which is characterized by multiple lumens (arrow). **(B)** Immediate angiogram of the left ICA after recanalization showed distal-narrowness. **(C)** CTA performed 1 week postoperatively showed a dilated left ICA. Case-4 **(D–F)** A 59-year-old man complaining of expressive aphasia 1 month was hospitalized. **(D)** Preoperative DSA revealed a left ICACO. **(E)** Immediate angiogram of left ICA after recanalization showed distal-narrowness. **(F)** (CTA) performed 1 week postoperatively showed dilated left ICA.

In our 30 patients with ICANO, six patients underwent spontaneous recanalization of atheromatous chronic ICA occlusion. ICANO with total occlusion and recanalization is likely to show multiple lumens caused by large neovascular channels on angiography (**Figure 2A**) (19). Although spontaneous recanalization partly causes recovery of the flow, there is less improvement in the forward flow of the distal ICA. Moreover, ICANO with total occlusion and recanalization may represent a longer course of illness and is more likely to show distal-narrowness.

The incidence of postoperative hyperperfusion syndrome was about 0.2–18.9% (20), but once it happens, it caused serious consequences (21). In perioperative complications, one distal-dilatation patient with ICANO had a CHS and suffered from subsequent intracranial hematoma caused by CHS in the perioperative period. We speculate that a sudden increase of blood flow in distal-dilatation ICA may partially cause this malignant event. Hayakawa et al. (22) reported that staged angioplasty was effective to avoid CHS after carotid revascularization. The process from narrowness to dilatation

TABLE 2 | Results of logistic regression analysis for distal-narrowness group.

	Odds ratio	95% Confidence interval		*P*-value
		Lower	Upper	
ICACO	5.30	1.26	22.29	0.02
Men	8.83	1.33	58.81	0.02

of the distal ICA after CEA actually can be seen as natural staged angioplasty and may be helpful to prevent CHS. The process from narrowness to dilatation of the distal ICA after CEA actually can be seen as natural staged angioplasty and may be helpful to prevent CHS. Therefore, we think that distal-dilatation patients may require more strict blood pressure management and more intensive medical monitor to prevent and early find the occurrence of CHS after recanalization. CT perfusion (CTP), single-photon emission computed tomography or transcranial Doppler (TCD) examinations to monitor the perfusion of brain may be helpful for further research to illustrate the significance of distal-narrowness for avoidance of CHS.

In EI and some hybrid surgeries for ICACO, the distal ICA can be dilated by reconstructing with balloons and stents (23, 24). We occasionally performed a balloon and stent angioplasty distally, specifically in the petrous/cavernous segment, so reduced diameter of the distal ICA still existed in our distal-narrowness group. However, we discovered that the distal ICA was dilated in 32 of 33 patients in the follow-up examination. The average recovery time was 1.125 week. Partial cases were shown in **Figures 1**, **2**. We think that the restoration of the vessel diameter is an adaptation to increased postoperative blood flow, and slowly progressed by remodeling the vessel wall. However, the ICA/CCA ratio of one patient was still <0.42. Distal ICA of the patient showed local stenosis of the siphonage segment after 1 month, but the lesion was not observed on intraoperative angiography. We assume that homogeneous narrowness of the distal ICA covered up local atherosclerotic stenosis, and the existence of distal local stenosis prevents the flow of ICA from increasing in these cases.

Although the balloon-mounted stent angioplasty can achieve distal-dilatation, we think that the homogeneous stenosis of the whole course of distal ICA is a low-perfusion narrowness, which does not require intervention and will shortly expand with an increase in the forward flow after successful recanalization. However, unobserved and unperformed tandem lesion in intraoperative angiography will prevent distal ICA from recovering, so regular follow-up is needed in patients with distal-narrowness ICA.

There are limitations deserving mention in our study. Firstly, the sample size in the present study was relatively small. Secondly, our study was a retrospective one. Thirdly, the lack of data of postoperative cerebral perfusion limited assessment of significance of distal-narrowness in avoiding CHS. Finally, histological data on distal vessel wall obtained by high resolution magnetic resonance (HR-MRI), optical coherence tomography and carotid endarterectomy may be helpful to clarify the potential mechanisms about the changes in the distal ICA.

CONCLUSIONS

In summary, hybrid recanalization is an effective method for patients with ICANO or ICACO. The diameter changes in the distal ICAs after recanalization were classified into two groups, a distal-dilatation group and distal-narrowness group. Patients in the distal-narrowness group were more likely to have ICACO and to be males. The homogeneous stenosis of the whole course of distal ICA is a low-perfusion narrowness, which does not require intervention, and will recover spontaneously after successful recanalization with an increase in the forward flow.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Ethics Committee of the Qilu Hospital, Shandong University. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

XL and DW established the study idea, designed the manuscript structure. TS, MH, YH, and FW were responsible for the data collection. TS and CW analyzed the data and wrote the manuscript. XL, DW, and YW modified and revised the manuscript. All authors have read and approved the final version of the manuscript.

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ORIGINAL RESEARCH
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Endovascular Therapy for Basilar Arterial Trunk Aneurysms

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Background: Although aneurysms rarely occur in the basilar artery (BA) trunk, the majority of those that do are dissection aneurysms. Currently, the mainstream therapy for BA trunk aneurysms is endovascular therapy (EVT), which mainly includes single coiling or conventional low-metal-coverage stent-assisted EVT, but the efficacy remains to be evaluated.

Methods: A retrospective study was performed for the patients who were admitted to our institution for BA trunk aneurysms and underwent EVT. A total of 28 patients were collected in this study.

Results: The patients were aged 23–71 years (53.7 ± 11.5 years on average); nine were female (32.1%, 9/28), and 19 were male (67.9%, 19/28). The patients were given single coiling or conventional low-metal-coverage stent-assisted EVT. Among the 28 patients, 10 (35.7%, 10/28) developed complications, 90% (9/10) of which were ischemic and 10% (1/10) were hemorrhagic. Among the 28 patients, 5 (17.9%, 5/28) died. The surviving 23 patients (82.1%, 23/28) recovered well.

Conclusions: This study found that for BA trunk aneurysms, single coiling or conventional low-metal-coverage stent-assisted EVT still had some risks. The risks are mainly from brainstem ischemia. Therefore, the perforators of the BA trunk must be carefully evaluated and prevented from receiving damage from the EVT procedure. This study also shows that 82.1% of patients recovered well. Therefore, EVT can result in an acceptable prognosis.

Keywords: basilar artery, trunk, aneurysm, endovascular therapy, prognosis

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INTRODUCTION

Although aneurysms rarely occur in the basilar artery (BA) trunk, some are routine saccular aneurysms at the initial part of the perforating branch (1), while most are dissection aneurysms involving part of the BA trunk (2). Since the BA trunk is anatomically deep, craniotomy clipping of BA aneurysms is a high-risk procedure. Instead, endovascular therapy (EVT) is mainly used for treatment today (2, 3).

Moreover, the BA trunk is rich in branches, so the application of a flow-diverting stent will lead to the brainstem perforator-related infarction (4). Therefore, single coiling or conventional low-metal-coverage stent-assisted EVT is still mainly used for BA trunk aneurysms. However, is single coiling or conventional low-metal-coverage stent-assisted EVT also very safe for BA trunk aneurysms? Does it have a high incidence of complications?

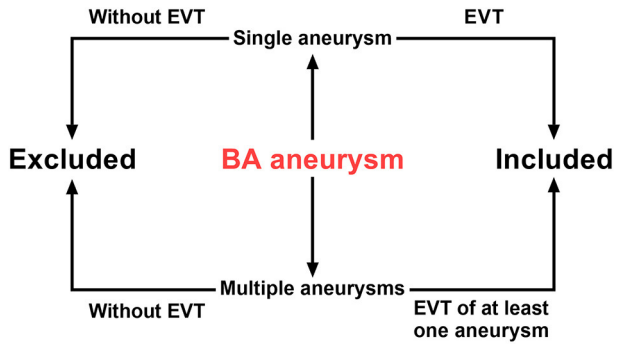

FIGURE 1 | Flow chart of inclusion and exclusion criteria. BA, basilar artery; EVT, endovascular therapy.

In this report, 28 patients with BA trunk aneurysms who were treated with single coiling or conventional low-metal-coverage stent-assisted EVT in our center over the past 5 years were enrolled to evaluate the effect. The results are summarized and reported and will be of great importance as a reference.

MATERIALS AND METHODS

A retrospective study was performed for patients who were admitted to The First Hospital of Jilin University diagnosed with BA trunk aneurysms from January 2015 to January 2020. This study was approved by the institutional ethics committee (No. 2020-588).

Inclusion and Exclusion Criteria

Patients with aneurysms located in the BA trunk and treated with EVT were included. These included EVT performed for a single aneurysm and EVT of at least one aneurysm performed for multiple aneurysms. In addition, patients with aneurysms located at the BA tip or with aneurysms involving the vertebral artery (VA) were excluded. A flow chart is shown in **Figure 1**.

Aneurysm Site and Classification

The length of the BA ranges from 20–40 mm. In terms of basilar artery infarction, BA can be subdivided anatomically into three segments: the inferior segment from the VA to the anterior inferior cerebellar arteries (AICA), the middle segment from the AICA to the origin of the superior cerebellar arteries (SCA) and the superior segment from the SCA to the terminal posterior cerebral arteries (PCA) (5). For BA trunk aneurysms, the segmentation can be referential. However, while the inferior segment was reasonable, the superior segment was too short. Consequently, it is reasonable to divide the part between the BA termination and the AICA into superior and middle segments.

Therefore, in our study, the BA trunk aneurysms were classified into superior, middle and inferior aneurysms according to their anatomical location within the BA trunk, then into saccular, spherical and fusiform aneurysms according to the morphology. The saccular aneurysms were further divided into narrow-necked and wide-necked aneurysms, and the spherical and fusiform aneurysms were divided into lateral and annular aneurysms according to their location within the BA.

EVT Scheme

BA aneurysms were divided into single coiling or low-metal-coverage stent-assisted EVT depending on their treatment.

EVT Evaluation

The effects of EVT were recorded and evaluated with the Modified Raymond-Roy Classification (MRRC) (6). Complications and follow-up results were recorded. The modified Rankin Scale (mRS) was used to grade the results (7).

RESULTS

General Information

The 28 patients were aged 23–71 years old (53.7 ± 11.5 years on average). Among them, nine were female (32.1%, 9/28), and 19 were male (67.9%, 19/28). Among the 28 patients, 13 (46.4%, 13/28) were found to have aneurysms by asymptomatic physical examination, and 5 (17.9%, 5/28) were found to have aneurysms by cerebral infarction examination. Ten patients (35.7%, 10/28) presented with subarachnoid hemorrhage (SAH). There were 3 cases of Grade I, two cases of Grade II and five cases of Grade III SAH according to the Hunt-Hess classification.

Image Characteristics

Among 28 patients, there were 29 BA trunk aneurysms; one patient had two aneurysms. The 29 aneurysms were 1–22 mm in diameter (7.2 ± 6.1 mm on average). Three were superior aneurysms (10.3%, 3/29), 10 were middle aneurysms (34.5%, 10/29), and 16 were inferior aneurysms (55.2%, 16/29) (six of which were located within five fenestrations).

With regard to morphology, there were 21 saccular aneurysms (72.4%, 21/29) (including 17 wide-necked and four narrow-necked saccular aneurysms), five spherical aneurysms (17.2%, 5/29) (three lateral and two annular spherical aneurysms around the BA), and three fusiform aneurysms (10.3%, 3/29) (two lateral and one annular aneurysm around the BA).

EVT Scheme

Among the 29 aneurysms, one aneurysm in a case with two aneurysms was monitored conservatively, and the remaining 28 aneurysms in 28 patients were treated with EVT. Among the 28 treated aneurysms, four were treated by single coiling (14.3%, 4/28), and 24 were treated with low-metal-coverage stent-assisted embolization (85.7%, 24/28). Twenty-three of the EVT-treated aneurysms were MRRC Grade I (82.1%, 23/28), and five were MRRC Grade IIIa (17.9%, 5/28).

EVT Results

Perioperative Results

Of the 28 EVT-treated patients, 18 recovered well (64.3%, 18/28), and 10 patients developed complications (35.7%, 10/28).

TABLE 1 | Clinical Data of BA trunk aneurysm.

No.	Age/sex	Onset	HH Grade	Site	Morphology	Neck	Size	EVT	Immediate MRRC	Complications	Onset time of complication	Recovery time of complication	Follow-up time	Follow-up MRRC	Others	mRS
1	34/M	Occasional	NA	Superior	Spherical (lateral)	NA	13.5 mm	Stent + coil	I	Perforator ischemia/ hemiplegia	Immediate	1 month	9 months	I	N	0
2	60/F	Occasional	NA	Inferior	Saccular	Narrow	3.5 mm	Stent + coil	I	N	NA	NA	6 months	I	N	0
3	54/F	SAH	3	Inferior	Saccular	Wide	4.5 mm	Stent + coil	I	BA ischemia/ coma	Immediate	NA	NA	NA	NA	Death
4	68/M	SAH	3	Inferior	Fusiform (annular)	NA	20 mm	Stent + coil	IIIa	Perforator ischemia/ hemiplegia	2 h postoperatively	6 months	2 years	N	N	0
5	60/F	SAH	2	Inferior (fenestration)	Saccular (2)	Both narrow	1.5 mm & 3 mm	Coil (Large aneurysm)	I and observation	N	NA	NA	10 months	N	Hydrocephalus shunting	1
6	46/M	SAH	1	Middle	Saccular	Wide	8 mm	Stent + coil	I	Perforator ischemia/ hemiplegia	2 hours postoperatively	9 days	2 years	N	N	0
7	63/F	Occasional	NA	Middle	Spherical (annular)	NA	12 mm	Stent + coil	IIIa	N	NA	NA	1 year	IIIa	N	0
8	63/M	Occasional	NA	Inferior	Saccular	Wide	3.5 mm	Stent + coil	I	N	NA	NA	1 year	I	N	0
9	61/M	Occasional	NA	Superior	Saccular	Narrow	10 mm	Coil	I	N	NA	NA	2 years	I	N	0
10	38/M	Occasional	NA	Inferior	Saccular	Wide	11.5 mm	Stent + coil	I	N	NA	NA	2 years	I	N	0
11	59/M	Cerebral infarction	NA	Inferior	Saccular	Wide	5.5 mm	Stent + coil	I	N	NA	NA	6 months	I	N	0
12	59/M	Occasional	NA	Inferior	Spherical (lateral)	NA	22 mm	Coil	IIIa	Aneurysm rupture/coma	Postoperative 1 month	NA	NA	NA	NA	Death
13	53/M	Cerebral infarction	NA	Middle	Saccular	Wide	4 mm	Stent + coil	I	N	NA	NA	6 months	I	N	0
14	67/M	Cerebral infarction	NA	Middle	Saccular	Wide	5 mm	Stent + coil	I	N	NA	NA	1 and a half year	N	N	0
15	52/M	Cerebral infarction	NA	Middle	Saccular	Wide	2.5 mm	Stent + coil	IIIa	N	NA	NA	6 months	IIIa	N	0
16	66/M	Cerebral infarction	NA	Middle	Fusiform (lateral)	NA	4.5 mm	Stent + coil	I	N	NA	NA	1 and a half year	N	N	0
17	49/M	SAH	3	Inferior	Saccular	Wide	2 mm	Stent + coil	I	BA ischemia/ coma	Postoperative 20 days	NA	NA	NA	NA	Death
18	54/M	Occasional	NA	Middle	Saccular	Wide	5 mm	Stent + coil	I	N	NA	NA	1 and a half year	N	N	0
19	56/M	Occasional	NA	Inferior	Spherical (annular)	NA	20 mm	Stent + coil	IIIa	N	NA	NA	6 months	I	N	1
20	49/F	Occasional	NA	Inferior (fenestration)	Saccular	Wide	5.5 mm	Coil	I	N	NA	NA	1 year	N	N	0

(Continued)

TABLE 1 | Continued

No.	Age/sex	Onset	HH Grade	Site	Morphology	Neck	Size	EVT	Immediate MRRC	Complications	Onset time of complication	Recovery time of complication	Follow-up time	Follow-up MRRC	Others	mRS
21	28/F	Occasional	NA	Inferior	Fusiform (lateral)	NA	4 mm	Stent + coil	I	N	NA	NA	1 and a half year	I	N	1
22	71/M	SAH	3	Middle	Saccular	Wide	2.5 mm	Stent + coil	I	BA ischemia/ coma	Immediate	NA	NA	NA	NA	Death
23	53/F	SAH	2	Inferior (fenestration)	Saccular	Wide	4 mm	Stent + coil	I	Perforator ischemia/ hemiplegia	Postoperative 2 days	7 days	2 years	N	N	0
24	23/F	SAH	3	Inferior (fenestration)	Saccular	Wide	5 mm	Stent + coil	I	Perforator ischemia/ hemiplegia	Postoperative 1 day	20 days	3 years	N	N	0
25	60/M	Occasional	NA	Middle	Saccular	Wide	4 mmm	Stent + coil	I	N	NA	NA	3 years	N	N	0
26	50/M	Occasional	NA	Superior	Spherical (lateral)	NA	18 mm	Stent + coil	I	Perforator ischemia/coma	Postoperative 6 months	NA	NA	NA	NA	Death
27	53/M	SAH	1	Middle	Saccular	Wide	2.5 mm	Stent + coil	I	N	NA	NA	1 year	N	N	0
28	54/F	SAH	1	Inferior (fenestration)	Saccular	Wide	8 mm	Stent + coil	I	N	NA	NA	6 months	N	N	0

EVT, endovascular therapy; F, female; HH grade, Hunt-Hess grade; M, male; MRRC, Modified Raymond-Roy Classification; mRS, modified Rankin Scale; N, No; NA, Not applicable; SAH, subarachnoid hemorrhage.

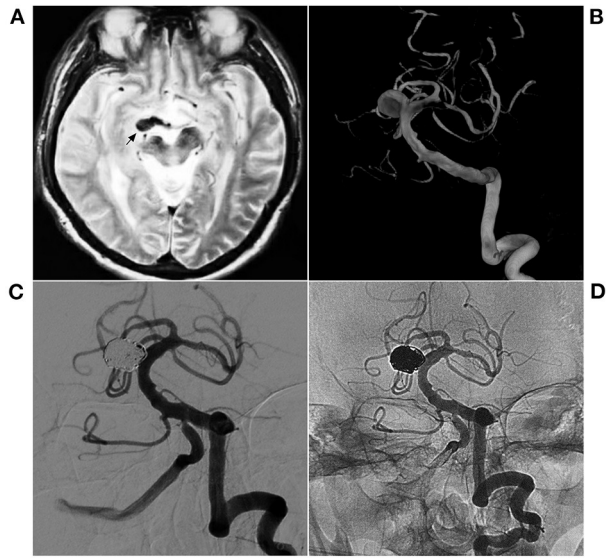

FIGURE 2 | EVT with single coiling of a narrow-neck aneurysm. **(A)** MR T2WI shows an aneurysm in the right midbrain (arrow); **(B)** 3D-reconstructed DSA shows a saccular aneurysm in the superior BA. **(C,D)** Postoperative VA-DSA shows the aneurysm following coiling embolization, MRRC Grade I. BA, basilar artery; DSA, digital subtraction angiography; EVT, endovascular therapy; MR, magnetic resonance; MRRC, Modified Raymond-Roy Classification; VA, vertebral artery.

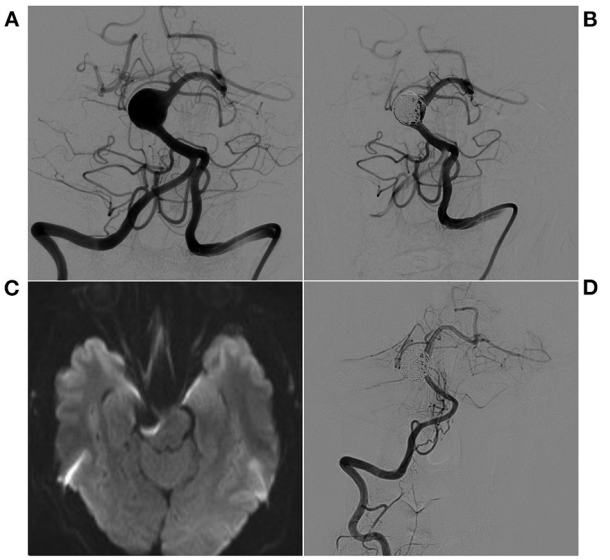

FIGURE 3 | EVT with stent-assisted coiling of a spherical aneurysm. **(A)** Preoperative VA-DSA shows a spherical aneurysm in the superior BA, eccentric type. **(B)** Postoperative VA-DSA shows the aneurysm with stent-assisted embolization, MRRC Grade I. **(C)** After EVT, the patient suffered hemiplegia, and an immediate MR diffusion sequence showed no infarctions. **(D)** Postoperative 9-month follow-up VA-DSA shows no recurrence of the aneurysm. BA, basilar artery; DSA, digital subtraction angiography; EVT, endovascular therapy; MR, magnetic resonance; MRRC, Modified Raymond-Roy Classification; VA, vertebral artery.

Complication

Among the 10 patients (35.7%, 10/28) who experienced complications, 5 (17.9%, 5/28) had hemiplegia due to perforation ischemia, 4 (14.3%, 4/28) developed coma due to perforation and BA ischemia, and 1 (3.6%, 1/28) died due to delayed aneurysm rupture. With regard to the onset of complications, three patients were stricken immediately after EVT, two at 2 h postoperatively, one at 1 day postoperatively, one at 2 days postoperatively, one at 20 days postoperatively, one at 1 month postoperatively, and one at 6 months postoperatively.

Concerning the prognoses of the complications in the 10 patients, in addition to the patient who died due to delayed aneurysm rupture, the four patients who developed coma caused by perforation and BA ischemia all died after the operation. The remaining five patients who experienced hemiplegia caused by perforating ischemia returned to normal between 7 days and 6 months after the operation without sequelae. One patient had hydrocephalus and underwent ventriculoperitoneal shunt implantation.

Long-Term Follow-Up

In addition to the five patients (17.9%, 5/28) who died of complications, the remaining 23 patients (82.1%, 23/28) were followed up for 6–36 months (16.0 ± 9.3 months on average). A total of 20 patients had an mRS score of 0, and three patients had an mRS score of 1, indicating good results. Among these 23 patients, 12 did not undergo follow-up imaging, while the other 11 underwent follow-up digital subtraction anisotropy (DSA). There were nine cases of Grade I and 2 cases of Grade IIIa aneurysms according to MRRC.

The clinical data of BA trunk aneurysms is summarized in **Table 1**. Several key parameters are included, such as the site, morphology and size of the aneurysm, the aneurysm neck, the immediate and follow-up EVT MRRC, the complications and mRS. Typical aneurysms and their EVT results are shown in **Figures 2**–**7**.

DISCUSSION

The BA trunk contains many perforators supplying the brainstem. Aneurysms rarely occur on the perforators; therefore, BA trunk aneurysms are more often dissection aneurysms rather than saccular bifurcation aneurysms (8). Imaging results of dissection aneurysms of the BA trunk suggest lateral saccular dissection and spherical or fusiform dissection (9). In this study, 72.4% of the aneurysms were characterized by a saccular dissection.

Most posterior circulation dissection aneurysms are stable, similar to VA dissection aneurysms, and rupture hemorrhage is rare (10). In this study, 35.7% of the BA trunk aneurysms ruptured and bled, indicating that BA trunk aneurysms are not always stable and can increase in size over time, as there is an increased risk of SAH formation (8). Therefore, it is necessary to apply appropriate treatment.

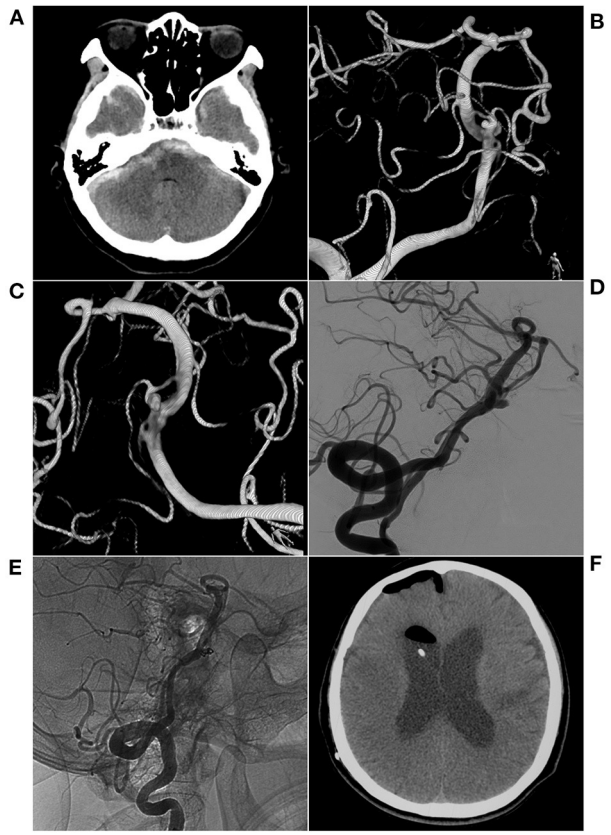

FIGURE 4 | EVT with single coiling of an aneurysm in the fenestration. **(A)** CT shows subarachnoid hemorrhage in the anterior brainstem; **(B,C)** 3D reconstructed DSA shows two fenestrations in the inferior BA and two aneurysms in the superior fenestration. **(D)** Preoperative VA-DSA shows a large aneurysm. **(E)** Postoperative VA-DSA images show a large aneurysm with simple coiling, MRRC Grade I. **(F)** The patient had hydrocephalus after EVT and underwent ventriculoperitoneal shunting at the 10-month follow-up. BA, basilar artery; CT, computed tomography; DSA, digital subtraction angiography; EVT, endovascular therapy; MRRC, Modified Raymond-Roy Classification; VA, vertebral artery.

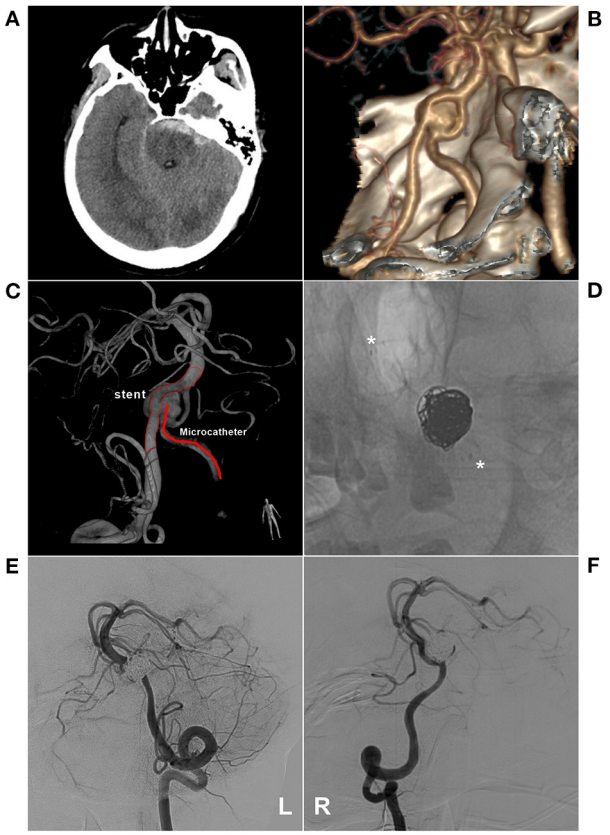

FIGURE 5 | EVT with stent-assisted coiling of an aneurysm in the fenestration. **(A)** CT shows subarachnoid hemorrhage at the front of the brainstem; **(B)** CTA shows an aneurysm in a fenestration of the inferior BA. **(C)** 3D-reconstructed DSA shows the aneurysm and EVT schemes. The stent was placed into a coarse VA and microcatheter-walked to a finer VA to embolize the aneurysm; **(D)** X-ray image shows coiling with stent-assisted EVT (asterisk); E-F: VA-DSA on the left **(E)** and right **(F)** side show the aneurysm embolization, MRRC Grade IIIa. BA, basilar artery; CT, computed tomography; CTA, CT angiography; DSA, digital subtraction angiography; EVT, endovascular therapy; MRRC, Modified Raymond-Roy Classification; VA, vertebral artery.

The BA trunk is relatively short, but it can still be divided into superior, middle and inferior segments, with corresponding aneurysms (11). BA trunk aneurysms occur most frequently in the inferior segment. Among the 28 aneurysms in this study, 55.2% occurred in the inferior BA trunk. This may be because the inferior BA often contains fenestrations, which are the predilection sites of aneurysm formation.

In the study by van Rooij et al. BA fenestrations were detected in 4% of patients with a suspected ruptured aneurysm (12). The rate of fenestration in this study was higher than the above report. Among the 28 cases, the fenestrations were observed in the inferior BA trunk in five patients (17.9%) who were afflicted with a total of 6 aneurysms. The cases are shown in **Figures 4**, **5**.

The majority of BA trunk aneurysms are dissection aneurysms, but those occurring within fenestrations are located in regions of bifurcation and are therefore saccular bifurcation aneurysms (13). Among the 29 combined aneurysms in the 28 patients in this study, the six aneurysms located within fenestrations of the inferior BA were not dissection aneurysms, while the remaining 23 aneurysms were.

Since craniotomy clipping is very difficult, EVT remains the first procedure of choice for BA trunk aneurysms (14). In the current choices for EVT, the flow-diverting stent has been widely used in cerebral aneurysms (2, 15). However, the flow-diverting stent is rarely used for BA trunk aneurysms. This is because the BA is short, with limited space for operations. Furthermore, the perforators of the BA are tiny, and each is extremely important. Therefore, brain stem infarctions caused by perforator ischemia after the application of flow-diverting stents will lead to a poor patient prognosis.

Therefore, conventional low-metal-coverage EVT techniques are still preferred for BA trunk aneurysms (16). These low-metal-coverage stents include the Neuroform stent (Stryker Neurovascular, Fremont, CA, USA), Enterprise stent (Codman

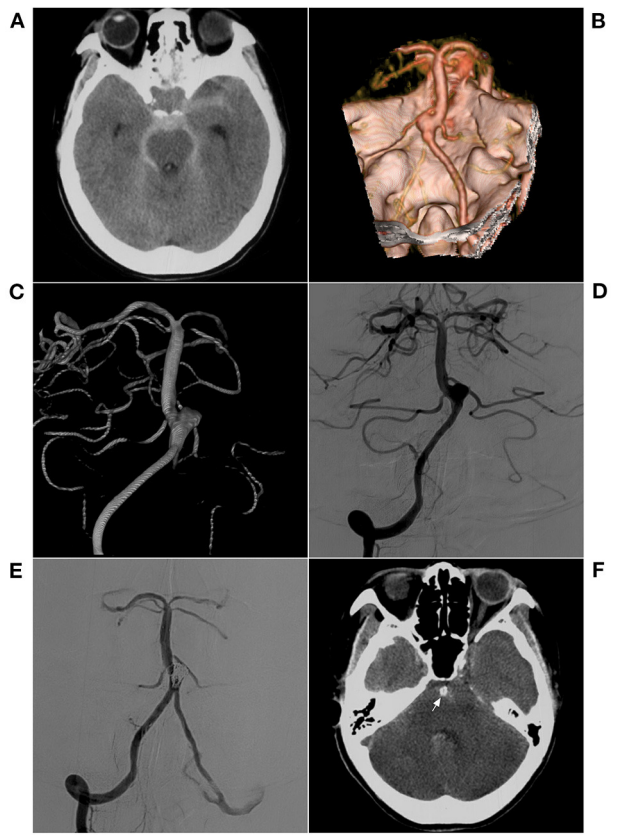

FIGURE 6 | EVT with an ischemic complication. **(A)** CT shows hemorrhage in the anterior brainstem and subarachnoid space of the cisterna; **(B)** CTA shows a saccular wide-necked lateral-wall aneurysm in the inferior BA. **(C,D)** Preoperative VA-DSA (C for 3D reconstruction, D for 2D embolization) shows a saccular aneurysm in the inferior BA, lateral-wall type. **(E)** Postoperative VA-DSA shows the aneurysm following stent-assisted EVT, MRRC Grade I. **(F)** For the patient who immediately developed coma after EVT, the postoperative CT shows no hemorrhage and the coil (arrow) in the BA lumen. BA, basilar artery; CT, computed tomography; CTA, CT angiography; DSA, digital subtraction angiography; EVT, endovascular therapy; MRRC, Modified Raymond-Roy Classification; VA, vertebral artery.

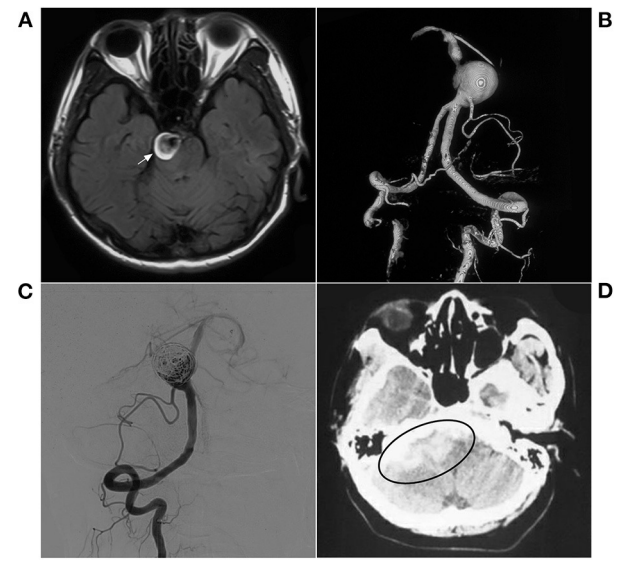

FIGURE 7 | EVT with a delayed hemorrhage. **(A)** MR T2WI shows an aneurysm in the right pons (arrow); **(B)** 3D-reconstructed DSA shows a spherical aneurysm in the inferior BA. **(C)** Postoperative VA-DSA shows the aneurysm following simple coiling embolization, MRRC Grade IIIa. **(D)** 1-month postoperative CT shows hemorrhage in the lateral brain stem (ellipse). BA, basilar artery; CT, computerized tomography; DSA, digital subtraction angiography; EVT, endovascular therapy; MR, magnetic resonance; MRRC, Modified Raymond-Roy Classification; VA, vertebral artery.

Neurovascular, Raynham, MA, USA), Solitaire (Medtronic, Irvine, California, USA), low-profile visualized intraluminal support (LVIS) stent (MicroVention Inc., Aliso Viejo, CA, USA), and LEO stent (Balt Extrusion, Montmorency, France) (17).

Among saccular aneurysms, single coiling can be used for narrow-necked aneurysms, while a low-metal-coverage stent is needed for wide-necked aneurysms to reduce the impact of the stent on BA perforations (18). When aneurysms involve spherical or fusiform dissections of the BA, they can only be coiled at first, followed by BA channel reconstruction with a stent (19). Nevertheless, we realize that even very successful EVT operations may develop serious complications or consequences postoperatively. This is because the greatest obstacle for EVT in treating BA trunk aneurysms lies in the abundant branches of the BA.

Among the 28 patients in this study, nine patients experienced ischemic complications, with an incidence of 32.1%. This high incidence of complications is notable for aneurysms treated by EVT. All nine incidents of ischemic complications were caused by perforator occlusion or BA ischemia. Since hemorrhage was not found on postoperative CT reexamination, perforator ischemia may not necessarily manifest on MR despite the severity of the symptoms, such as the patient in **Figure 3**. Ischemic complications during the EVT of BA trunk aneurysms may be caused by traction or coverage of BA perforations caused by coils or stents. A typical BA ischemia is shown in **Figure 6**.

Our study found that patients with mild complications, such as hemiplegia, gradually recovered with satisfactory prognoses, while the patients who developed coma had poor prognoses and eventually died. In addition, for palliatively embolized aneurysms, coiling may result in a worse prognosis. For example, in our study, a patient experienced aneurysm rupture 1 month after MRRC IIIa embolization, which is also noteworthy (**Figure 7**).

LIMITATIONS

This was a retrospective single-center study between 2015 and 2020. While the data were distributed across 5 years, the follow-up time was short in the cases close to 2020. As a result of the economic status in rural areas in China, angiographic follow-up data could be obtained only for a small proportion of the patients in this series, which affected the interpretation of the angiographic outcomes.

CONCLUSION

This study indicates that conventional EVT is still a high-risk procedure for BA trunk aneurysms, with a 35.7% incidence of complications. Therefore, it is necessary to actively and carefully evaluate the perforators of the BA trunk to ensure that EVT does not damage them. This study also shows that 82.1% of patients recovered well. Therefore, EVT can nevertheless result in an acceptable prognosis.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

AUTHOR CONTRIBUTIONS

JY and KX: contributed to the conception and design of the manuscript and critically revised the manuscript. YW and JS: collected the medical records of the patients and wrote the manuscript. All authors approved the final version this manuscript.

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Neurology

ORIGINAL RESEARCH
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Utility of CT Perfusion Imaging in Patients With Vertebral Artery Stenosis Treated With Balloon Expandable Stent

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Objective: To investigate the clinical value of CT perfusion (CTP) imaging in vertebral artery stenosis stenting, so as to provide the basis for preoperative and postoperative evaluation. Ninety-seven patients with vertebral artery stenosis were accepted for endovascular stenting between Jan 2016 and Jan 2020. CT angiography, Digital Subtraction Angiography, and CTP were performed pre-operation and post-operation. The cerebral blood volume (CBV), cerebral blood flow (CBF), and mean transmit time (MTT) between the health and affected sides were analyzed statistically, and the imaging results pre- and post-operation were evaluated. The stenosis was relieved by endovascular stents in all 97 patients without serious complications. The abnormal perfusion was observed in 66 patients (68%). The differences in CBF and MTT between the diseased side and healthy side were statistically significant ($P < 0.05$). Compared with the preoperative imaging, the postoperative CTP was improved in 59 patients (89%). The differences in CBF and MTT between pre-operation and post-operation were statistically significant ($P < 0.05$). But there was no significant difference in CBV. CTP can sensitively reflect the perfusion of brain, and can also be used for preoperative and postoperative evaluation of vertebral artery stenting. It may be helpful as an adequate indicator of vertebral artery stenosis stent surgery.

Keywords: vertebral artery stenosis, stent, CT perfusion, cerebral blood flow, mean transmit time, cerebral blood volume

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INTRODUCTION

Stroke is a serious threat to human health, ∼87% of all strokes are ischemic strokes (1), among which posterior circulation (PC) ischemic stroke accounts for about 20%. Nearly 25% of patients with vertebral artery stenosis or basilar artery stenosis have progressed cerebral infarction, and symptomatic vertebrobasilar artery stenosis is especially prone to recurrent stroke (2). Vertebral artery (VA) stenosis can be effective treated with balloon dilatation or vertebral artery stenting (3, 4). Very low complication rates (1–1.5%) have been suggested with stenting for extracranial VA stenosis, however higher complication rates for intracranial stenosis about 7–10% (5–7). Patients with vertebral artery stenosis may only show dizziness, but dizziness can be caused by several diseases. This symptom is not very objective. Even if vertebral artery stenosis causes cerebral ischemia, CT and MRI do not show ischemic lesions due to the compensation of

collateral circulation. So far, the indication of vertebral artery stenosis stent surgery has often been determined by clinical symptoms which sometimes may be not obvious and easily neglected, the degree of imaging stenosis, and lack of objective indicators. CT perfusion (CTP) imaging could quantitatively analyze the cerebral blood flow through the cerebral blood volume (CBV), the cerebral blood flow (CBF), and mean transit time (MTT), which were used to show the cerebral blood supply and perfusion of ischemic cerebrovascular disease (8, 9). Therefore, CTP may be helpful as an adequate indicator of vertebral artery stenosis stent surgery.

METHODS

Patient Data

From Jan 2016 to Jan 2020, 97 patients in Dalian Municipal Central Hospital Affiliated of Dalian Medical University were diagnosed with vertebral artery stenosis by CT angiography (CTA) or Digital Subtraction Angiography (DSA), and received endovascular stent treatment in our department.

Inclusion and Exclusion Criteria

Inclusion criteria: (1) The unilateral vertebral artery opening stenosis which was at least 50% was confirmed by CTA or DSA, with posterior circulation ischemia symptoms. (2) The vertebral artery stenosis is on the dominant side. (3) No other intracranial vascular diseases. Exclusion criteria: (1) The unilateral vertebral artery stenosis was <50%. (2) Non-dominant side vertebral artery stenosis was >50%. (3) Vertebral artery intracranial segment with multiple stenosis.

Perioperative Management

In our study DSA or CTA and CT perfusion (CTP) were arranged within 3 days before and after surgery to evaluate the ischemic degree of the vertebral artery. All patients were injected with 40 ml iodixanol with a high-pressure syringe in the median cubital vein, scanned CT with 5 mm, and reconstructed with 1.5 mm slice thickness. The reconstruction and perfusion analysis of images were carried out using the advantage work station version 4.5 software (AW45, USA). The CBF, CBV, and MTT of the diseased side and the healthy side, as well as pre-operation and post-operation were measured. DSA procedure: After successful local anesthesia, Seldinger technique was used to puncture the radial artery or femoral artery, and a 6F artery sheath was routinely used to perform bilateral subclavian artery and common carotid artery angiography, respectively. The angiography tube could be placed in the subclavian artery to better display the vertebral artery opening, and the degree and length of vascular stenosis were shown at an appropriate Angle. According to North American symptomatic carotid endarterectomy trial (NASCET), the vertebral artery stenosis was graded, the moderate stenosis rate was 50–70%, and the severe stenosis rate was 70–99%. All patients started receiving aspirin (100 mg/d) and clopidogrel (75 mg/d) daily at least 3 days before stenting or a loading dose of aspirin and clopidogrel of 300 mg, respectively, if emergency surgery was needed. After surgery, they were maintained on aspirin (100 mg/d) and clopidogrel (75 mg/d) for no <6 months.

Vertebral Artery Stenting Procedure

All the patients were confirmed by DSA or CTA as vertebral artery origin stenosis. The patients were treated with Apolo balloon expandable stent (Shanghai minimally invasive company) or Vertebral artery balloon expandable stent (Boston Scientific, USA).

After anesthesia, with the Seldinger technique, a right femoral artery puncture was performed to place an 8F arterial sheath, the patients received intravenous injection of 3,000 U low-molecular-weight heparin sodium for systemic heparinization. Then a Gateway balloon was chosen and placed across the stenotic segment for balloon dilation. After successful expansion, the balloon was withdrawn. According to the normal diameter and stenosis length of the vertebral artery, the size of the stent was selected. Then the stent was placed in the lesioned vessel. When radiographic examination reported the degree of stenosis improved significantly, the stent delivery system was removed. Intracranial angiography was repeated after observation for 30 min, if no abnormalities were found, the operation was finally finished.

Statistical Methods

All analyses were performed using the SPSS 25.0 software (SPSS Inc., Chicago, IL, USA). Measurement data is expressed in $\overline{x} \pm s$. The parameters of the diseased side and the healthy side, as well as pre-operation and post-operation, were compared by *t*-test.

RESULTS

A total of 97 patients with vertebral artery stenosis which accepted vertebral artery stenting were enrolled in this study. There were 45 males and 42 females, aged from 50 to 80 years old (median age 65 years). Clinical manifestations: dizziness in 60 cases, walking instability in 22 cases, headache with nausea in 15 cases. Preoperative DSA confirmed moderate stenosis in 47 cases, severe stenosis 50 cases. All patients were examined by CTP in peri-operation period, the abnormal perfusion was observed in 66 patients (68%). The positive rate of abnormal perfusion area corresponding to clinical symptoms found in MTT was 100%. And the abnormal perfusion area was found in 40 cases on CBF, the positive rate was 61%. In CBV the positive rate was only 26%. And total 58 cases (88%) had significant improvement in CT perfusion after vertebral artery stenting. Compared with the healthy side, the difference of CBF and MTT in the diseased side was statistically significant. Besides, compared with pre-operation, CBF was significantly increased and MTT was decreased after vertebral artery stent implantation. But there was no significant difference in CBV (The detailed discrepancy was shown in **Tables 1, 2**).

TABLE 1 | Comparison of CTP perfusion parameters between diseased side and healthy side.

Parameter	Healthy side	Diseased side	*t*-value	*P*-value
CBF [ml/(100 g·min)], ($\bar{x}$± s)	45.47 ± 6.69	35.79 ± 5.49	−8.869	0.000*
CBV (ml/100 g), ($\bar{x}$ ± s)	1.82 ± 0.25	1.92 ± 0.38	1.63	0.106
MTT (s)	3.86 ± 0.26	4.78 ± 0.56	11.79	0.000*

*$P < 0.05$, with statistical significance.

TABLE 2 | Comparison of CTP perfusion parameters between pre-operation and post-operation.

Parameter	Pre-operation	Post-operation	*t*-value	*P*-value
CBF [ml/(100 g·min)], ($\bar{x}$ ± s)	35.16 ± 4.09	46.79 ± 5.55	−13.70	0.000*
CBV (ml/100 g), ($\bar{x}$ ± s)	1.71 ± 0.31	1.78 ± 0.21	−1.61	0.100
MTT (s)	4.43 ± 0.56	3.96 ± 0.21	6.34	0.000*

*$P < 0.05$, with statistical significance.

DISCUSSION

In clinic, vertebrobasilar artery stenosis was a common disease leading to recurrent PC strokes, the main treatment for this disease was stent implantation. At present, the indications of stenting for vertebral artery stenosis are usually determined by whether the degree of stenosis is more than 50% which is detected by CTA or DSA examination before operation, and corresponding clinical symptoms such as dizziness, walking unsteadily, or the other symptoms (10–13). However, there was no objective assessment of the blood flow in the posterior circulation. The CTP examination often used MTT, CBF, and CBV to evaluate the perfusion state of brain tissue. Sometimes, there may be no abnormal expression of MRI and CT before clinical onset of cerebral infarction. Several studies suggested that CTP, MTT, and CBF can quantitatively and effectively evaluate cerebral hemodynamic abnormalities before cerebral infarction (14). The changes of the above parameters represented corresponding brain function, and CTP was very sensitive to early cerebral hemodynamic changes (15–18). In our study, the abnormal perfusion was observed in 66 patients (68%). Among them MTT was 100%, which was consistent with the corresponding clinical symptoms. And the abnormal perfusion area was found in 40 cases on CBF (61%) and 17 cases on CBV (26%). It was shown that CTP could sensitively demonstrate the abnormal perfusion of posterior circulation, especially MTT. Among the above three parameters, MTT was the most sensitive in early detection of perfusion abnormalities. The results of our study were similar to those of previous studies, which suggested that CTP may be utilized in the posterior circulation (19–22), and MTT parameters are more sensitive than CBF or CBV for identifying lacunar infarcts (23). In addition, in our study 31 patients with the stenosis at the opening of the vertebral artery more than 50% confirmed by CTA or DSA, but the changes of CBF and CBV were not obvious. It was speculated that the mechanism may be as follows: There are many collateral circulations which were normally not open in cerebral vessels. However, when chronic stenosis or occlusion occurs, the collateral vessels proliferate, the distal vessels dilate, and the blood flow increases to maintain the normal level of CBF. In addition, even though the feeding artery was completely occluded, the collateral circulation has already been established in the process of chronic occlusion, which could also maintain normal cerebral blood flow and cerebral perfusion. Therefore, patients did not necessarily benefit from stenting in such patients. Besides, when the vertebral artery stenosis occurred in the non-dominant blood supply side, the cerebral blood flow and perfusion was not affected, and there was also no indication of vertebral artery stenting.

Based on our findings, DSA or CTA may be more sensitive as an indicator of vertebral artery stenosis stent surgery compared with CT imaging, and as we know that DSA was the gold standard for the diagnosis of cerebrovascular diseases, this could accurately demonstrate the degree of cerebral vascular stenosis and the state of cerebral vascular collateral circulation. However, it was an invasive examination and expensive, so sometimes it was not easy for patients to accept. Although CTA was a non-invasive examination, its imaging was sometimes affected by bone calcification, which is not as accurate as DSA. Compared with the above two examinations, CTP could directly reflect the cerebral blood flow perfusion, rather than simply taking the degree of vascular stenosis as the surgical indication (24–26). In our study, there were a total of 66 patients with abnormal preoperative CT perfusion, and 58 of them has been improved significantly after operation. This suggested that CTP could not only evaluate the effect of vertebral artery stenting, but also observe the improvement of cerebral perfusion. In summary, CTP can sensitively reflect the perfusion of the brain, and can also be used for preoperative and postoperative evaluation of vertebral artery stenting. So, it may be helpful as an adequate indicator of vertebral artery stenosis stent surgery.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Dalian Municipal Central Hospital. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

WW and CS collected the data and wrote the original manuscript draft. WW analyzed the data. XL and DJ revised the manuscript and approved the final version. All authors contributed to the article and approved the submitted version.

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Safety and Efficacy of Endovascular Therapy for Blood Blister-Like Aneurysms: Willis Covered Stents and Double Stents Assistant Coils—A Single Center Cohort Study

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Objective: To summarize and discuss the application of Willis covered stents (WCSs) and double stent-assisted coils in the treatment of blood blister-like aneurysms (BBAs).

Materials and Methods: Thirty-two patients with BBAs treated from January 2015 to October 2020 were included in the study. Among them, 18 were treated using WCSs and 14 using double stents-assisted coils. The indications for treatment, perioperative findings, and postoperative follow-up results were collected and analyzed.

Results: All 32 patients had successful stent deployments. Complete aneurysm occlusion was achieved in all 18 patients treated with WCSs immediately. WCS-related adverse events included 2 cases of mild vasospasm and 4 aggressive procedure-related vasospasms during WCS deployment, a case of dissection after WCS deployment, and 1 death due to ipsilateral temporal lobe rebleeding at the sixth day after WCS deployment. In patients treated with double stent-assisted coils, there were 3 cases of neck remnants, 1 acute occlusion of the ipsilateral MCA branch, and 4 mild procedure-related intraoperative vasospasms. The mean follow-up period was 4.2±1.6 months (range 3–6 months). Follow-up imaging data were available for 25 patients (78.1%). In the first postoperative angiographic follow-up, all BBAs were completely occluded. Mild asymptomatic stent stenosis was observed in 3 patients treated with WCSs. Follow-up examination at 6 months after the employment of WCSs showed that the modified Rankin score (mRs) was 0 in 6 patients, 1 in 5 patients, 2 in 3 patients, 3 in 1 patient, 4 in 2 patients, and 6 in 1 patient. After treatment with double stents-assisted coils, the mRs was 0 in 4 patients, 1 in 5 patients, 2 in 3 patients, and 4 in 2 patients.

Conclusions: WCSs and double stent-assisted coils for the treatment of BBAs are both safe and efficient. WCSs provide a higher rate of immediate occlusion; however, there was no significant difference in the long term.

Keywords: digital subtraction angiography, embolization procedures, endovascular therapy, blood blister aneurysms, Willis covered stents

INTRODUCTION

Blood blister-like aneurysm (BBA) is a special type of intracranial aneurysm with a relatively low morbidity and high mortality (1–3). Most BBAs are located in the anterior wall or the anterior medial wall of the non-branching sites of the supraclinoid segment of the internal carotid artery (ICA). Their typical clinical manifestation is subarachnoid hemorrhage (SAH). Histologically, BBAs are characterized by the presence of blood clots in the arterial walls, thinned tunica adventitia, absence of collagen in the tunica media, and defective endovascular membranes (4).

These unique morphological and histological features present a challenge to neurosurgeons and neurointerventionalists. The current treatment strategy mainly includes surgical and endovascular methods. The former includes clipping, wrapping, suturing, and isolation coupled with arterial bypass, while the latter includes endovascular ICA ligation, coils, stent-assisted coils, multiple overlapping stents, WCSs, and flow diverters (5).

Although multiple clinical trials have employed various surgical and endovascular techniques, no unified BBA diagnosis and treatment standard has been established due to its complexity. Compared with endovascular methods, microsurgery can provide a higher occlusion rate. However, the disadvantages of microsurgery include the higher rate of complications and neurologic impairments (6–8). Technological improvements in intervention devices have led to improved safety and recovery rates associated with endovascular methods (5). A previous double-center study reported that the rates of complete occlusion and recovery in BBAs when using endovascular treatment were 72.9 and 64%, respectively (3, 9, 10). Owing to the lack of an ideal therapeutic strategy for BBAs, we reported the safety and efficacy of WCSs and double stent-assisted coils in the treatment of BBAs. Herein, we report our strategy and analysis of BBA treatment using endovascular methods.

PATIENTS

We retrospectively reviewed 32 patients with BBAs treated in **Province Hospital between 2015 and 2020. All patients were treated by WCSs or double stents-assisted coils. The following information on the patients was extracted: patient demographics, aneurysm information (location, size, prior treatment), operation timing, periprocedural complications, and follow-up information. The initial clinical status of the patients was evaluated by the Hunt and Hess grading system and the post operational clinical status of the patients was evaluated by modified Rankin Scale (mRS).

DIAGNOSIS

The inclusion criteria include (1) aneurysms located at supraclinoid ICA's anterior wall or anterior medial; (2) non-branching sites; and (3) SAH corresponding to the aneurysm. An aneurysm was included as a BBA of the ICA when criteria 1–3 were all matched. Diagnosis results were independently adjudicated by at least two authors.

TREATMENT PROCEDURE

All patients had undergone emergency surgeries as early as possible after diagnosis. The duration between operation and the onset of SAH is 2 days in the patients treated by WCSs and 2.2 days in patients treated by double stents assisted coils ($P = 0.64$). Endovascular treatment was performed under general anesthesia using a right femoral approach. After completing cerebral angiography, device type, WCSs or double overlapping stent-assisted coils, was selected. The initial delivery system was a 6F Navien catheter (Ev3) for WCS and a 6F ENVOY catheter (Cordis) for porous stents.

Navien guide catheter was deployed over the neck of the aneurysm to achieve greater support. The stent extended at least 2 mm beyond the neck of the aneurysm on both sides. The diameter of the stent used was ∼0.5 mm wider than the diameter of the parent artery. WCS was guided to cross the neck of the aneurysm using a guidewire and deployed with a pressure of 5–6 atmospheres under roadmap guidance after confirming that no branches were influenced repeatedly. If endoleaks were observed, re-expansion of the stent was performed with greater pressure to unfold the stent completely.

ENVOY guide catheter was deployed in the C4 segment of ICA. Stent size was selected according to the largest diameter of the parent artery and the length of the aneurysm. It was ensured that the porous stent extended at least 7 mm beyond the neck of the aneurysm on both sides because at both the ends 2 mm of the stent is unusable. The PLUS (Johnson & Johnson) was guided over the neck for 3 cm by a guidewire that was placed in the middle cerebral artery. The Echelon-10 microcatheter was guided into the aneurysmal sac after condensation molding. Then, half of the first stent was released, and the coil was placed into the aneurysmal sac with the assistance of the stent. After the BBA disappeared, the stent was released completely and the second stent deployed. To enhance the rate of occlusion of the aneurysmal neck, the "lantern technology" was adopted by "pushing and pulling" the LVIS stents.

ANTIPLATELET AND ANTICOAGULANT PROTOCOLS

Once the patient was definitively diagnosed and decided to receive interventional treatment, a dose of 300 mg clopidogrel and 300 mg aspirin was administered through a nasogastric tube before the treatment procedure. During the operation, all patients received intravenous heparin injection to maintain an activated clotting time of 250–300 s. In the case of appearance of fresh stent thrombosis, arterial tirofiban injection was administered through guide catheter as a remedial measure. And intravenous tirofiban injection would last for 8 h. After operation, all patients took dual antiplatelet therapy (clopidogrel 75 mg/day and aspirin 100 mg/day) orally for at least 3 months and single antiplatelet therapy (aspirin 100 mg/day) orally for at least 1 year. On

the third day of dual antiplatelet therapy, a thrombelastogram test was performed and suggested the inhibitory rate of AA (arachidonic acid) and ADP (adenosine diphosphate). When the AA inhibitory rate was lower than 50% or the ADP inhibitory rate lower than 30%, adjunctive cilostazol (100 mg, twice a day) was an alternative antiplatelet medicine. For those patients with acute hydrocephalus and altered mental status, external ventricular drainage was immediately performed in the hybrid operating room after neutralizing heparin with protamine.

CLINICAL AND ANGIOGRAPHIC FOLLOW-UP

Results of angiography were categorized using the Raymond Classification as Raymond 1 (complete occlusion: no contrast filling the sack and neck of aneurysm), Raymond 2 (subtotal occlusion: decreased contrast filling the neck of aneurysm), and Raymond 3 (recurrence: contrast filling the sac of aneurysm). On appearance of any uncomfortable symptoms, the patients were made to obtain a brain computerized tomography (CT) or magnetic resonance imaging (MRI) scan. Angiographic and clinical follow-ups were performed for a period of 3–6 months after discharge from the hospital. All patients were assessed using digital subtraction angiography (DSA), and postoperative neurologic disability was evaluated using modified Rankin scale (mRS). Twenty-five patients were evaluated using DSA in our medical center, and their clinical and angiographic data were analyzed. Additionally, MRI once a year would be recommended for those patients with in-stent stenosis.

STATISTICAL ANALYSIS

Continuous variables are expressed as the mean value ± standard deviation (SD). Categorical variables are presented as the count (percentage). Continuous variables were compared using the unpaired Student's *t*-test. The *p*-values < 0.05 were considered statistically significant.

RESULTS

This study included 19 men and 13 women, with a mean age of 52.5 years (range, 29–75 years). Among the 32 patients with BBAs, 18 patients were treated using WCSs and others were treated using double overlapping stents-assisted coils. The porous stents including 24 LVISs and 4 EPs (ENTERPRISE) were placed in 14 patients. Demographic information on the patients is provided in **Table 1**. The preoperative Hunt-Hess grades were I in 1 patient with the deployment of WCSs, II in 7 patients, III in 7 patients, and IV in 3 patients. And the preoperative Hunt-Hess grades were I in 1 patient with the deployment of porous stents, II in 7 patients, III in 5 patients, and IV in 1 patient ($P = 0.41$).

In all patients, deployment of the WCSs and porous stents was technically successful. Complete occlusion of the aneurysm was achieved in all 18 patients after the placement of 1 WCS. The procedure of double stents assistant coils resulted in Raymond 1 occlusions in 11 patients (78.6%) and neck remnants (Raymond 2) in 3 patients (21.4%). And 1 acute occlusion of ipsilateral MCA branch and 4 mild vasospasms occurred intraoperationally treated by double stents assistant coils. Six vasospasms happened during the deployment of WCSs and a patient died for ipsilateral temporal lobe rebleeding at 6 days after the deployment of the WCS. A mild dissection was caused by the guiding catheter during the deployment of the WCS. After endovascular therapy, three patients treated by WCS and one patient treated with double stents assistant coils were performed external ventricular drainages immediately due to acute hydrocephalus after neutralizing heparin with protamine in hybrid operation room. And a patient treated by double LVISs assistant coils was performed ventriculoperitoneal shunt after the discontinuation of antiplatelet agents for 3 days in the third month after endovascular therapy due to communicating hydrocephalus. No hemorrhage was detected by CT scans after these invasive operations.

Follow-Up Results

The mean follow-up period was 4.2 ± 1.6 months (range 3–6 months). Twenty-five patients were available for the imaging follow-ups. All BBAs had been occluded while preserving the patency of the ICA. Additionally, the Raymond 2 occlusions in the 2 patients that had neck remnants improved to Raymond 1 occlusion. And the mild dissection disappeared in the follow-up. However, 3 patients showed in-stent asymptomatic stenosis with the deployment of WCSs and they continued to receive dual antiplatelet therapy orally and were followed up regularly. Follow-up examination after the endovascular treatment showed that good clinical outcome (mRS score of 0–2) were achieved in 14 patients (77.8%) treated by WCSs and 12 patients (85.7%) treated by double stents-assisted coils ($P = 0.66$). Illustrative cases were shown in **Figures 1**, **2**.

DISCUSSION

With the improvement in endovascular interventional devices, interventional therapy has gradually become mainstream in BBA treatment (5, 11). Despite the lack of a uniform treatment guideline, various interventional treatment strategies have achieved satisfying outcomes, including WCSs, double porous stent-assisted coils, and flow diverters. A former study reported that 76.5% of patients achieved complete aneurysm occlusion and only 9.2% of patients encountered serious complications (12). The use of double porous stent-assisted coils results in higher recurrence and intraoperative rebleeding rates compared with WCSs and flow diverters. However, the use of flow diverters for BBAs is limited in China. Therefore, the use of WCSs and double porose stent-assisted coils are the main treatment strategies in our center. To our knowledge, this is the first study comparing WCSs with double stent-assisted coils in a single clinical setting. In the present study, we reported the comparison of results from the use of WCSs and double porous stent-assisted coils in patients with BBAs.

TABLE 1 | Endovascular treatment, outcome, and follow-up data for 32 patients with blister-like aneurysms (BBAs).

Number	Aneurysm type	diameter/mm	Pre- Op H-H	Operation Timing (after SAH)	Immediate results/ Raymond	Post-op mRS	Complications	Stents type
1	L-ICA	4.2*5.2	III	1	1	6	Vasospasm/death	WCS 4.0*10
2	R-ICA	3.7*5.7	IV	3	1	2	/	WCS 4.0*13
3	R-ICA	2.6*3.3	IV	1	1	2	Vasospasm	WCS 4.5*16
4	R-ICA	4.2*5.1	II	2	1	0	Stenosis	WCS 4.5*13
5	L-ICA	3.2*6.6	III	1	1	4	Vasospasm	WCS 3.5*13
6	L-ICA	4.8*5.6	II	1	1	1	Dissection	WCS 4.5*16
7	L-ICA	3.2*3.8	III	3	1	2	/	WCS 4.0*13
8	R-ICA	2.6*3.5	III	6	1	1	Vasospasm	WCS 4.5*16
9	L-ICA	4.5*1.7	II	1	1	0	/	WCS 3.5*13
10	L-ICA	3.1*5.6	III	1	1	1	Stenosis	WCS 4.5*16
11	R-ICA	4.2*5.2	II	2	1	0	/	WCS 4.0*13
12	L-ICA	5.2*5.4	IV	1	1	0	Vasospasm	WCS 4.0*16
13	L-ICA	3.2*2.9	I	2	1	0	/	WCS 4.0*16
14	R-ICA	4.1*3.7	II	3	1	1	/	WCS 4.5*16
15	L-ICA	3.3*4.2	III	2	1	3	/	WCS 4.0*13
16	L-ICA	2.9*3.9	II	1	1	1	Stenosis	WCS 4.0*16
17	R-ICA	1.9*2.7	II	2	1	0	/	WCS 3.5*13
18	L-ICA	2.8*3.5	III	3	1	4	Vasospasm	WCS 4.5*16
19	R-ICA	2.1*4.5	II	2	1	2	/	LVIS 4.5*15 EP 4.5*27
20	L-ICA	2.7*3.5	III	3	1	1	Vasospasm	LVIS 4.5*20 LVIS 4.5*20
21	L-ICA	2.4*3.6	III	2	1	1	/	LVIS 4.5*30 LVIS 4.5*20
22	R-ICA	4.2*6.2	III	1	2	0	/	LVIS 4.5*30 LVIS 4.5*20
23	R-ICA	4.7*5.2	II	2	1	4	/	LVIS 4.5*30 LVIS 4.5*30
24	L-ICA	3.4*3.9	II	1	2	1	Vasospasm	LVIS 4.5*30 EP 4.5*27
25	L-ICA	3.2*3.6	III	1	1	2	MCA thrombogenesis	LVIS 4.5*20 LVIS 4.5*20
26	L-ICA	3.4*4.6	II	6	1	1	/	LVIS 4.5*20 EP 4.5*27
27	R-ICA	2.5*3.4	II	3	1	0	/	LVIS 4.5*15 LVIS 4.5*20
28	R-ICA	2.9*3.8	I	2	1	0	/	LVIS 4.5*15 LVIS 4.5*20
29	L-ICA	2.6*3.4	II	2	2	1	/	LVIS 4.5*20 LVIS 4.5*20
30	R-ICA	3.2*3.9	III	3	1	2	Vasospasm	LVIS 4.5*20 EP 4.5*27
31	L-ICA	3.8*4.1	IV	2	1	3	/	LVIS 4.5*30 LVIS 4.5*20
32	R-ICA	2.4*3.9	II	1	1	0	Vasospasm	LVIS 4.5*30 LVIS 4.5*20

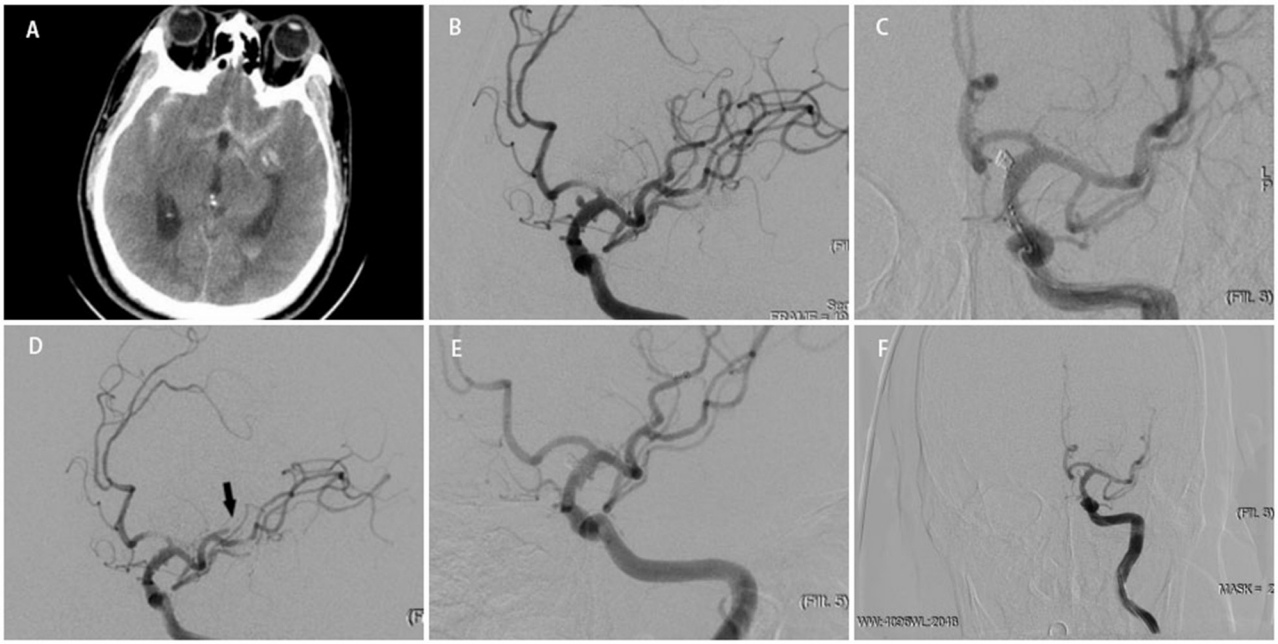

FIGURE 1 | A middle-aged person was admitted to our hospital for sudden headache 10 h earlier (H-H grade 3). An emergency cranial CT revealed diffuse subarachnoid hemorrhage **(A).** Cerebral angiography at different angles showed a BBA located at the side wall of the C7 segment of right ICA. Multiple stents+coils got the nod to protecting anterior choroidal artery and posterior communicating artery from acute occlusion **(B).**Two LVIS stents (LVIS 4.5 * 20 mm) combined with coiling were delivered and deployed successfully, and the instant angiographic result revealed no contrast filling into the aneurysm **(C).** Intraoperative angiographic revealed that a branch of MCA occluded(black arrow) **(D).** After tirofiban injection, angiographic revealed the reappearance of MCA branch and total occlusion of the aneurysm **(E).** Angiographic follow-up at 5 months revealed total occlusion of the aneurysm **(F)**.

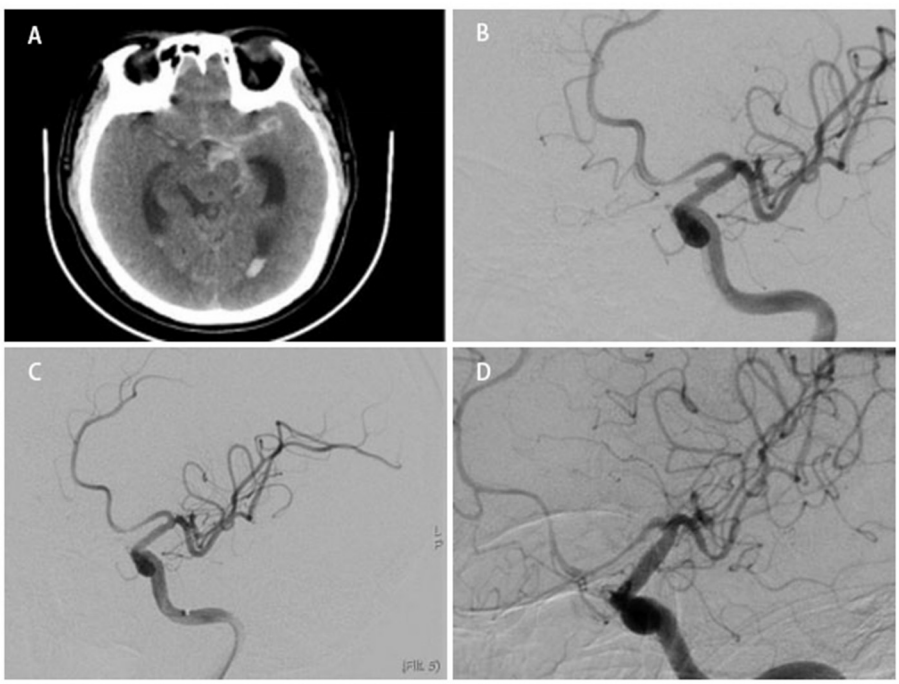

FIGURE 2 | A middle-aged person was admitted to our hospital for sudden headache 8 h earlier (H-H grade 2). An emergency cranial CT revealed diffuse subarachnoid hemorrhage **(A)**. Cerebral angiography showed a BBA located at the side wall of the C7 segment of left ICA **(B)**. After a WCS (3.5 * 13 mm) deployed successfully, the instant angiographic after once balloon dilation revealed no contrast filling into the aneurysm **(C)**. Angiographic follow-up at 4 months revealed total occlusion of the aneurysm **(D)**.

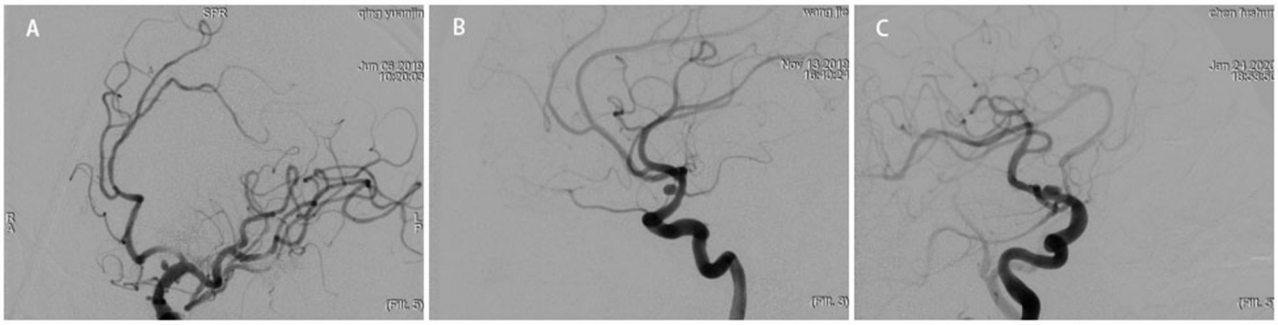

FIGURE 3 | Preoperative digital subtraction angiography (DSA) revealed that the aneurysm was located between the AChA and PCoA **(A)** and in opposite side of the AChA **(B)**. Preoperative DSA revealed that the ICA was too tortuous to use a WCS **(C)**.

Indication

Given their unique histological and pathological characteristics, BBAs must be treated as early as possible once definitively diagnosed. Theoretically, covered stents such as WCSs are the first choice due to their ability to block the aneurysmal neck and occlude the aneurysm immediately. In fact, the use of covered stents in clinical practice is strictly restricted due to their design (9). In our medical center, we give priority to the use of covered stents in treatment of aneurysm except in the following three situations: (1) when the clinoid segment of the ipsilateral ICA is too tortuous for WCSs; (2) when the distance between the lesion and the anterior choroidal artery (AChA) is <2 mm; or (3) when the difference between the proximal and distal diameters of the artery is >0.5 mm (**Figure 3**). Compared with WCSs, porose stents such as LVIS and EP have excellent compliance when dealing with tortuous arteries and are less likely to cause branch occlusion. Despite the poor immediate occlusion rate, the blood flow direction of double overlapping stents guarantees favorable outcomes more often. However, WCSs are restricted to treating aneurysms close to branched vessels. The majority of BBAs are located at the C5–C7 segments of the ICA, where the ophthalmic, anterior choroidal, and posterior communicating artery (PoCA) originate. To avoid infarction, we selected porous stents and coils over WCSs to occlude aneurysms since WCSs work by the plying-up of the polytetrafluoroethylene membrane against the vascular wall. This membrane is easily compromised when deployed inside vessels when the proximal and distal diameters have a difference over 0.5 mm. In this study, we employed ENVOY as a guiding catheter, which is sufficient to support deploying porous stents. For deploying WCSs, we used the Navien catheter. Greater support would accompany with a higher risk of vasospasm and intimal injury.

Despite the above-mentioned limitations, WCSs are still preferred over porous stents for the treatment of BBAs due to the following advantages: (1) haemodynamically, WCSs can rebuild vascular pathways effectively and supply an attachment for the tunica intima; (2) the deployment of WCSs is safe, swift, invasive, and technically simple; (3) WCSs can occlude BBAs immediately, which decreases rebleeding during the perioperative period; and (4) no space-occupying lesions occur after WCSs placement (11, 13, 14). On the contrary, double overlapping porose stents rarely cause side branch acute occlusion and easily pass through tortuous vessels. Surgeons also can achieve a better plying-up by massaging and pushing the porose stents.

Rebleeding

Owing to the lack of collagen and internal elastic membranes and because of the need to administer antiplatelet and anticoagulant therapy, the perioperative rebleeding rate was higher than in other types of aneurysms, irrespective of the method performed. Even in experienced centers, intraoperative rupture rates in BBAs have been reported to be up to 50% compared with the rate of 7% seen with saccular aneurysms (7). Compared with WCSs, double stent-assisted coils have the possibility of puncturing the aneurysm during the treatment procedure. During the acute phase of treatment, only several patients achieved Raymond 1 occlusion. The remnants of the aneurysmal neck and sac were potential risk factors for rebleeding. Additionally, WCSs can block the blood flow to occlude aneurysms immediately. However, a single patient who had a WCS deployed suffered from cardiac arrest 6 days after surgery and died in the hospital. Immediate computed tomography scans that were performed for this patient showed ipsilateral temporal lobe rebleeding. Upon inspection of the intraoperative images and vital signs, we speculated that an endoleak with relief vasospasm could cause the rebleeding. Regretfully, our conjecture was not proven correct by cerebrovascular imaging.

Stent Deployment

During our treatment procedures, we transported stents using 6F ENVOY and Navien catheters. The former was positioned into the C4 segment of the ICA and the latter was positioned as close as possible to the lesion. In this study, all 28 porose stents (24 LVISs and 4 EPs) were successfully deployed. There was no arterial dissection and only 4 cases of mild vasospasm occurred, which were alleviated instantly by arterial injection of nimodipine. However, there were 2 cases of mild vasospasm and 4 cases of aggressive vasospasms during the transport of

WCSs. The aggressive vasospasms were usually caused by the stimulation caused by WCSs for arterial wall. When aggressive vasospasms occurred, we usually enhanced the support by positioning the Navien catheter as close to the lesion as possible to transport the WCS through the bending blood vessels easily and quickly. After the WCS was in place, nimodipine was injected intravenously until the end of surgery. Two of the cases of aggressive vasospasm were not relieved until the end of the procedure, which may explain the postoperative rebleeding. Liu et al. have reported that about half the patients suffered vasospasm when treating carotid cavernous fistulas with WCSs (15, 16). Except for reversible vasospasm, artery dissections caused by rigid catheters and stents also cannot be ignored, especially when passing through the cavernous sinus segment.

Porose stents proved superior in reducing the infarction rate by completely unfolding in case of tortuous parent arteries. WCS lacked adaptability due to its complex structure, which consists of three parts: a bare stent, an expandable polytetrafluoroethylene membrane, and a balloon catheter. To ensure better wall adherence and reduce endoleaks, shorter stents that expand repeatedly are preferred. However, this may increase the procedural difficulty and the risk of vascular damage. In the present study, 12 aneurysms disappeared after a single balloon dilation and 6 endoleaks occurred. Although the endoleaks were resolved by adjusting and expanding repeatedly, this may cause potential complications, such as intimal injuries and thrombogenesis.

Despite the preoperative administration of antiplatelet and intraoperative anticoagulant therapy, the risk of acute thrombogenesis should still be taken seriously (17). The main risk factors include intimal injury and coagulation reaction from stents and catheters. A former study reported that 12.5% of patients (5 of 40) experienced perioperative thrombosis (18). Incomplete stent apposition should also not be ignored. Repeated and multi-angle angiography can provide immediate evidence of thrombus formation as filling defects or branch occlusions. The possibility of acute thrombus formation increases with longer operative time and poor stent adherence. Therefore, suitable operation planning and stent models are vitally important. In our present study, LVIS stents were used more frequently (24/28) than EPs. The tail of these stents often shows inadequate adherence when placed in a tortuous vessel and a J-shaped microconductance wire can be used to knead the stents repeatedly to unfold completely. Additionally, laser-carving stents such as the EP rarely show incomplete apposition and are a better first choice compared with braided stents (19, 20). The incomplete stent apposition of WCSs can be solved by expanding them repeatedly. A postoperative intravenous tirofiban drip is an appropriate treatment to prevent thrombosis. In the present study, only 1 patient treated by LVIS and coils showed an acute branch occlusion (middle cerebral artery upper branch), which was resolved using tirofiban injected through an arterial catheter. During the postoperative follow-up, 3 cases of asymptomatic stenosis (both stenoses $< 50\%$) were detected. However, there were no abnormal detections after thrombelastography testing. The underlying reason for the stenosis could be poor stent adherence and resistance to dual antiplatelet therapy (DAPT) (9, 19). Tan et al. reported that the mean in-stent stenosis rates with WCS deployment at 2 and 6 years were 18.0 and 29.0%, respectively (21). The timing of invasive surgery after antiplatelet therapy remains controversial. Although no hemorrhage was detected in our 4 cases, the risk of procedure-related hemorrhage should be taken seriously. However, Hudson et al. (22) suggested that both antiplatelet-associated hemorrhaging and the timing between external ventricular drain placement and DAPT initiation did not appear to be clinically significant.

Comparison With Pipeline Embolization Device (PED)

Recently, the application of PEDs in the treatment of intracranial aneurysms has been widely recommended, and BBA embolization by PED is also being attempted. PEDs show good compliance when navigating tortuous arteries, lower risk of branch occlusion, and better complete aneurysm occlusion rate at follow-up evaluations. However, the rebleeding risk in the acute period remains unknown. Mokin et al. (4) noted that although the immediate complete occlusion rate was relatively low, a good clinical outcome was achieved in 68% of patients, complete occlusion was observed in 90% of cases on follow-up angiography, and only 1 case of rebleeding occurred during the perioperative period. Thus, PED is also a safe and effective therapeutic modality for BBAs. Regrettably, the use of PED for BBAs is subject to health insurance policies in our country.

Study Limitations

This study has several limitations. First, this study did not follow a double-blinded contrast design. The selection of cases was biased because of medical ethics. Second, the number of patients was less and the follow-up period was too short. Third, this study lacks a comparison with flow diversion method because of the restrictions enforced by health care policies.

CONCLUSION

Despite achieving 100% immediate occlusion rate, the postoperative mRs scores in patients who were treated with WCSs did not show a clear advantage due to the higher complication rate and increased complication severity.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the studies involving human participants were

reviewed and approved by Jiangsu Province Hospital. The patients/participants provided their written informed consent to participate in this study. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

HL and HaC put forward the viewpoint of this article. HaC wrote this report. CL, ZL, and HuC participated in those operation. HL, HaC, and YS collected the data. All authors contributed to the article and approved the submitted version.

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The SMART Registry: Long-Term Results on the Utility of the Penumbra SMART COIL System for Treatment of Intracranial Aneurysms and Other Malformations

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Introduction: Penumbra SMART COIL® (SMART) System is a novel generation embolic coil with varying stiffness. The study purpose was to report real-world usage of the SMART System in patients with intracranial aneurysms (ICA) and non-aneurysm vascular lesions.

Materials and Methods: The SMART Registry is a post-market, prospective, multicenter registry requiring ≥75% Penumbra Coils, including SMART, PC400, and/or POD coils. The primary efficacy endpoint was retreatment rate at 1-year and the primary safety endpoint was the procedural device-related serious adverse event rate.

Results: Between June 2016 and August 2018, 995 patients (mean age 59.6 years, 72.1% female) were enrolled at 68 sites in the U.S. and Canada. Target lesions were intracranial aneurysms in 91.0% of patients; 63.5% were wide-neck and 31.8% were ruptured. Adjunctive devices were used in 55.2% of patients. Mean packing density was 32.3%. Procedural device-related serious adverse events occurred in 2.6% of patients. The rate of immediate post-procedure adequate occlusion was 97.1% in aneurysms and the rate of complete occlusion was 85.2% in non-aneurysms. At 1-year, the retreatment rate was 6.8%, Raymond Roy Occlusion Classification (RROC) I or II was 90.0% for aneurysms, and Modified Rankin Scale (mRS) 0-2 was achieved in 83.1% of all patients. Predictors of 1-year for RROC III or retreatment (incomplete occlusion) were rupture

status ($P < 0.0001$), balloon-assisted coiling ($P = 0.0354$), aneurysm size ($P = 0.0071$), and RROC III immediate post-procedure ($P = 0.0086$) in a model that also included bifurcation aneurysm ($P = 0.7788$). Predictors of aneurysm retreatment at 1-year was rupture status ($P < 0.0001$).

Conclusions: Lesions treated with SMART System coils achieved low long-term retreatment rates.

Clinical Trial Registration: https://www.clinicaltrials.gov/, identifier NCT02729740.

Keywords: embolization coil, intracranial aneurysm, SMART COIL, intracranial fistula, intracranial malformations

INTRODUCTION

Intracranial aneurysm rupture is a catastrophic clinical outcome and occurs annually in ∼30,000 people in the U.S. (1) Endovascular coiling is widely accepted as treatment for intracranial aneurysms following the results from ISAT (2). Endovascular coiling was shown to be safe and efficacious and resulted in less disability than surgical clipping. However, retreatment rate at 1-year was higher for coiling (17.4%) than for surgical clipping (3.8%) (3). In the decade since the ISAT results were published, advances in coiling technology, including deliverability, materials, and design, have been developed. Endovascular coiling remains a viable treatment alternative to flow diverters and intrasaccular devices.

The Penumbra SMART COIL® (SMART) System is a microcoil system, which includes SMART COIL®, Penumbra Coil 400™ (PC400™), and Penumbra Occlusive Device® (POD®) indicated for endovascular embolization in the peripheral and neuro vasculature. All devices were available in the U.S market at the start of enrollment in 2016. The SMART System's unique design feature is varying levels of softness that increase toward the proximal tip. This progressive softness enhances deliverability in multiple aneurysm sizes and shapes. The SMART System design may improve deployment by stabilizing the microcatheter positioning, compared to other coils with uniform stiffness (4). The unique design of the SMART System may possibly assist with achieving higher packing density and adequate occlusion in multiple aneurysm types.

Other SMART Coil study results reported adequate aneurysm occlusion between 71.2 and 100% of treated aneurysms, low rebleeds, and low retreatment rates (5–8). Those studies had either small sample sizes, few study sites, or lacked long-term follow-up. The SMART Registry was a prospective, post-market study, designed to evaluate the SMART System in the treatment of intracranial aneurysms and other neurovascular lesions. We report the results of the SMART Registry procedural and long-term study endpoints in patients with intracranial aneurysm or other, non-aneurysm lesions, and investigate predictors of aneurysm retreatment and inadequate occlusion at 1-year. The SMART Registry provides valuable insights on treatment practices in the U.S. and real-world data on common safety and efficacy outcome measures.

MATERIALS AND METHODS

Design

The SMART Registry was a prospective, single-arm, post-market, multicenter registry of the SMART System (Penumbra, Inc.). A maximum of 1,000 patients were planned to be enrolled in up to 100 international sites. Patients were treated in accordance with the cleared indications for the SMART, PC 400, and POD for intracranial aneurysms and other, non-aneurysm vascular lesions. The study received approval from the Institutional Review Board (IRB) and Ethics Committee (EC) from each participating site with oversite for the duration of the registry. The study was designed in accordance with the relevant aspects of clinical research regulations. Written informed consent was provided by patients or their legally authorized representative (LAR). For patients that were treated in emergent cases, they were allowed to be enrolled if they signed the consent within one calendar day after the procedure, or if a LAR signed on their behalf. Penumbra, Inc. sponsored the oversite of this trial.

Eligibility Criteria

Patients included in the SMART Registry were required to have a signed consent form and undergo embolization of an intracranial aneurysm or other neurovascular abnormalities such as an arteriovenous malformations or an arteriovenous fistula (non-aneurysm lesions) according to the cleared indications. Patients were excluded if SMART, PC400, or POD coils accounted for <75% of the total number of coils implanted; if their life expectancy was <1 year; if they were already enrolled in the SMART Registry, or if they were participating in another investigation(s) that could confound results.

Endpoints

The primary efficacy endpoint was retreatment at 1-year (±6 months), and the primary safety outcome was procedural device-related serious adverse events (SAEs) within 24 h of the procedural arterial puncture. The secondary efficacy endpoints were ability to achieve adequate occlusion immediate post-procedure and the number of times re-access with the microwire was required due to catheter kickout. Other clinical outcomes were adequate occlusion, recanalization, and modified Rankin Scale (mRS) 0-2 at 1-year; all-cause mortality within 24 h of procedure and at 1-year; and all SAEs that were intraprocedural

or within 24 h of procedure, after 24 h and up to 365 days (±180 days for visits in window).

Procedures and Data Collection

Demographics and medical history were recorded at the baseline visit and all patients were assessed in accordance with the institutional standard of care. Endovascular embolization procedures were completed per each investigational site's standard of care. Coil diameter and lengths were selected on the basis of aneurysm dimensions and physician preference. All lesions were treated with ≥75% SMART coils. Patients were administered local, conscious, or general sedation per physician preference. Target lesions were accessed by transfemoral, transradial, or other approaches. All adjunctive techniques and devices were permitted. Cerebral angiograms were obtained immediate post-procedure and at 1-year (±6 months). The aneurysm occlusion status was determined by the treating physician immediately post-procedure and the results were used to compare to the follow-up assessment. From the time of enrollment through study exit, safety endpoints were monitored, and adverse events were collected and assessed for whether they were serious, device related, or procedure related. Study data was collected by investigational sites using Inform electronic data capture (EDC) system.

Study Definitions

The RROC was used to determine angiographic aneurysm occlusion status, with Class I as complete occlusion, Class II as residual neck, and Class III as residual aneurysm (9). For non-aneurysm lesions, occlusion was recorded as complete or incomplete as determined by the treating physician's assessment of whether blood flow remained on post-procedure imaging. The Hunt and Hess scale (10) was used at admission to determine severity of ruptured aneurysms; all scores were eligible for enrollment. For device-related and procedure-related SAEs, relationship to the device (definite/probable/possible/unrelated) was determined by the investigator. Events reported as "definite, probable, or possible" were classified as "related." Coil packing density was calculated by using either software calculators or by calculating aneurysm volume assuming an ellipsoid model and coil volume [$V = \pi\ (p/2)^2 \times L$], where p represents primary coil diameter, and L represents coil length. Packing density was not calculated for patients with deconstructive treatment, fusiform or dissecting aneurysms, or non-aneurysmal lesions. A wide-necked aneurysm was defined as having a dome-to-neck ratio < 2 or a neck width of at least 4 mm. The Modified Rankin Scale (mRS) was captured at admission and at 1-year if available per the site standard of care.

Statistical Analysis

The predetermined sample size ($n = 1{,}000$) allowed the expected retreatment rate of 8.3% at 1 year to be estimated with $> \pm$ 2% precision. Summary statistics for all patients, patients with aneurysm, and patients with non-aneurysm lesions were developed separately. Descriptive statistics with a 95% two-sided confidence interval were presented for most analyses. Continuous variables were summarized with descriptive statistics [n, mean, standard deviation, median, and interquartile range (IQR)]. For categorical data, frequency counts and percentage of patients within each category were included. Predictive analyses were performed for 1-year outcomes after aneurysm treatment—incomplete occlusion (RROC III or retreatment) and retreatment. The analyses were run by using binary logistic regression models with stepwise selection (alpha-to-enter ≤ 0.20, alpha-to-leave > 0.05). The following variables were considered for predictive models when their univariate logistic regression p-value was ≤0.20: patient age, sex, history of hypertension history of smoking, cocaine use, and family history of aneurysm or malformation; aneurysm type, size, and location; aneurysm status as ruptured, wide-necked, and neck width at least 4 mm; stent-assisted coiling; balloon-assisted coiling; deconstructive treatment; coil packing density; and RROC immediately post-procedure. SAS 9.4 (SAS Institute) was used for statistical programming.

RESULTS

All Patient Outcomes

Demographics and Baseline Characteristics

Between June 2016 and August 2018, 995 patients were enrolled at 67 US sites (989 patients) and one Canadian site (6 patients). **Figure 1** illustrates the study Flow Diagram. Baseline characteristics and medical history for all patients and by aneurysm and non-aneurysm cohort are presented in **Table 1**. The target lesion was an intracranial aneurysm in 905 (91.0%) patients; the remaining 90 (0.9%) lesion types were arteriovenous fistula, arteriovenous malformation, and vessel sacrifice or other pseudoaneurysm. For the overall population, mean age of patients was 59.6 years (SD 13.00, range 12–93 years), 72.1% of the patients were female, 61.2% had a history of smoking, 60.6% had a history of hypertension, and 17.1% had a family history of aneurysm or malformation.

Lesion characteristics are described in **Table 2**. Most (75.2%) lesions were located in the anterior circulation. The lesion was on the left side in 35.6% patients, on the right side in 35.6% patients, and on the midline in 28.8% patients. Lesion locations included 3.7% (37/995) extradural ICA, 33.0% (328/995) ICA, 26.7% (52/995) ACA, 11.8% (117/995) MCA, 18.9% (188/995) posterior circulation, 2.4% (24/995) venous circulation, and 3.5% (35/995) other.

Procedural Characteristics

Procedural characteristics are described in **Table 3**. The mean time from first coil deployment to last coil detached was 24.1 min (SD 25.73) and the median time was 16.0 (IQR 8.0, 32.0).

Performance Outcomes

Adequate occlusion at immediate post-procedure was achieved in 97.1% (965/994) of patients. The first framing coil was completely conformed to the lesion morphology in 83.1% (766/922) of cases. At 1-year, retreatment occurred in 6.8% (53/784) of patients and 83.1% (463/557) had mRS 0-2. Patient outcomes are provided in **Table 4**.

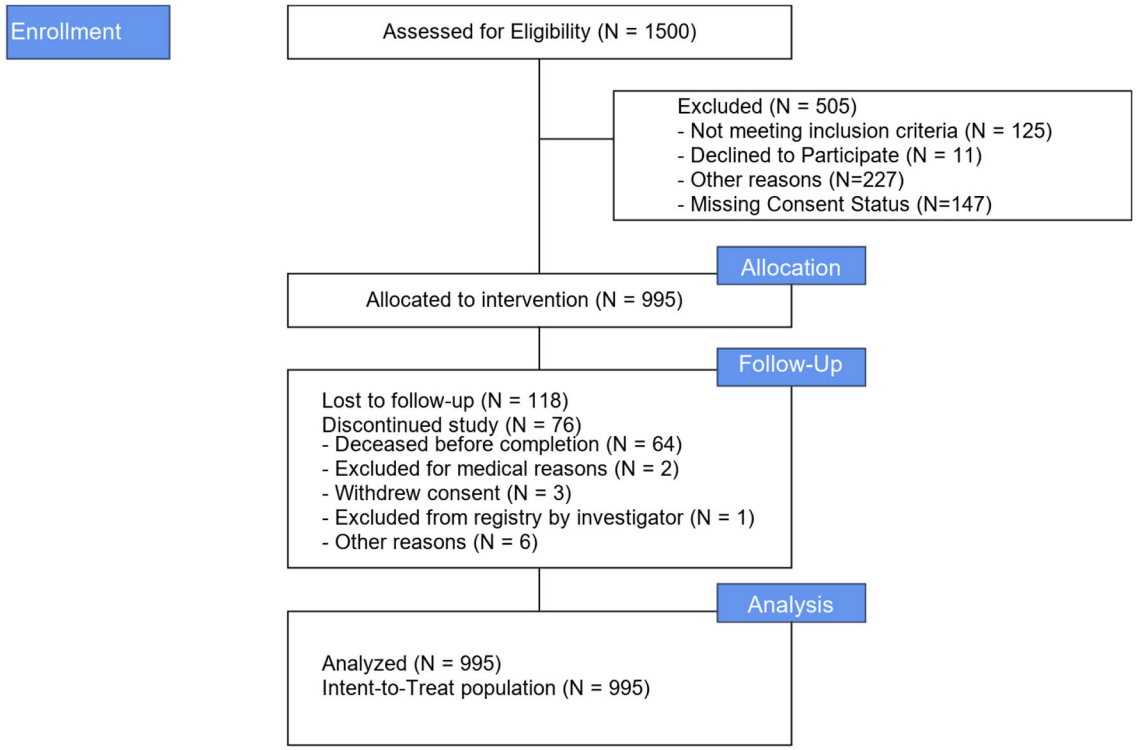

FIGURE 1 | Study flow diagram.

Safety Outcomes

Procedural device-related SAEs occurred in 2.6% (26/995) of patients. The rate of device malfunctions associated with an AE was 0.2% (2/995); one patient experienced an aneurysm perforation and one patient experienced a coil herniation into the parent artery. The overall mortality rate for all patients within 24 h of the procedure was 0.2% (2/995). Neither of the two deaths were related to the device or the index procedure. The 1-year mortality rate was 6.0% (60/995). The SAE rate was 9.4% (intraprocedural or within 24 h) and 22.7% after 24 h through 365 days.

Aneurysm Cohort Outcomes

Demographics and Baseline Characteristics

Of the 905 patients treated for aneurysms, the mean age was 59.8 year (SD 12.64), 74.7% were female, and 78.6% were white. There were 18.3% (166/905) of patients that had a familial history of aneurysms and 61.8% (559/905) had hypertension.

Procedural Characteristics

Average aneurysm size was 6.9 mm (SD 3.62) and 19.0% of aneurysms were small ($\leq$4 mm). Patient aneurysm types were 86.3% saccular, 63.5% wide-necked, and 31.8% ruptured; 43.5% of patients with a ruptured aneurysm had Hunt and Hess $\geq$ 3 severity. Unassisted coiling (UAC) was used in 43.3% (392/905) of cases, stent-assisted coiling (SAC) was used in 37.2% (337/905) and balloon-assisted coiling (BAC) was used in 20.3% (184/905). The mean packing density was 32.3% (SD 18.21). The median time from first coil deployment to last coil detachment was 16.0 min (IQR 8.0, 31.0) and the median fluoroscopy time was 37.0 min (IQR 24.0, 55.0). In 80.7% (729/903) of cases, no re-access attempt was made due to catheter kick-out.

Performance Outcomes

Adequate occlusion at immediate post-procedure was achieved in 97.1% (879/905) of patients. Catheter kick-back (requiring re-access at least once or twice) occurred in 8.2% (74/903) of cases. The first framing coil was completely conformed to the lesion morphology in 83.3% (724/869) of cases. The immediate post-procedure RROC Class I or II was reported in 79.7% (717/900) of all aneurysm cases and at 1-year was 90% (641/712). The overall 1-year retreatment rate was 7.1% (52/731) and the recanalization rate was 12.4%. RROC I or II at 1-year was achieved in 84.3% (161/191) of ruptured aneurysms and in 92.1% (480/521) of unruptured aneurysms. The retreatment rate for ruptured aneurysms (N = 288) at 1-year was 16.5% (33/200) and for unruptured aneurysms was 3.6% (19/531). The retreatment rate for wide-neck aneurysm (WNA, N = 554) at 1-year was 7.4% (34/458) compared to 6.4% (16/251) for non-WNA. **Supplementary Table 1** shows the outcomes for RROC at 1-year by immediate post-procedure RROC.

Safety Outcomes

Procedural device-related SAEs occurred in 2.9% (26/905) of patients and one patient died within 24 h of the procedure

TABLE 1 | Demographics and baseline characteristics.

	All patients (*N* = 995)	Aneurysm patients (*N* = 905)	Non-aneurysm patients (*N* = 90)
Age, years [average (SD)]	59.6 (13.00) (*N* = 995)	59.8 (12.64) (*N* = 905)	57.9 (16.18) (*N* = 90)
Age ≥ 65 years	38.3% (381/995)	38.0% (344/905)	41.1% (37/90)
Female	72.1% (717/995)	74.7% (676/905)	45.6% (41/90)
Hispanic or latino ethnicity	10.1% (33/326)	10.4% (31/299)	7.4% (2/27)
Race			
American Indian or Alaska Native	1.2% (4/326)	1.0% (3/299)	3.7% (1/27)
Asian	1.8% (6/326)	2.0% (6/299)	0.0%
Black or African American	13.2% (43/326)	12.7% (38/299)	18.5% (5/27)
White	78.5% (256/326)	78.6% (235/299)	77.8% (21/27)
Native Hawaiian or Other Pacific Islander	0.0%	0.0%	0.0%
Other	5.2% (17/326)	5.7% (17/299)	0.0%
Medical history			
Previous hemorrhagic stroke	8.8% (88/995)	9.6% (87/905)	1.1% (1/90)
Previous ischemic stroke	6.1% (61/995)	6.3% (57/905)	4.4% (4/90)
Hypertension	60.6% (603/995)	61.8% (559/905)	48.9% (44/90)
Family history of aneurysm or malformation	17.1% (170/995)	18.3% (166/905)	4.4% (4/90)
Diabetes	14.1% (140/995)	14.1% (128/905)	13.3% (12/90)
Smoking (current or former)	61.2% (609/995)	63.0% (570/905)	43.3% (39/90)
Polycystic kidney disease	0.6% (6/995)	0.7% (6/905)	0.0%

TABLE 2 | Lesion characteristics.

	All patients (*N* = 995)	Aneurysm patients (*N* = 905)	Non-aneurysm patients (*N* = 90)
Fistula	—	—	45.6% (41/90)
Arteriovenous malformation	—	—	12.2% (11/90)
Vessel sacrifice or pseudoaneurysm	—	—	42.2% (38/90)
Lesion location			
Extradural ICA	3.7% (37/995)	2.2% (20/905)	18.9% (17/90)
Intradural ICA	33.0% (328/995)	36.1% (327/905)	1.1% (1/90)
ACA	26.7% (266/995)	29.3% (265/905)	1.1% (1/90)
MCA	11.8% (117/995)	12.5% (113/905)	4.4% (4/90)
Posterior circulation	18.9% (188/995)	19.8% (179/905)	10.0% (9/90)
Venous circulation	2.4% (24/995)	0.1% (1/905)	25.6% (23/90)
Other	3.5% (35/995)	0.0%	38.9% (35/90)
Lesion laterality			
Left	35.6% (354/995)	33.9% (307/905)	52.2% (47/90)
Right	35.6% (354/995)	34.8% (315/905)	43.3% (39/90)
Midline	28.8% (287/995)	31.3% (283/905)	4.4% (4/90)
Aneurysm characteristics			
Aneurysm size, mm [average (SD)]	—	6.9 (3.62) (*N* = 905)	—
Aneurysm size group			
Small (≤4 mm)	—	19.0% (172/905)	—
Medium (>4–10 mm)		66.3% (600/905)	
Large (>10–25 mm)	—	14.5% (131/905)	—
Giant (>25 mm)	—	0.2% (2/905)	—
Aneurysm type			
Saccular	—	86.3% (778/901)	—
Dissecting		2.6% (23/901)	
Fusiform		2.4% (22/901)	
Other		8.7% (78/901)	
Wide neck	—	63.5% (554/872)	—
Ruptured	—	31.8% (288/905)	—
Hunt and Hess ≥ 3	—	43.5% (123/283)	—

(described above in "All Patient Results"). The mortality rate at 1-year was 5.4% (49/905); 11.8% for patients with ruptured aneurysms and 2.4% for patients with unruptured aneurysms. At 1-year, there were 84.4% (429/508) of patients with mRS 0-2; 65.3% for ruptured aneurysms and 92.2% in unruptured aneurysms. The procedural device-related SAE rate for patients treated for ruptured aneurysms was 3.1% (9/288) and for unruptured aneurysms was 2.8% (17/617). In patients with WNA, the procedural device-related SAEs rate was 2.5% (n/*N*) and this rate for non-WNA was 3.8% (12/318).

Predictive Analysis

Predictors of 1-year for RROC III or retreatment (incomplete occlusion) were rupture status (OR 3.61, 95% CI 2.27–5.74, $P < 0.0001$), balloon-assisted coiling (OR 1.72, 95%

TABLE 3 | Procedural characteristics.

	All patients (*N* = 995)	Aneurysm patients (*N* = 905)	Non-aneurysm patients (*N* = 90)
Adjunctive device use			
Unassisted coiling	44.8% (446/995)	43.3% (392/905)	60.0% (54/90)
Stent-assisted coiling	34.4% (342/995)	37.2% (337/905)	5.6% (5/90)
Balloon-assisted coiling	18.7% (186/995)	20.3% (184/905)	2.2% (2/90)
Flow diverter	1.6% (16/995)	1.8% (16/905)	0.0% (0/90)
Liquid embolic	2.1% (21/995)	0.1% (1/905)	22.2% (20/90)
Particulate/plug embolic	1.2% (12/995)	0.3% (3/905)	10.0% (9/90)
Number of coils implanted [SMART/PC400/POD, average (SD)]	5.4 (5.03) (*N* = 994)	5.0 (3.88) (*N* = 904)	9.3 (10.62) (*N* = 90)
Packing density, % [average (SD)]	—	32.3 (18.21) (*N* = 819)	—
Procedural times			
Fluoroscopic time, min [median (IQR)]	37.0 (24.0, 56.0) (*N* = 992)	37.0 (24.0, 55.0) (*N* = 902)	41.0 (25.0, 73.0) (*N* = 90)
Time from first coil deployment to last coil detachment, min [median (IQR)]	16.0 (8.0, 32.0) (*N* = 952)	16.0 (8.0, 31.0) (*N* = 868)	20.5 (3.0, 53.0) (*N* = 84)

TABLE 4 | Study outcomes.

	All patients (*N* = 995)	Aneurysm patients (*N* = 905)	Non-aneurysm patients (*N* = 90)
Peri-procedural outcomes			
Procedural device-related serious adverse events (SAEs)	2.6% (26/995)	2.9% (26/905)	0.0%
All SAEs (intraprocedural or within 24 h)	9.4% (94/995)	9.7% (88/905)	6.7% (6/90)
Mortality within 24 h of procedure	0.2%* (2/995)	0.1% (1/905)	1.1% (1/90)
Adequate occlusion at immediate post-procedure		97.1% (879/905)	
Complete angiographic occlusion immediate post-procedure	—	—	85.2% (23/27)
Re-access attempts with guidewire due to catheter kickout (SMART/PC400/POD)			
0	81.7% (811/993)	80.7% (729/903)	91.1% (82/90)
1	10.6% (105/993)	11.1% (100/903)	5.6% (5/90)
2+	7.8% (77/993)	8.2% (74/903)	3.3% (3/90)
Outcomes at 1-year			
Retreatment	6.8% (53/784)	7.1% (52/731)	1.9% (1/53)
RROC I or II	—	90.0% (641/712)	—
Recanalization	12.4% (94/757)	12.9% (91/708)	6.1% (3/49)
mRS 0–2	83.1% (463/557)	84.4% (429/508)	69.4% (34/49)
All-cause mortality	6.0% (60/995)	5.4% (49/905)	12.2% (11/90)
All serious adverse events			
After 24 h through 365 days†	22.7% (226/995)	22.2% (201/905)	27.8% (25/90)

**Not procedure-related or device-related.*
† Defined as adverse events that started after the date of registry completion.

CI 1.04–2.87, $P = 0.0354$), aneurysm size (OR 2.23, 95% CI 1.24–4.00, $P = 0.0071$), and incomplete occlusion immediate post-procedure (OR 2.01, 95% CI 1.19–3.37, $P = 0.0086$). Predictor of aneurysm retreatment at 1-year was rupture status (OR 5.32, 95% CI 2.95–9.61, $P < 0.0001$).

Non-aneurysm Cohort Outcomes

Of the 90 patients treated for non-aneurysms; 45.6% (41/90) were fistulas, 12.2% (11/90) were arteriovenous malformations, and 42.2% (38/90) were vessel sacrifice or pseudoaneurysm. In non-aneurysm treated patients, UAC was used in 60.0% (54/90), liquid embolics in 22.2% (20/90), and 10.0% (9/90) particulate/plug embolics. 79.2% (42/53) of all patients had the first coil conformed to the lesion. The median time from first coil to last coil deployment was 20.5 min (IQR 3.0, 53.0) and the median fluoroscopy time was 41.0 min (IQR 25.0, 73.0). Retreatment at 1-year was 1.9% (1/53) and the recanalization rate was 6.1% (3/49). At 1-year, 90.9% (20/22) of fistula treated patients, 54.5% (12/22) of patients treated for other lesions, and 40% (2/5) of patients treated for malformation had mRS 0-2. There were no procedural device-related SAEs (0.0%) and the mortality rate within 24 h of the procedure was 1.1% (1/90). The mortality rate at 1-year was 12.2% (11/90).

DISCUSSION

The results of the SMART Registry provide clinical evidence of the treatment with SMART, PC400, and POD in intracranial aneurysms and other neurovascular abnormalities. Patients in this registry had low retreatment rates through 1 year. The procedural device-related SAE rate was low. A high rate of patients achieved adequate occlusion post-procedure and at 1-year, and our rates were consistent or better than rates reported in other SMART COIL series (5–8, 11). Mortality within 24 h of the procedure occurred in two patients due to progression of baseline SAH from a ruptured aneurysm. The SMART Registry results confirm the safety and durability of

the SMART System for treatment of intracranial aneurysms and other neurovascular abnormalities.

The SMART Registry outcomes are comparable to contemporary studies of other coils. The TARGET Registry was a prospective, single-arm registry that compared outcomes for patients with saccular (ruptured and unruptured) intracranial aneurysms treated exclusively with TARGET-360° (Stryker Corp., Fremont, California) complex shape coils (designated for framing, filling, and finishing) vs. patients treated with both complex shape and helical coils (12). There were no significant differences between the groups for complete or near complete occlusion and in retreatment rates at 6 months, or for any other safety or efficacy outcomes. In the combined group analysis, median packing density was 28.8%, 6-month RROC I or II was 90.4%, and recanalization was 15.2%. In comparison to the SMART Registry, the mean packing density was 32.3%; and at 1-year, RROC I or II was 90% and recanalization was 12.9%. Despite the SMART Registry having longer follow-up than the TARGET Registry (12 $\pm$ 6 months), the SMART Registry occlusion rate was comparable and the recanalization rate was lower than in TARGET registry. In addition, TARGET excluded fusiform and dissecting aneurysms as well as patients with severe aneurysm ruptures (Hunt and Hess $>$ 3), while in the SMART Registry 20.5% (58/283) of patients had severe aneurysm ruptures.

In the prospective randomized GREAT Trial, intracranial aneurysms ranging 4–12 mm diameter were treated with either second generation hydrogel coils or platinum coils (13). There were no significant differences in procedural outcomes between the two coil types. The angiographic follow-up at 18 months showed that the platinum coil arm had adequate occlusion (per core lab RROC I + II) in 73% of patients and retreatment rate of 6%. The hydrocoil arm had higher adequate occlusion (80%) and a lower retreatment rate (3.0%) than the platinum coil arm. In comparison, the SMART Registry rate of adequate occlusion at 12 months was higher (90.0%) than both treatment arms in GREAT and retreatment rates for the SMART Registry and GREAT were similar. In a large systematic review including 8,161 aneurysms treated with standard and modified (hydrocoils and coated) coils, the retreatment rate was 10.3% (95% CI 9.5%, 11.0%) (14).

The SMART Registry provides evidence of safety of treatment in aneurysms and other neurovascular lesions. Mortality within 24 h of the procedure in the overall population was low (0.2%) and none were procedural or device-related. In the TARGET real-world randomized trial that evaluated outcomes after coiling aneurysms, the periprocedural mortality rate was 0.7% (12). In the GREAT trial for aneurysms, the 14-day mortality was 2.1% in the bare platinum coil arm (13). In the SMART Registry, there were no device complications associated with an AE and safety was demonstrated across multiple complex lesion types. In the non-aneurysm subgroup of the SMART Registry, which included fistulas, arteriovenous malformations, pseudoaneurysms, and vessel sacrifices, there were no procedural device-related SAEs, adequate occlusion immediate post-procedure was high (96.6%), and retreatment at 1-year was low (1.9%). These results are consistent with previous POD studies and also alternative treatments (15–17).

The SMART Registry included several complex lesion subgroups, such as a large number of patients treated for wide-neck aneurysms (WNA), ruptured aneurysms, and patients with non-saccular aneurysms (e.g., fusiform and dissecting). The patients treated for WNA had low procedural device-related safety events (2.5%) and low retreatment rates (7.4%) through 1-year. These outcomes are consistent with other reports of coiled WNA (18–23). Patients with ruptured aneurysms in our study achieved high occlusion rates at 1-year (RROC I + II 84.3%) and as expected, these patients had higher rates of recanalization and retreatment compared to those patients treated for unruptured aneurysms. These findings are consistent with previous reports in real-world registries treating ruptured aneurysms with endovascular coiling (24–26). The SMART ruptured aneurysm subgroup achieved occlusion comparable to other studies evaluating ruptured aneurysms treated with bare metal coils (24). Another study of ruptured aneurysms treated with coiling reported a periprocedural safety complication rate as high as 12.7% compared to 3.1% in the SMART Ruptured population (27). Therefore, SMART Coil appears to maintain safety and performance across multiple complex lesion types. Further investigation into complex subgroups from this study will be presented in subsequent reports from the SMART Registry.

The unique design of the SMART System features progressive coil softness and polymer technology that are not present in other commercially available coils. The coil tip is a softened loop and is designed to help reduce kickback and vessel perforations. The progressive coil softness potentially can lead to less compartmentalization and better packing density (28). Rigid coils are typically effective for framing, while softer coils are more effective for filling and finishing. The SMART COIL design decreases compartmentalization with stable framing of the aneurysm wall and supports durable occlusion through 1 year. In the SMART Registry, compartmentalization rate was low (2.0%) and demonstrated the ability to treat a variety of complex lesion types and treat distal lesion locations safely, such as the anterior, mid, and posterior communicating arteries. Previous studies have suggested a correlation between coil packing density and recanalization (29). Increased packing density promotes accelerated healing and decrease recurrence and retreatment (30). In other neurovascular embolization coil studies, packing density has been reported between 27.4 and 37.9% (7, 31–34). The mean packing density was 32.3% in the SMART Registry and this may have contributed to low rates of recanalization.

In this study population, we found that predictors at 1-year for retreatment was ruptured status. RROC III immediate post-procedure, aneurysm size, balloon-assisted coiling, and ruptured aneurysm were predictors for RROC III or retreatment (incomplete occlusion) at 1-year. The predictors for occlusion in the TARGET Registry were aneurysm location, size, and immediate occlusion grade (12).

The SMART Registry is one of the largest real-world prospective embolization coil studies completed to date and included a large sample size of complex lesions. The study included ruptured and unruptured aneurysms ranging from small to giant sizes, wide-neck and complex shaped

aneurysms; and other malformations, including arterial fistula, malformations, and vessel embolization for treatment of tumors or hemorrhages. Heterogenicity of the patient and lesion population allows future insight into multiple complex subgroups and provides good reflection of current treatment techniques and long-term outcomes using contemporary coils. A key limitation of the study is the lack of a comparator arm. Another limitation was that this study did not have a centralized angiographic core lab performing independent occlusion assessments.

CONCLUSION

This study provides clinical evidence of the SMART System in real-world clinical settings. The findings demonstrated that the SMART System is safe and efficacious and substantiate the durability of the coils at 1-year. Additional analysis of subgroups will be beneficial.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/**Supplementary Material**, further inquiries can be directed to the corresponding author/s.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by all investigational study sites received approval and oversite from their ethics committee. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

All authors were responsible for conducting research, data collection, analysis, interpretation, review of the article, final draft approval, and primary investigators at their institutions and were responsible for protocol execution within local and international regulatory requirements. AS was the Principal Investigator and lead author.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2021.637551/full#supplementary-material

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Balloon-Assisted Coils Embolization for Ophthalmic Segment Aneurysms of the Internal Carotid Artery

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Objective: To explore the role of balloon-assisted coils technique for ophthalmic segment aneurysms (OSAS).

Methods: Clinical data of 30 patients with OSAS were reviewed between December 2017 and December 2018. OSAS were defined as arising from the internal carotid artery (ICA), reaching from the distal dural ring to the origin of the posterior communicating artery. OSAS were classified into four types based on the angiographic findings. The balloon-assisted coils technique was used for the embolization of aneurysms. The duration of balloon inflation cycles, as well as difficulty and complications during the embolization procedure, were recorded. The immediate angiographic results were evaluated according to the Raymond scale. Clinical results were evaluated based on the MRS score. Follow-ups were performed at 18 months post-embolization by DSA or MRA at our institution.

Results: Thirty-two aneurysms in 30 patients were detected by digital subtraction angiography (DSA), which included 30 unruptured and two ruptured cases. The patients with ruptured aneurysms were grade II status according to the Hunt-Hess scale. Three cases were type A, nine cases were type B, 17 cases were type C, and three cases were type D. According to aneurysm size, there were 19 cases of small, 11 cases of medium, two cases of large aneurysm. Thirty-two aneurysms were successfully embolized in 30 patients by balloon-assisted coils technique. The ophthalmic artery could be protected by an engorged balloon in the procedure, especially for type A aneurysms. Considering that type D aneurysm arises from the side-wall of the artery and near to tortuous ICA siphon, the balloon catheter was inflated to stabilize the microcatheter allowing for overinflation when necessary. The average duration of balloon dilatation was 4 min, and the average time was 2.5 times. Raymond class was one in 28 aneurysms and two in four aneurysms according to the immediate post-embolization angiographic results. All the patients achieved good clinical effects, except for one patient who presented with brain ischemia resulting in dizziness and contralateral limb weakness for 10 h due to prolonged temporary clamping of the responsible ICA. The follow-up angiography results were satisfactory at 18 months post-embolization.

Conclusion: OSAS endovascular treatment with balloon-assisted coils has different advantages in a different classification. The technique is safe, effective, and relatively inexpensive, especially for small and medium OSAS.

Keywords: ophthalmic segment aneurysms, balloon assisted coils, small and medium type, effective, safe

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INTRODUCTION

Intracranial aneurysms are the most common causes of subarachnoid hemorrhage affecting humans, which leads to high mortality and morbidity rates (1). Ophthalmic segment aneurysms (OSAS) are defined as aneurysms arising from the internal carotid artery (ICA), reaching from the distal dural ring to the posterior communicating artery's origin. Many reports indicated slower growth and lower risk of rupture for OSAS as compared to other intra-dural aneurysms (2, 3). Kumon et al. (4) proposed the treatment of all unruptured asymptomatic OSAS to prevent lethal subarachnoid hemorrhage. In contrast, De Jesus et al. (5) suggested that only patients with life expectancy >10 years should be treated if the aneurysm was >4 mm.

The endovascular intervention has been the main choice for intracranial aneurysm treatment since the international subarachnoid aneurysm trial (ISAT). Thus far, for endovascular management of OSAS, stent-assisted coils and flow-diverting devices have been mainly reported (6, 7). However, coiling and stent release in the endovascular procedure is difficult due to the tortuous ICA siphon. It is also challenging to treat OSAS by surgical clipping due to complex adjacent anatomy, proximity to the optic chiasma, and the clinoid process. Visual morbidity and loss were encountered due to optic damage during the surgery (8–12). Interestingly, Alberto et al. (13) found no difference in clinical outcomes after endovascular coiling or surgical clipping for ruptured carotid ophthalmic aneurysms.

The endovascular interventional strategy includes sole coils embolization, balloon-assisted coils, stent-assisted coils, or flow diversion. Yet, high bleeding risk due to dual antiplatelet therapy during the perioperative period (14), in-stent thrombosis (15), and stent malposition (16) can lead to poor prognosis if the patient received stent-assisted coils embolization or flow diversion implant. In contrast, the balloon-assisted coils embolization technique does not require dual antiplatelet medication, has low thrombosis formation, and more dense

TABLE 1 | Patients' data and aneurysm characteristics.

Patient No.	Gender/age	Clinical symptom	History	R/L	Type	Size (N & D) mm	Complication	Results (Raymond)	MRS (discharge)	18 months
1	F/65	Incidental	Hp	R	C(N)	3 × 4	NO	1	0	Stable
2	F/26	Sudden headache	Prenant	R	C(N)	4 × 5	NO	1	1	Stable
3	F/56	Incidental	Hp	R	C(w)	6 × 9	NO	1	0	Stable
4	F/59	Incidental	Gu	R	B (w)	6 × 15	NO	1	0	Stable
5	F/59	Incidental	DB smoking	R	C(w)	6 × 8	NO	1	0	Stable
6	F/50	Incidental	—	L	C(w)	3 × 5	NO	2	0	Stable
7	F/64	Incidental	—	R	B(w)	3.5 × 5	NO	1	0	—
8	F/61	Incidental	Hp	L	C(w)	4 × 6	NO	1	0	Stable
9	F/36	Incidental	—	L	A(w)	3 × 4	NO	1	0	—
10	M/59	Incidental	Hp smoking	R	B(w)	4 × 6	NO	2	0	Recurrent
11	F/48	Incidental	—	R	D(N)	3 × 5	NO	1	0	Stable
12	F/53	Incidental	Hp & CAD	L	B(N)	3 × 4	NO	1	0	Stable
13	M/61	Incidental	Smoking	L	C(w)	5 × 6	NO	2	0	—
14	F/65	Incidental	Hp	R	B(w)	5 × 11	NO	1	0	Stable
15	M/49	Visual disorder	Smoking & Hp	R	B(w)	4 × 13	NO	1	0	Stable
16	F/57	Incidental	Hp	R	C(w)	5 × 8	NO	1	0	Stable
17	F/37	Incidental	—	L	D(w)	4 × 6	NO	1	0	Stable
18	F/65	Incidental	Hp & CAD smoking	R	C(w)	4 × 6	YES	1	0	—
19	F/46	Incidental	Hp	R	C(w)	4.5 × 6	NO	1	0	Stable
20	F/51	Sudden headache	Hp	L	A(w)	5 × 7	NO	1	0	Stable
21	F/39	Incidental	—	L	C(w)	5x6	NO	1	0	Stable
22	F/61	Incidental	—	b	B(w): C(N)	3 × 5 & 3 × 7	NO	1	0	Stable
23	F/50	Incidental	Graves	R	B(w)	4 × 5	NO	1	0	Stable
24	F/56	Incidental	—	R	D(w)	3.5 × 4	NO	1	0	Stable
25	F/67	Incidental	Hp	R	C(w)	6 × 10	NO	2	0	—
26	F/64	Incidental	DB	b	C(w)	4 × 8 & 3 × 4	NO	1	0	Stable
27	F/64	Incidental	Hp	R	B(w)	10 × 12	NO	1	0	Stable
28	F/60	Incidental	Hp	L	C(w)	6 × 9	NO	1	0	Stable
29	F/53	Incidental	—	L	C(w)	7 × 11	NO	1	0	Stable
30	M/53	Incidental	Hp & CAD	L	A(w)	4 × 6	NO	1	0	Stable

Hp, hypertension; GU, gastric ulcer; DB, diabetes; CAD, coronary heart disease; b, bilateral; W, wide neck; N, narrow neck.

packing in the aneurysm sac, as was first reported by Moret (17) in 1997. The aim of this study was to share our experiences with balloon-assisted coils embolization in 30 patients with OSAS.

MATERIALS AND METHODS

Study Subjects

A total of 30 patients with 32 OSAS, who were admitted at the Second Hospital of Hebei Medical University between December 2017 and December 2018, were included in this study. The inclusion criteria were: patients with life expectancy >10 years; the aneurysm sac of ≥4 mm in size. The exclusion criteria were: dissection, fusiform aneurysm, and giant aneurysm; the aneurysm sac of <4 mm in size. All the patients were consecutively enrolled in this study and had no family medical history. The patients or their relatives signed the informed consent for the surgery. All the patients who died of diseases other than intracranial aneurysms or unexpected events were excluded from the analysis.

The study was approved by the ethics committee of the Second Hospital of Hebei Medical University (Shijiazhuang, China).

Treatment Regimen

All the patients received balloon-assisted coils embolization for the aneurysms under general anesthesia. Transarterial embolization was accomplished with a standard Seldinger puncture through the right femoral artery. A 6-F guiding catheter (Cordis Corporation, Miami Lakes, FL, USA) was advanced over a 0.035-inch guidewire (Terumo Corporation, Tokyo, Japan) into the petrous segment of the ICA. Heparin was intravenously administered, first as a 3,000 U bolus, followed by infusions at 1,000 U/hour. The size of the aneurysm neck and dome were measured by three-dimensional rotational angiography. A "working projection" was selected in sequence. Hyperglide balloon (4 mm × 15 mm/20 mm, Covidien/ev3, Irvine, CA, USA) or Scepter balloon (Microvention Corporation, USA) was navigated with the guidewire (0.010 & 0.014, Covidien/ev3, Irvine, CA, USA) to cover the aneurysm neck. Then, a micro-catheter tip with a transcend 0.014 soft-tip guide microwire (Stryker Neurovascular, CA, USA) was assisted into the aneurysm sac. The balloon was selected according to the sizes of the parent artery. The first coil was deployed under the dilation of the balloon. A contrast media/saline mixture of 50:50 was used to inflate the balloon catheter with a 1cc syringe. The balloon was inflated while placing the coils into the aneurysm until the stable coil frame appeared. The coil stability and its relationship with the parent artery were carefully observed when the balloon was slowly released in case the coils protruded into the parent artery. The duration of balloon inflation cycles was limited to no more than 5 min at a time, alternating with periods of at least

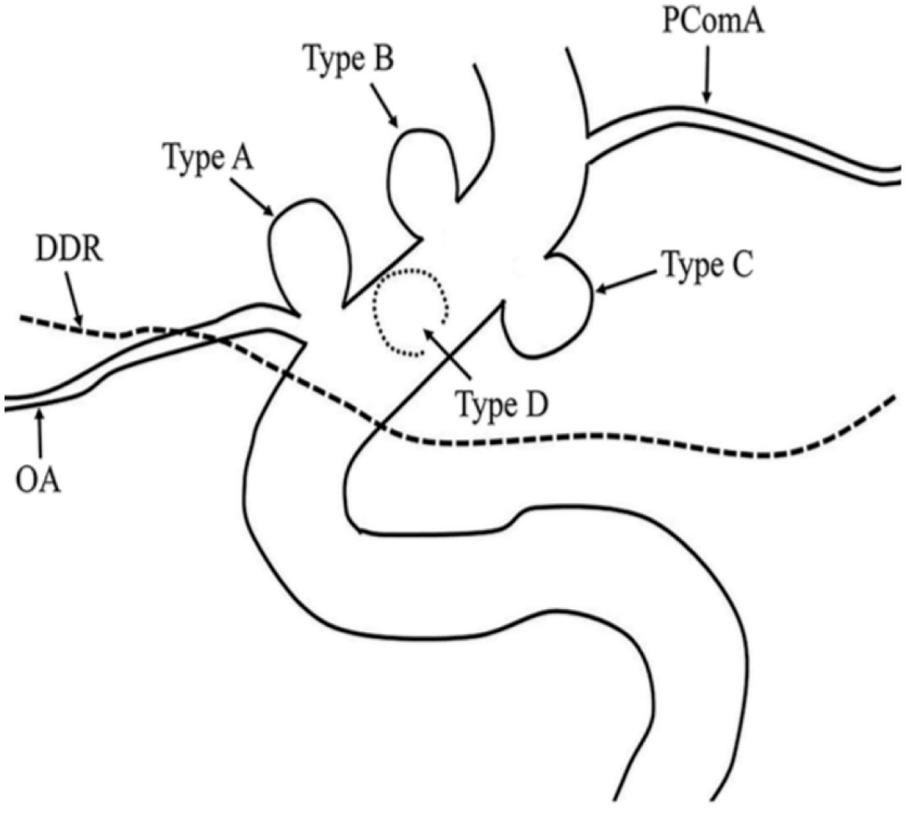

FIGURE 1 | Ophthalmic segment aneurysm classification. Aneurysms arising from the superior ophthalmic segment of the internal carotid artery (ICA) with (Type A) and without (Type B) involvement of the ophthalmic artery. Aneurysms arising from the ventral (Type C) and medial (Type D) ophthalmic segment of the ICA.

1 min of balloon deflation. The patients' balloon inflation cycles, difficulty, and complications during the embolization procedure were recorded, respectively. The packing process was terminated when the aneurysm staining disappeared in digital subtraction angiography. The catheter was removed under the protection of the dilated balloon.

Therapeutic Evaluation

After the procedure, multiple angiographic projections were obtained to assess the immediate embolization effect. The embolization effect was graded according to the Raymond-Roy occlusion classification scale (18). The postoperative MRS scores of patients were recorded.

Follow-Up and Prognosis Evaluation

Follow-ups were performed at 18 months post-embolization by DSA or MRA at our center. Meanwhile, clinical results were evaluated according to the MRS scores.

RESULTS

Patient Data

In total, there were 30 patients, 26 female and four male, with a mean age of 54.87 ± 9.67 years (range, 26–67 years). The aneurysms included 30 unruptured and two ruptured cases. CT scan showed subarachnoid hemorrhage in the latter cases. In the unruptured group, one patient had a chief complaint of visual disorders for eight months, while the other 27 cases were incidentally identified. The patients with ruptured aneurysms were grade II according to the Hunt-Hess scale. The status of all patients was evaluated on admission according to the modified ranking scale (MRS). The MRS score of two patients with ruptured aneurysms was one point, and for others was 0 point. The patients' data and aneurysm characteristics are shown in **Table 1**.

Aneurysm Characteristics

OSAS were classified into four types based on the angiographic findings and endovascular considerations from previous reports

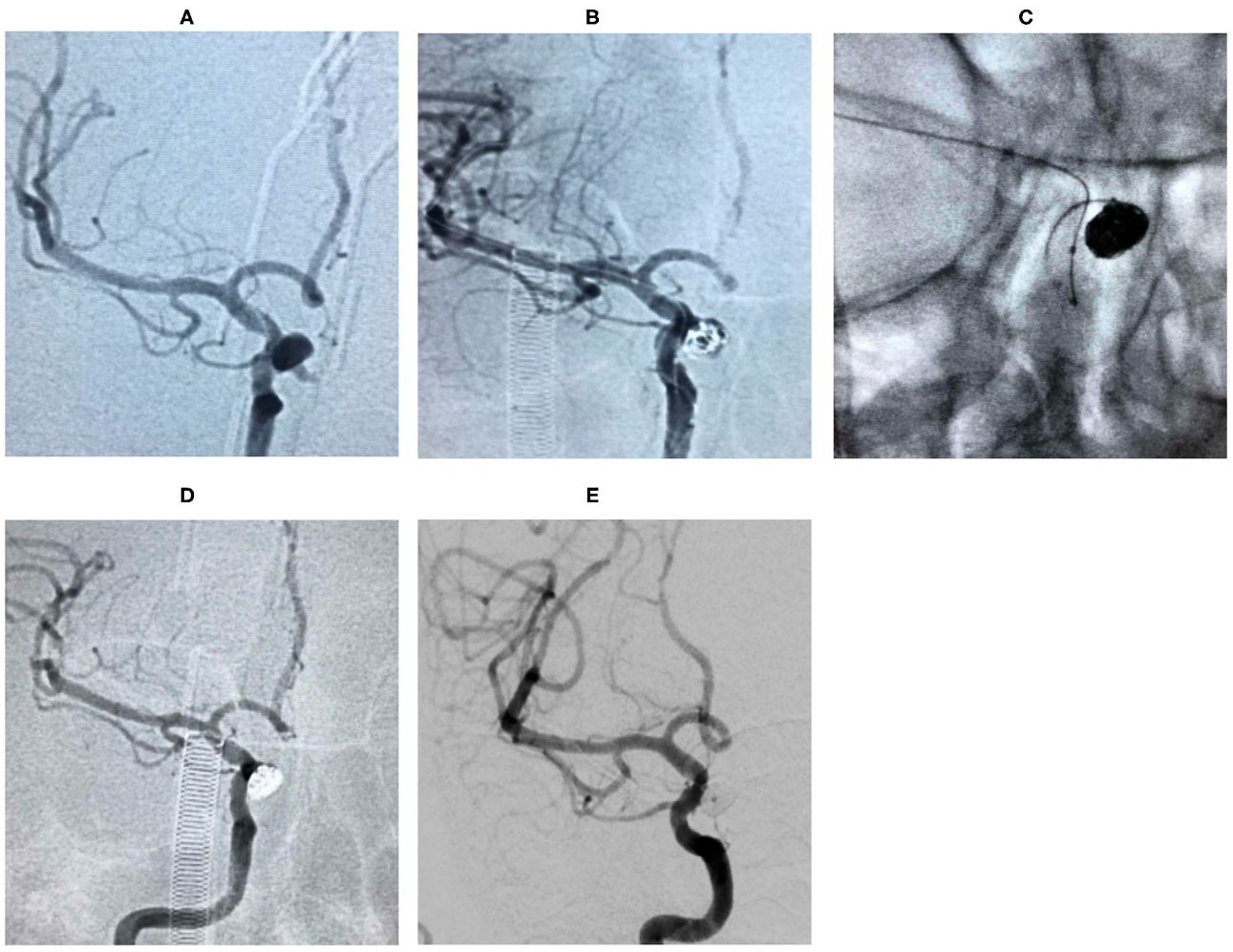

FIGURE 2 | Digital subtraction angiography (DSA) showed that the aneurysm originated from the right ophthalmic segment of ICA **(A)**. The aneurysm was treated during the procedure **(B,C)**. The lesion was completely embolized in the immediate angiographic results **(D)** and 18 months follow-up **(E)**.

(19). The types of aneurysms in this study are shown in **Figure 1**. Three cases were type A, nine cases were type B, 17 cases were type C, and three cases were type D. The neck of the aneurysm was manually measured based on DSA. Aneurysms were considered as wide-necked if the neck was ≥4 mm or the aneurysm had a dome-to-neck ratio <2. There were 27 cases of wide-necked aneurysms and five cases of narrow-necked aneurysms. The size of the dome was classified based on the International Study of Unruptured Intracranial Aneurysms (ISUIA) (2) standard into <7 mm (small), 7–12 mm (medium), 13–24 mm (large), and >25 mm (giant). There were 19 cases of small, 11 cases of medium, and two cases of large aneurysms.

Clinical Status of the Patients

Thirty-two aneurysms were successfully treated with the balloon-assisted coils technique. The average duration of balloon dilatation was 4 min, and the average time was 2.5 times. One patient (case 18) developed procedure-related complications. She presented with transient brain ischemia resulting in dizziness and contralateral limb weakness lasting for 10 h due to prolonged temporary clamping of the responsible ICA (balloon inflation time, in this case, was 7 and 3 min, respectively). The patient with visual disorders (case 15) showed no aggravation post-procedure. No persistent complications occurred in this group. MRS scores were 0 in all the cases, except for one case (case 2, MRS 1) at discharge.

Immediate Angiography Results and Follow-Up

According to the immediate post-embolization angiographic results, Raymond class 1 was found in 28 aneurysms (total aneurysm occlusion 87.5%), while Raymond class 2 was found in four aneurysms (partial aneurysm occlusion 12.5%). Twenty-five patients received angiography during the follow-up at 18 months post-embolization. Five patients were lost to follow-up. Twenty-four patients showed stable results, while one patient had aneurysm neck residue (case 10) and further stent cover at the 18

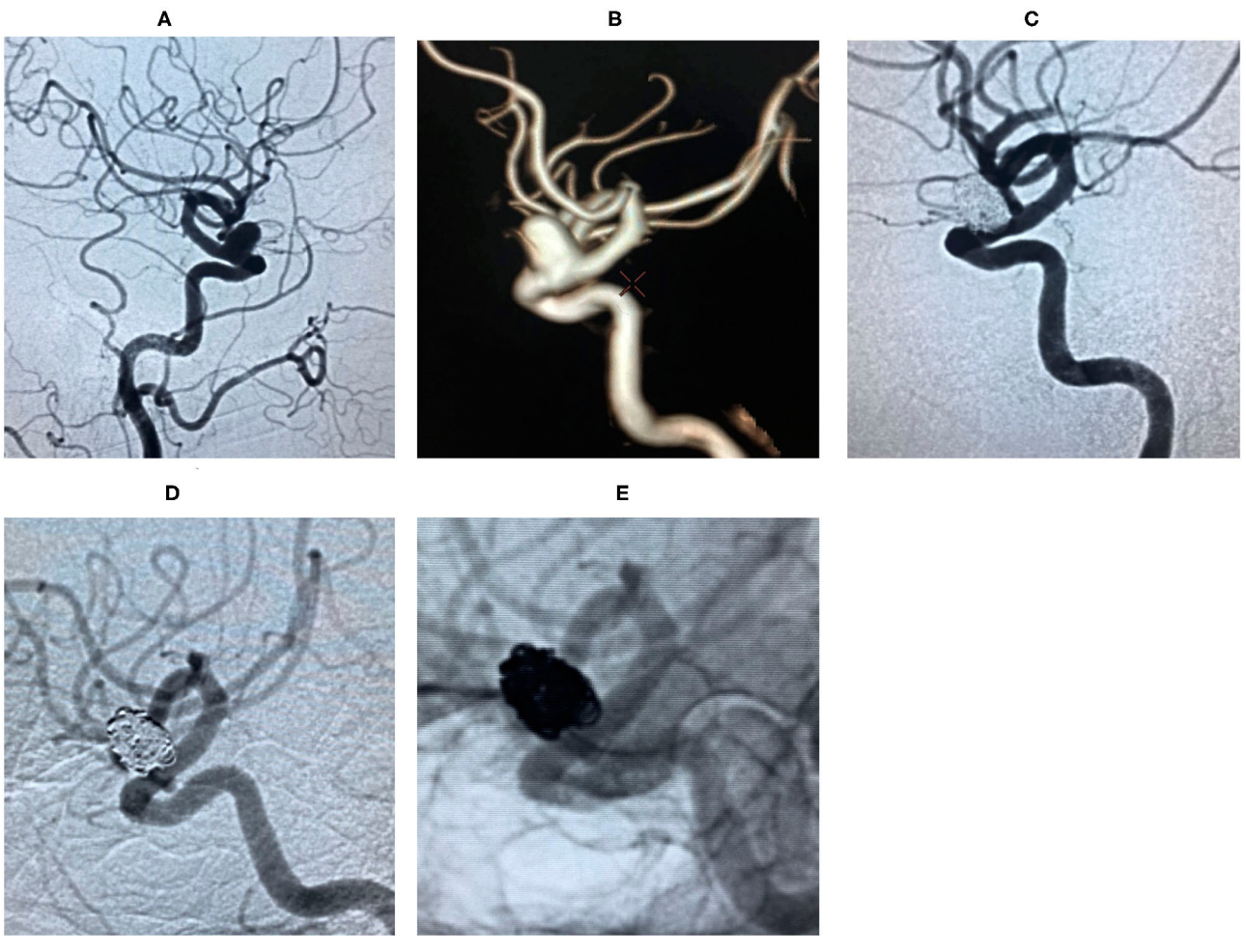

FIGURE 3 | Digital subtraction angiography (DSA) revealed right ophthalmic segment aneurysm ~15 mm wide, with a neck size of 6 mm **(A,B)**. The aneurysm was completely embolized by balloon-assisted coils technique and the immediate post-embolization angiographic result is shown in **(C)**. The lesion was stable by DSA at the 18 months follow-up **(D,E)**.

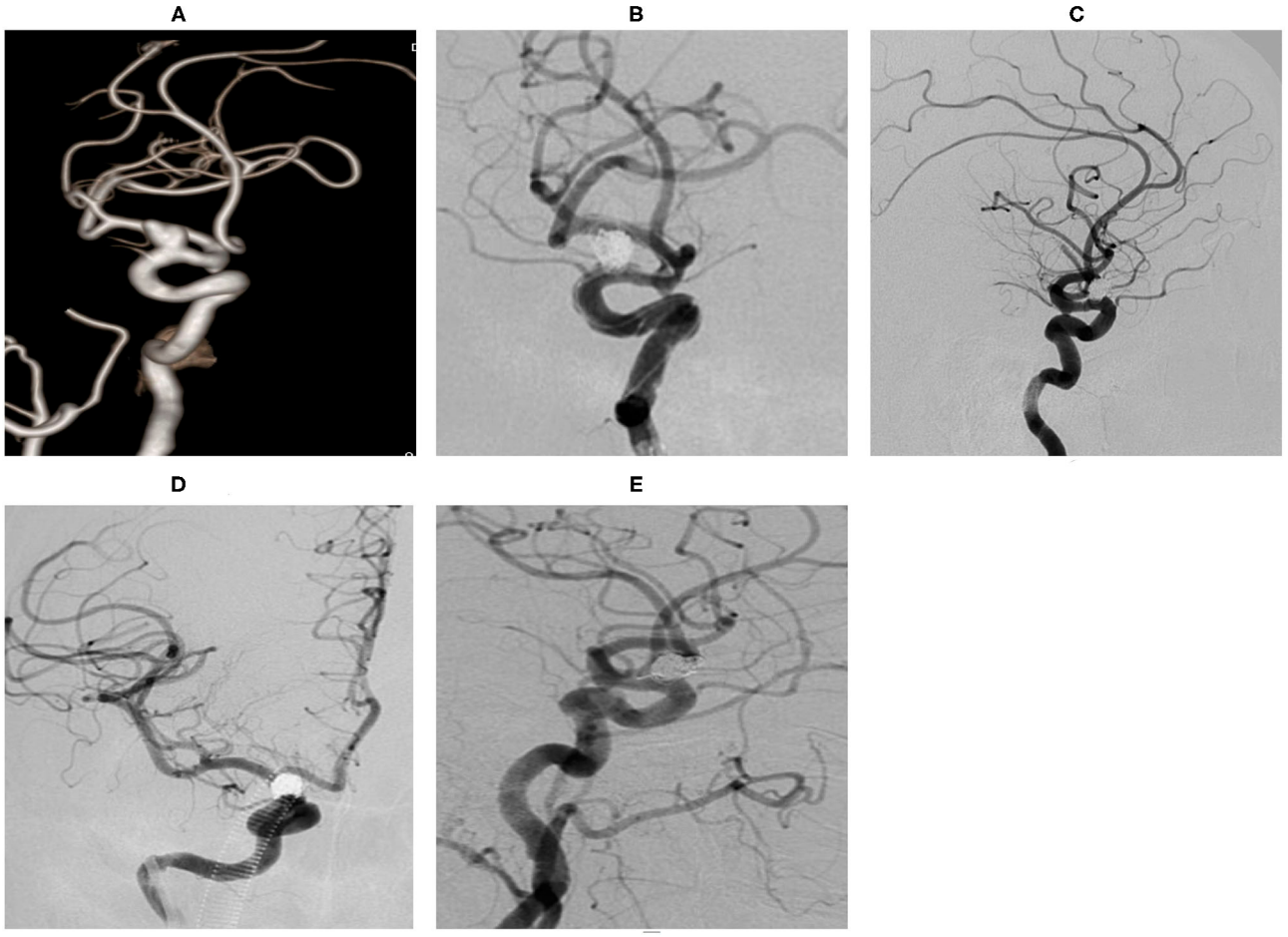

FIGURE 4 | An ophthalmic segment aneurysm ~11 mm wide, with a neck size of 5 mm was detected by angiography **(A)**. A protective balloon covered the aneurysm neck in the procedure **(B)**. The aneurysm was completely embolized and the immediate post-embolization angiographic result is shown in **(C)**. The aneurysm had disappeared at the 18 months follow-up by DSA **(D,E)**.

months follow-up. No new bleeding occurred during the follow-up period. The patients' data, clinical symptoms, aneurysm characteristics, immediate embolization outcomes, and follow-up results are presented in **Table 1**.

Case Illustrations

Case 3. During the physical examination, magnetic resonance angiography (MRA) detected an intracranial aneurysm in a 56-year-old female patient (**Figure 2**).

Case 4. During a physical examination, MRA detected an intracranial aneurysm for 1 month in a 59-year-old male. He suffered from gastric ulcer for 1 year (**Figure 3**).

Case 14. MRA detected an intracranial aneurysm for 1 week in a 65-year-old female (**Figure 4**).

Case 20. A 51-year-old female presented a sudden headache lasting for 2 days. CT scan showed subarachnoid hemorrhage (**Figure 5**).

Case 30. A 53-year-old male was found to have intracranial aneurysms for 1 month by magnetic resonance angiography (MRA) (**Figure 6**).

DISCUSSION

Ophthalmic segment aneurysms (OSAS) are defined as originating from the distal ring to post communication artery of the internal carotid artery (ICA). Gross (20) reported a higher risk of rupture, large size, aneurysm growth, and aneurysm irregularity for OSAS. However, other reports indicated slower growth and lower risk of rupture for OSAS as compared to other intra-dural aneurysms (2, 3). In this study, there were 30 unruptured and two ruptured aneurysms (4 × 5 mm and 4 × 6 mm in size, respectively). This study revealed that OSAS had lower rupture rates than other intracranial aneurysms.

In this study, satisfactory clinical results were obtained for OSAS patients with balloon-assisted coils technique. There were no deaths in this study. Only one patient presented with procedure-related complication in the form of transient brain ischemia, which resulted in dizziness and contralateral limb weakness for 10 h due to prolonged temporary clamping of the responsible ICA. Yet, due to the symptoms, it was not possible to exclude the tiny cerebral infarction caused by small

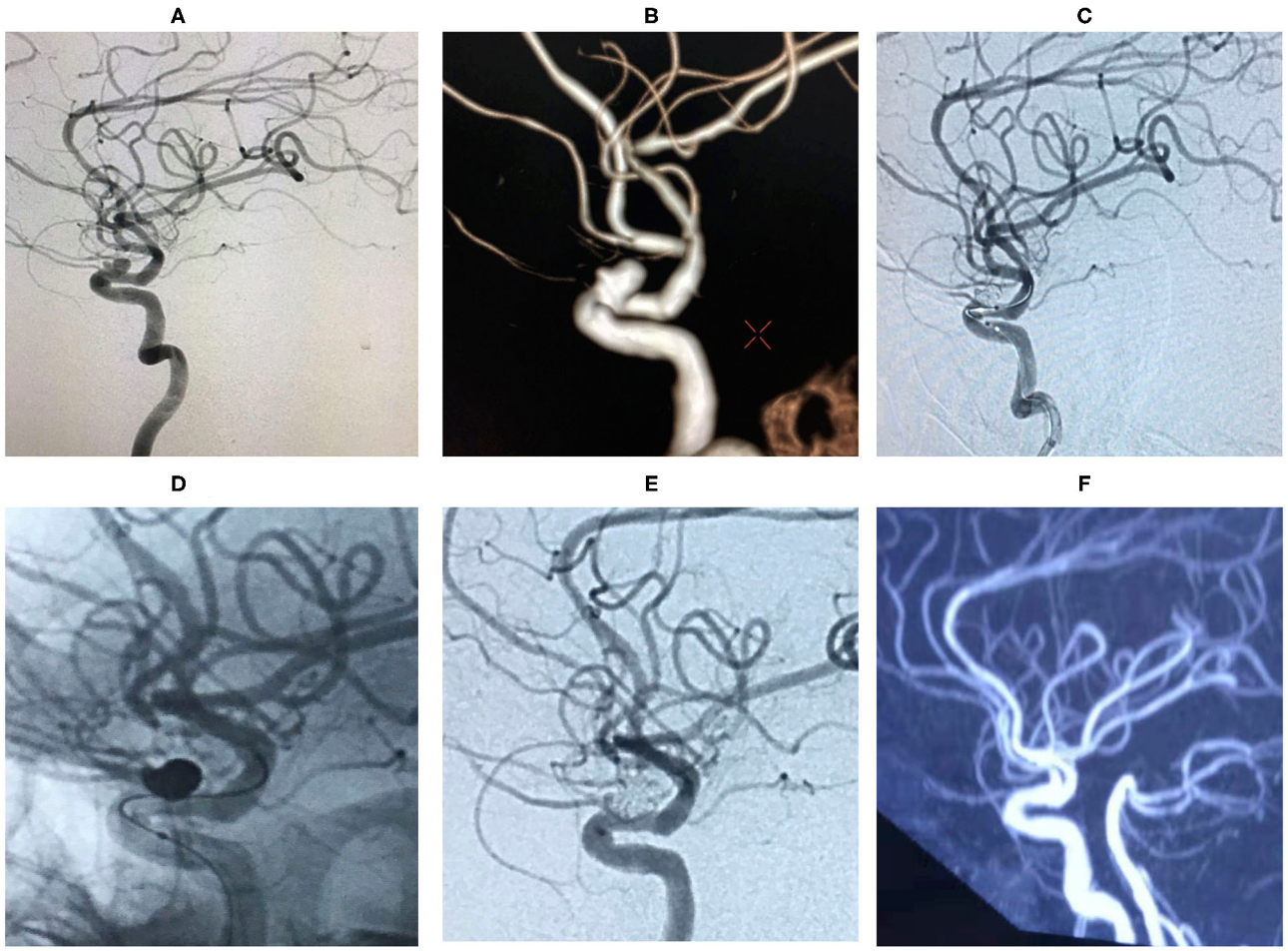

FIGURE 5 | An ophthalmic segment irregular aneurysm ~7 mm wide, with a neck size of 5 mm was detected by angiography **(A,B)**. A protective balloon covered the aneurysm neck in the procedure **(C,D)**. The aneurysm was completely embolized and ophthalmic artery patency, and the immediate post-embolization angiographic result is shown in **(E)**. The aneurysm had disappeared at the 18 months follow-up by Magnetic Resonance angiography (MRA) **(F)**.

atherosclerotic plaque falling off caused by balloon inflation. His symptoms were gradually relieved, and he completely recovered after the 10 h long procedure and no MRI scanning. Yadla et al. (21) reported 1.4% morbidity and 0% mortality in their study of 170 unruptured OSAS. Similarly, this study also achieved safe embolization and a good clinical prognosis.

The immediate angiography and 18 months follow-up results were also satisfactory. The complete occlusion incidence was 87.5% (28/32), and partial occlusion was seen in four cases (cases 6, 10, 13, and 25) in the angiographic results immediately post-embolization. Furthermore, only one aneurysm showed neck recurrence during the 18 months follow-up. Larger and wide-neck aneurysms have a higher recurrence rate (22). Flow-diversion is popular due to the high obliteration rate and low complication rate, and high rate of improvement of visual symptoms (23). The pipeline embolization device (PED) achieved higher complete occlusion than stent-coiling in cases with larger aneurysms (24–26). Still, visual blurring and visual field defects occur after PED treatment (27–30). The visual impairment may result from the direct mass effect of the aneurysm sac compressing the optic nerve, inflammation, or retinal artery thrombosis (27). Also, the rate of visual complications for type A aneurysms was higher than in other types (31). In this study, there were three cases of type A aneurysm. The ophthalmic artery could be protected by an engorged balloon, especially for type A aneurysms. The cases with visual symptoms (case 15) did not aggravate after the procedure because the aneurysm size was relatively small. In this study, there were only two large aneurysms (6 × 15 mm, 4 × 13 mm) treated by the balloon-assisted coils technique. Both patients achieved satisfactory angiographic results during the 18 months follow-up. Furthermore, the balloon-assisted coils technique is inexpensive as compared to PED in China. However, larger prospective studies with longer follow-up are warranted in the future, especially for large aneurysms.

The balloon-assisted coils technique has an important role in the aneurysm neck remodeling during the embolization procedure. In addition to the previously published advantages

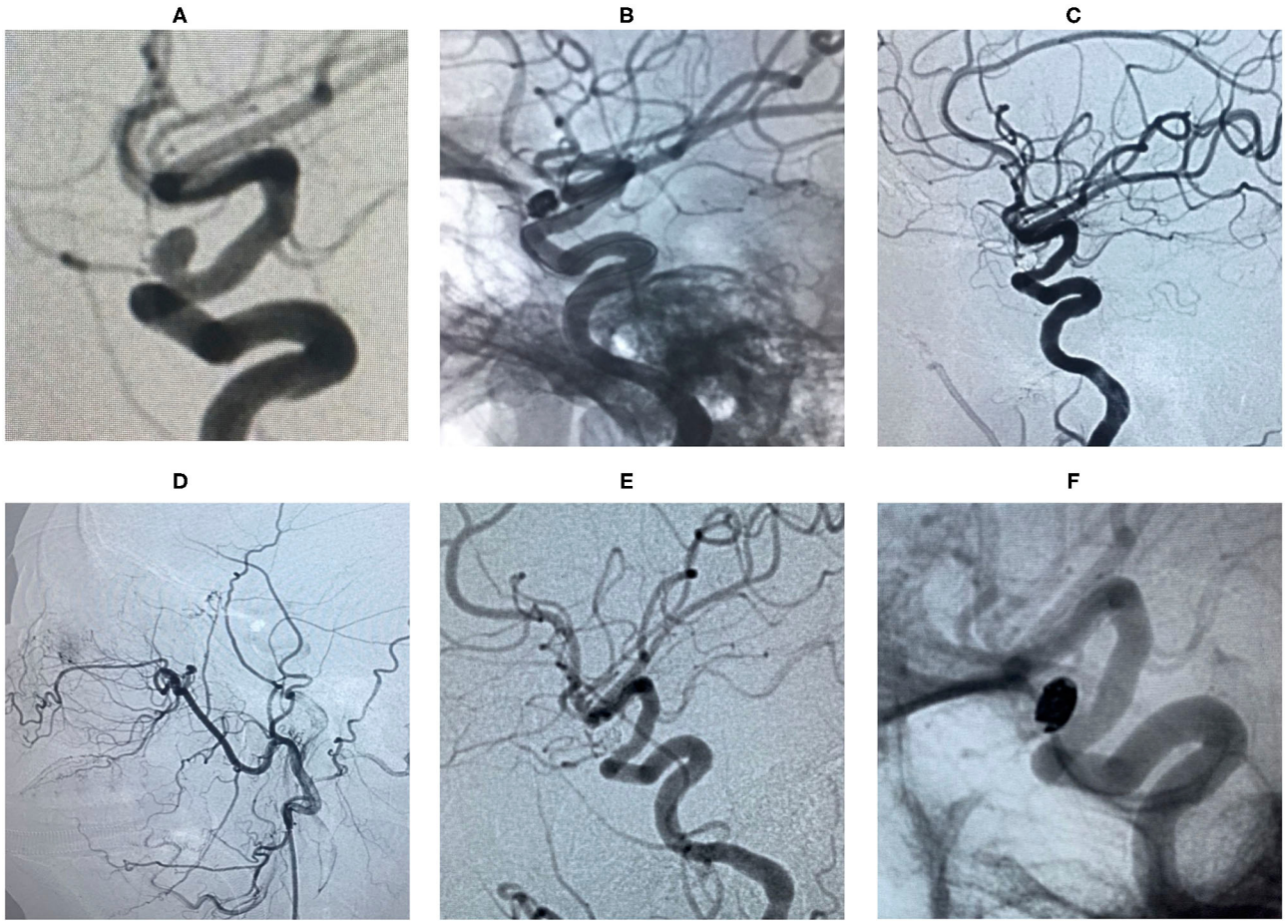

FIGURE 6 | An ophthalmic segment aneurysm ~6 mm wide, with a neck size of 4 mm was detected by angiography **(A)**. A protective balloon covered the aneurysm neck in the procedure **(B)**. The aneurysm was embolized and the immediate post-embolization angiographic result is shown in **(C)**. The patient has favorable collaterals in **(D)** and no visual disorders. The aneurysm had disappeared completely and ophthalmic artery patency at the 18 months follow-up by DSA **(E,F)**.

(17, 32, 33), we observed that the first coil could easily form the steady frame and conveniently achieve further compact embolization once the blood flow was temporarily blocked. The necks of aneurysms were remodeled by an engorged balloon. Thereafter, the coils formed a saddle structure to decrease the recurrence of the aneurysm. Second, type D aneurysm originated from the side wall of the vessels and near to the tortuous ICA siphon. In our experience, it is more difficult to navigate the microcatheter tip into an aneurysm sac for type D aneurysm than type A, type B, and type C ones.

The balloon catheter was inflated to stabilize the coil mass or the microcatheter allowing for overinflation when necessary. Third, the dual-lumen Scepter balloon catheters provide some advantages compared to single-lumen Hyperglide balloon catheters in the operation process. The Scepter balloon catheter is compatible with 0.014-inch microguidewires, and 0.010-inch microguidewires for Hyperglide balloon catheters. Distal tip length is 5 mm for the Scepter, 4 mm for the Hyperglide. Therefore, the Scepter balloon catheter can be used to improve trackability and stability during the embolization procedure.

Balloon-assisted coiling potentially causes significant technical stress for aneurysm and parent vessel. Stents have been increasingly used for the treatment of wide-necked or complex aneurysms with various deployment techniques. Nevertheless, deployment tends to be difficult, and the stents kink or easily twist in the case of ICA siphon. Thrombosis forms in the stent in the case of anti-platelet drug resistance and defective wall attachment of the stent (34, 35). Prolonged bleeding risks may be caused by drugs if the patient received stent-assisted coils embolization. Nishido et al. (36) reported 7.0% ischemic and 2.3% hemorrhagic complications, with a 2.7% overall rate of procedure-induced mortality with stent-assisted coils technique.

Thromboembolic events were reported to be induced by the balloon-assisted coils technique during the aneurysm embolization (37–39). It is important to select the fitting size balloon for the prevention of thromboembolic complications. The under-sized balloon was unstable during inflation and

showed a tendency to jump forward, inducing thromboembolic complications in the tortuous ICA siphon. Therefore, longer balloons had a more stable position during inflation and were particularly useful in a very wide-necked aneurysm. This study showed no permanent ischemia, even in patients with brain infarction. The patients with unruptured aneurysms were given 100 mg aspirin and 75 mg clopidogrel for 3 days before the procedure to reduce the ischemia events. Meanwhile, the balloon inflation time and frequency were also reduced during the operation to decrease the incidence of brain ischemia.

In summary, OSAS endovascular treatment with balloon-assisted coils has different advantages in a different classification. This is a safe, effective, and economical technique for treating OSAS, especially for small and medium aneurysms. Long-term follow-up is needed to ensure stable effects.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author/s.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the ethics committee of the Second Hospital of Hebei Medical University (Shijiazhuang, China). The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

LC: major in patients operation and management, follow-up, and write paper. ZY and HK: major in patients operation, management, and follow-up. All authors contributed to the article and approved the submitted version.

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CASE REPORT
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Case Report: *De novo* Vertebral Artery Dissection After Intravascular Stenting of the Contralateral Unruptured Vertebral Artery Aneurysm

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Spontaneous vertebral artery dissecting aneurysm has been increasingly attributed as a major cause of focal neurological deficits due to vertebrobasilar artery ischemia or subarachnoid hemorrhage (SAH). Although the development of spontaneous vertebral artery dissecting aneurysm (VADA) is rare, *de novo* VADA after treatment of contralateral vertebral artery (VA) is more less frequently observed. There are only a few reports related to *de novo* VADA after treatment of the contralateral VA in the medical literature. The mechanisms responsible for *de novo* dissection after treatment of unilateral VADA are still not clearly understood. In this manuscript, we report an unusual case of a patient with a *de novo* VADA after placement of a pipeline embolization device (PED) stent on the contralateral VA along with a thorough review of the literature. A 42-years old male patient was referred to the hospital with sudden onset of dizziness, nausea, and vomiting. Initial digital subtraction angiography (DSA) images demonstrated a VADA in the fourth segment of the left VA without the involvement of the posterior inferior cerebellar artery (PICA). There were no significant abnormalities found in the right vertebral artery. He underwent an endovascular pipeline embolization to treat the dissecting aneurysm (DA). Surprisingly, follow-up DSA imaging 14 months after the initial treatment showed a segmental dilatation and narrowing of the right VA, which suggested a *de novo* VADA on the right side that had occurred postoperatively. This was followed by a tent-assisted coil embolization therapy for occluding this *de novo* VADA. This patient showed an uneventful postoperative course with no neurological abnormalities. In addition to hemodynamic stress changes, the unique clinicopathological features of dissecting aneurysms may contribute significantly to the pathogenesis of *de novo* VA dissection. Given that VA in VADA patients may be vulnerable on both sides, it is important to consider the risk of *de novo* dissection after initial aneurysm treatment. The bilateral vertebral artery has to be carefully observed when treating any VADA patient to prevent any complications.

Keywords: vertebral artery dissecting aneurysm, *de novo* aneurysm, bilateral vertebral artery dissection, endovascular embolization, pipeline embolization device

INTRODUCTION

With a significant improvement in the understanding of the disease entity and angiographic appearance, the vertebral artery dissecting aneurysm (VADA) is considered rare, but has been increasingly reported as a fairly common cause of subarachnoid hemorrhage (SAH) or brain stem ischemia (1). In cases with SAH, previous studies have reported a high incidence of rebleeding with a high mortality rate during the time of recurrent bleeding (2, 3) thereby underscoring the necessity of early interventions. The development of spontaneous vertebral artery (VA) dissecting aneurysm is of rare occurrence, and *de novo* VADA after treatment of contralateral VA has been even less commonly observed. Mechanisms underlying *de novo* dissection after treatment of unilateral VADA have not been completely deciphered. In this manuscript, we report an unusual case of a patient with a *de novo* VADA after placement of a PED stent on the contralateral VA followed by an exhaustive literature review.

CASE DESCRIPTION

A 42-years old male patient was referred to a local hospital with a sudden onset of dizziness, nausea, as well as vomiting, and MRI revealed a partially thrombosed aneurysm adjacent to the left portion of the medulla (**Figure 1A**). The patient was admitted to our hospital without any major symptoms. An initial DSA image demonstrated dilatation at the fourth segment of the left VA, thus indicating a VADA without the involvement of the posterior inferior cerebellar artery (PICA) (**Figure 1B**). The right vertebral and basilar artery showed no major abnormalities. He had a medical history of hypertension and hyperlipidemia, but no previously reported head trauma and family history of aneurysm. The patient had a history of smoking 20 cigarettes a day for 20 years, which was ceased just at the time of this admission.

We treated the left VADA using endovascular pipeline embolization for preserving the normal blood flow. In addition, a dual antiplatelet therapy, comprising 300 mg aspirin and 300 mg clopidogrel were administered 5 days before the surgery. Under general anesthesia, a pipeline embolization device (PED) was successfully implanted with satisfactory adherence between the PED and vessel wall. No intraoperative complications were encountered, and the right VA was preserved. He was discharged home 1 week after the operation and prescribed dual antiplatelet therapy (aspirin 100 mg/day and clopidogrel l00 mg/ day) for 6 months. Angiography conducted at 5 months after initial treatment revealed the patency of the VA and partial aneurysm residues (**Figure 1C**). This residual of the left VADA persisted on 14 months (**Figure 1D**) and 2 years (**Figure 1F**), and completely occluded at 3 years angiography follow-up (**Figure 1G**). The volume of the aneurysm did not significantly alter from 14 months (**Figure 1E**) and as noted in 2 years of follow-up MR images (**Figure 1H**), and the patient did not display any adverse symptoms after the surgery.

In addition, no major abnormalities were found in the right VA at 5 months after initial treatment (**Figure 2A**). Surprisingly, follow-up imaging 14 months postoperatively showed a segmental dilatation and narrowing of the right VA (**Figure 2B**), which suggested the formation of a *de novo* VADA. Stent-assisted coiling was performed for this *de novo* VADA. Under general anesthesia, Guglielmi detachable coils were positioned in the dissecting aneurysms after placing an LVIS stent in the true lumen of the VA (**Figure 2C**). Dual antiplatelet therapy was prescribed to him as done before. The patient had an uneventful postoperative progression with no observation of any occurrence of neurological deficits. Moreover, a 20 months angiography follow-up revealed complete occlusion of the aneurysm (**Figure 2D**).

DISCUSSION

Dissecting aneurysms of the intracranial vertebral arteries are observed rarely, and either present themselves as ischemic symptoms of the brain stem or subarachnoid hemorrhage (SAH) (4–6). Unruptured dissecting aneurysms typically may have a benign course, and conservative measures such as antiplatelet or anticoagulation therapy are often recommended (6). However, once ruptured, vertebrobasilar aneurysms may have a poor prognosis with a mortality rate of approximately 50%, and recurrent hemorrhage can account for between 24 and 70% (4–6). Hence, appropriate treatment modalities are needed to avoid serious complications. When treating a VADA, a suitable consideration should be given to angioarchitecture including VA dominancy, location of the PICA origin, and anterior spinal artery involvement. Given its minimally invasive characteristics, endovascular treatment of VADA has become one of the most commonly used method, including internal trapping and stenting. Although internal trapping was the previously preferred treatment, with the advent of the appropriate use of antiplatelet agents and newly developed flow diverters, stenting has also shown favorable safety and efficacy in the management of VADA. Therefore, stent implantation was performed on the left VADA to maintain normal blood flow. The aneurysm reached complete occlusion at 3 years follow-up angiography. Numerous studies (7, 8) have revealed shrinkage of aneurysms following PED placement in cerebral aneurysms, however, the volume of the aneurysm in the present case was not significantly altered from follow-up MR images. The presence of substantial prior thrombosis appears to compromise the reduction of aneurysm volume after FD treatment.

Surprisingly, a follow-up angiography at 14 months after the initial treatment revealed a *de novo* VADA in the right vertebral artery, which is a very interesting observation. However, there is a paucity of data related to the *de novo* aneurysm formation rates in different patients with unruptured aneurysms. Moreover, in a systematic review and meta-analysis involving nearly 15,000 patients, the incidence of *de novo* aneurysms in patients with unruptured aneurysms was observed to be around 3% (9).

Abbreviations: SAH, subarachnoid hemorrhage; VA, Vetebral artery; DA, dissecting aneurysm; VADA, vertebral artery dissecting aneurysm; PED, pipeline embolization device; PICA, posterior inferior cerebellar artery; DSA, digital subtraction angiography; CFD, computational fluid dynamics.

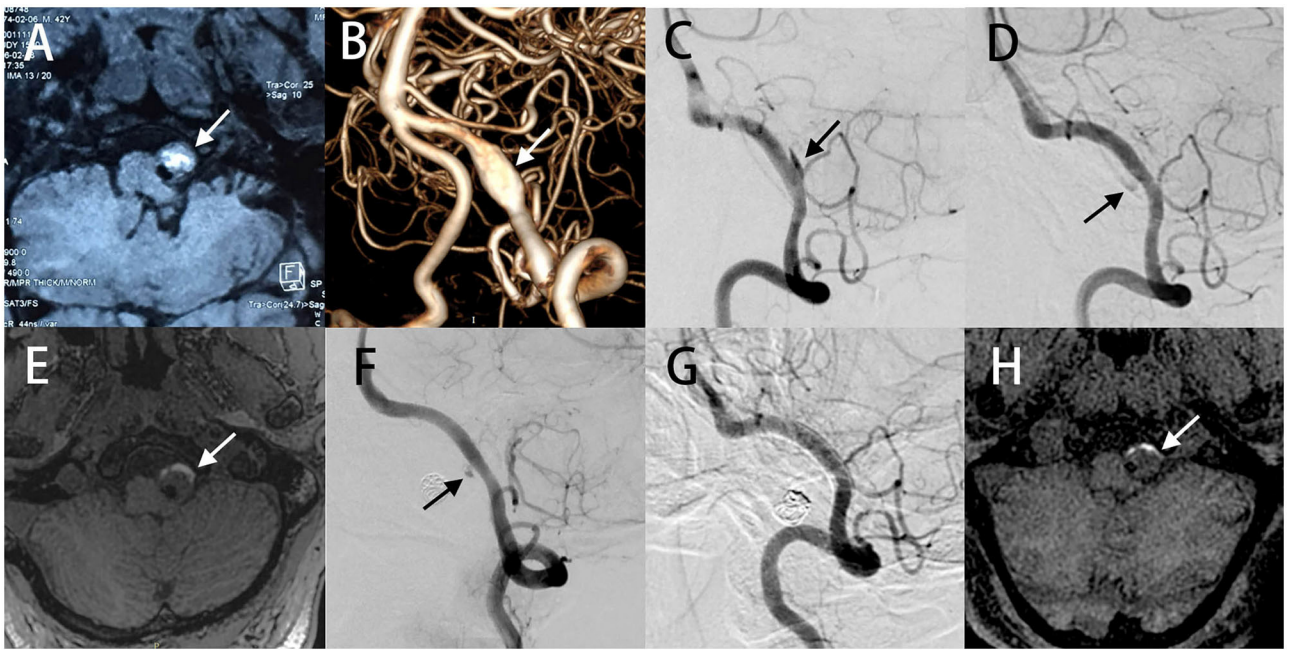

FIGURE 1 | MR image detected a partially thrombosed aneurysm adjacent to the left part of medulla **(A)**. 3D DSA image demonstrated a VADA in the fourth segment of the left VA **(B)**. Angiography at 5 months follow-up revealed that the stent were patent with partial aneurysm residues **(C)**. Partial residual aneurysm of the left VADA was observed on 14 months **(D)** and 2 years **(F)** follow-up angiography, and complete occlusion on 3 years (G). The volume of the aneurysm was not significantly changed from 14 months **(E)** and 2 years follow-up MR images **(H)**.

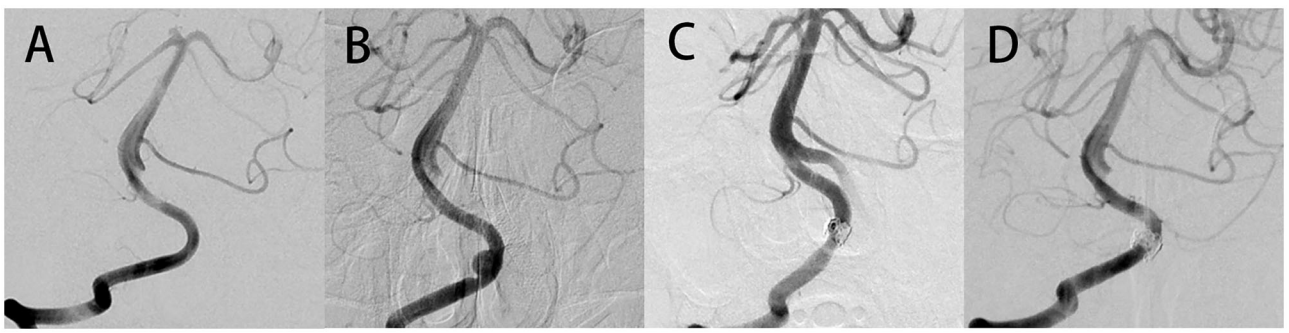

FIGURE 2 | No abnormalities were found in the right VA at the time of 5 months after initial treatment **(A)**. Follow-up imaging 14 months postoperatively showed a segmental dilatation and narrowing of the right VA, which suggested that a *de novo* VADA occurred **(B)**. Stent-assisted coil embolization therapy was performed to occlude this *de novo* VADA **(C)**. Angiography at 20 months follow-up after surgery revealed a complete occlusion of the aneurysm **(D)**.

In addition, history of smoking, hypertension, family history, and female gender are considered as high-risk factors for the development of *de novo* aneurysms (9, 10).

There are only a few reports about the *de novo* VADA after treatment of the contralateral VA in the existing literature. Previously reported cases are summarized in **Table 1** (11–17). Most initial aneurysms appear on the left side and manifest as SAH or infarction, and can be treated by trapping or occlusion of VA. The interval between the initial dissection and the discovery of *de novo* contralateral dissection varies from patient to patient. The mechanism responsible for *de novo* dissection after treatment of unilateral VADA has not been well-defined. It is however possible, that the unique clinicopathological features of dissecting aneurysms and changes in hemodynamic stress may significantly contribute to the pathogenesis of *de novo* VA dissection.

A few other studies suggest that sudden changes in hemodynamic stress may be the major causal factor behind the development of VA dissecting aneurysms. Two different cases have reported that the diameter of the VA increased after trapping of the contralateral VA (14, 18). Kono et al. performed the computational fluid dynamics (CFD) simulations of bilateral VADA and found that trapping of unilateral VA increased the wall shear stress in the dome surface of the

TABLE 1 | A summary of case reports of *de novo* VADA after the treatment of the contralateral VA.

References	Age (years)/Sex	Initial VADA			Interval	Second VADA			Outcome
		Location	Presentation	Treatment		Location	Presentation	Treatment	
Kubo et al. (11)	49/F	L	SAH	Proximal occlusion	3 W	R	Asymptomatic	Proximal occlusion	GR
Otawara et al. (13)	51/F	R	SAH	Surgical trapping	1 Mon	L	Asymptomatic	Conservation	GR
Inui et al. (14)	36/M	L	Infraction	Conservation	12 Mon	R	Infraction	Conservation	Dead
	45/M	L	SAH	Endovascular trapping	2 W	R	Infraction	Conservation	SD
Katsuno et al. (15)	39/M	L	SAH	Surgical trapping	8 H	R	SAH	Conservation	Dead
Kidani et al. (17)	55/F	L	SAH	Endovascular trapping	3 Mon	R	Asymptomatic	Conservation	GR
Tsuji et al. (16)	52/M	L	Infraction	Conservation	9 D	R	SAH	Endovascular trapping	GR
Present 2020	42/M	L	Asymptomatic	Endovascular stenting	14 Mon	R	Asymptomatic	SAC	GR

F, female; M, male; L, left; R, rightl; SAH, subarachnoid hemorrhage; W, week; Mon, month; H, hour; D, day; SAC, Stent-assisted coil; GR, good recovery.

contralateral aneurysm (19). Abrupt changes in hemodynamic stress after occlusion of unilateral VA may play an important role in the occurrence of contralateral VADA. However, as compared to the previously reported cases, our case retains the normal blood flow of unilateral VA, which may greatly alleviate the impact on hemodynamic changes. Furthermore, we noted that our patient had an uneventful postoperative with no neurological deficits and displayed good blood pressure control. Hemodynamic analysis by CFD can also aid in evaluating the formation and growth of aneurysms (20, 21), but there are few data available related to the correlation between hemodynamic changes after stenting and the occurrence of contralateral VADA (19). To the best of our knowledge, this is the first case of development of a *de novo* VADA after stent placing of the contralateral VA while the contralateral VAs blood flow was maintained in a normal manner.

The clinicopathological features associated with the intracranial dissecting aneurysms have been discussed in detail previously (22–24). The characteristic pathological features include defect or fragmentation of the internal elastic lamina, intimal thickening, and medial degeneration, which can lead to the formation of an aneurysm with or without relevant narrowing of the arterial lumen (24, 25). Generally, the main mechanism associated with intracranial arterial dissection is the diversion of the arterial stream into a weakened arterial wall. An important factor in this process is the development of multiple intramural hemorrhages, which are usually isolated and non-contiguous in the walls of the VA (22, 23, 26). However, these small intramural hemorrhages may be closely related to the disruption of vasa vasorum or new vessels. Although the pathogenesis and clinical manifestations of vertebral artery dissection and carotid artery dissection have not been fully explained, it is reported that patients with spontaneous intracranial artery dissection involve multiple arteries, and the incidence of spontaneous multivessel dissection has been found to be between 10 and 15% (27, 28). For example, Aronov et al. (29) reported a case of acute three-vessel carotid artery occlusion due to spontaneous quadruple carotid dissection occurring 1 week after cesarean section. Ro et al. (30) conducted a detailed pathological investigation of bilateral vertebral arteries in patients who died of SAH due to VADA. They found that 25 of the 58 patients had a latent previous dissection at a different location from the rupture point, with small disruption in the internal elastic lamina covered by an intimal thickening. Besides, they observed that the latent previous dissection had a tendency to occur as bilateral multiple lesions, thereby suggesting that the VA of patients with VADA may be vulnerable on both sides. It is unclear whether the *de novo* VADA, in this case, developed because of an extension of a latent previous dissection or by the occurrence of a possible new dissection. Therefore, the bilateral vertebral artery needs to be carefully observed when treating any VADA patient.

Many studies have suggested that smoking is a major risk factor for the formation of *de novo* aneurysms due to its propensity to result in an elastase/alpha antitrypsin imbalance, which may exacerbate the effect of hemodynamic stress on the aneurysm wall (31). Moreover, the other authors have speculated that hypertension may be a risk factor because the interval between identifying newly formed aneurysms has been noted to be significantly shorter in patients with hypertension (32). Furthermore, both smoking and hypertension may contribute to the degradation of the vessel wall and can lead to the development of *de novo* aneurysms as found in the present case.

It is worth mentioning that a recent Japanese survey of spontaneous cerebral arterial dissection showed that intracranial VA dissection can occur more frequently in Japan (33). This is completely different from the findings among the American population, which displayed a higher incidence of cervical internal carotid artery dissection (34). Actually, all previous case reports about *de novo* VA dissection were collected from Japan. The reason for this difference has not been clearly elucidated so far and may be possibly related to the variation in genes and the environment.

CONCLUSIONS

Endovascular treatment with stent placement can often preserve the normal blood flow of the VA and thereby reduce the changes observed in postoperative hemodynamic stress, but there

is still a substantial risk of *de novo* dissection. In addition to hemodynamic stress changes, the unique clinicopathological features of dissecting aneurysms may significantly contribute to the pathogenesis of *de novo* VA dissection. As VA in VADA patients may be at risk on both sides, the bilateral vertebral artery needs to be carefully monitored while treating VADA patients.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author/s.

AUTHOR CONTRIBUTIONS

WY wrote the manuscript and edited the figure and the table of the article. Together with QL, XL, and JF performed the revision of the current literature. WY and JL collection and interpretation of patient data. YL, YJ, and PL conceived and designed the research. All authors contributed to the article and approved the submitted version.

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REVIEW
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Clinical and Angiographic Outcomes After Stent-Assisted Coiling of Cerebral Aneurysms With Laser-Cut and Braided Stents: A Comparative Analysis of the Literatures

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Introduction: Stent-assisted coiling (SAC) plays an important role in endovascular treatment of intracranial aneurysms (IAs). This comparative analysis examines the safety and efficacy of SAC in general and compares clinical and angiographic outcomes between laser-cut stents and braided stents.

Methods: Relevant English-language studies were identified via a PubMed search for published articles regarding outcomes of SAC using laser-cut stents and braided stents published from 2015 to 2020. Data from 56 studies that met our inclusion criteria were pooled and statistically compared.

Results: A total of 4,373 patients harboring with 4,540 IAs were included. Patients were divided into two groups on the basis of stent type: laser-cut stents (2,076 aneurysms in 1991 patients; mean follow-up, 12.99 months) and braided stents (2,464 aneurysms in 2382 patients; mean follow-up, 18.41 months). Overall, the rates of successful stent deployment, thromboembolic events, stent stenosis, periprocedural intracranial hemorrhage, permanent morbidity, mortality, and recanalization were 97.72, 4.72, 2.87, 1.51, 2.14, 1.16, and 6.06%, respectively. Laser-cut stents were associated with a significantly higher rate of successful deployment ($p = 0.003$) and significantly lower rate of periprocedural intracranial hemorrhage ($p = 0.048$). Braided stents were associated with a significantly lower rate of permanent morbidity ($p = 0.015$).

Conclusion: SAC of IAs using laser-cut stents or braided stents was effective and safe. Rates of thromboembolic events, stent stenosis, mortality, and recanalization were comparable between the stent types. Braided stents were associated with lower permanent morbidity while laser-cut stents were associated with more favorable rates of successful deployment and periprocedural intracranial hemorrhage.

Keywords: intracranial aneurysm, endovascular treatment, stent-assisted coiling, the laser-cut stent, the braided stent

INTRODUCTION

Surgical clipping and endovascular therapy are the two main treatment options for patients with intracranial aneurysms (IAs). Detection of IAs is increasing because of widespread use of non-invasive intracranial vascular examination techniques such as magnetic resonance angiography. Since the use of Guglielmi detachable coils (GDC) for endovascular IA treatment was introduced in the 1990s (1), the advent of various types of coils and stents has ushered in a Golden Age of endovascular treatment, with stent-assisted coiling (SAC) playing an important role over the past decade.

Patients have widely accepted SAC because of good clinical outcomes (2, 3). In this technique, stent deployment serves as a scaffold to prevent coil prolapse, which preserves the parent artery and promotes thrombosis in the aneurysm and re-endothelialization, resulting in improved outcome (4). Laser-cut and braided stents are the primary intracranial stents in use today. Laser-cut stents are characterized by high vascular compliance, good flexibility, excellent stability, and fewer thromboembolic events in collateral vessels; examples include Neuroform (Stryker Neurovascular, Kalamazoo, MI, USA), Neuroform Atlas (Stryker Neurovascular), Enterprise (Codman Neuro, Raynham, MA, USA), and Solitaire (Medtronic, Dublin, Ireland). Self-expanding braided stents have greater metal surface coverage and provide greater flow diversion to promote aneurysmal occlusion; examples include LVIS (Microvention, Aliso Viejo, CA, USA), LVIS Jr (Microvention), and LEO Baby (Balt, Montmorency, France). Both stent types are widely used in IA management and type superiority has not been established (5, 6).

SAC studies have been increasing owing to a 2013 review of intracranial stenting (7), increased stenting experience, improvements in stenting technology, and increased IA detection; however, results have been variable. Therefore, an up-to-date review of this rapidly developing field is needed. This study aimed to review recent relevant literature to compare clinical and angiographic outcomes of SAC with laser-cut and braided stents and to comment on the safety and efficacy of SAC in general.

METHODS

Data Sources

The PubMed database was searched for relevant articles published from January 2015 to October 2020 regarding Neuroform, Neuroform Atlas, Enterprise, Solitaire, LVIS, LVIS Jr, and LEO Baby stents. Search terms included "[stent name]," "[stent name] + stent," and "[stent name] + intracranial aneurysm." Studies which met the following criteria were reviewed: (a) abstract and/or entire manuscript was published in English; (b) case series, prospective study, or clinical trial that included nine or more patients; (c) detailed clinical and/or radiological post-intracranial stenting data were reported; (d) multiple stent systems were studied with individual system data clearly reported. In cases of controversy, the entire article was thoroughly reviewed. Patients who received more than one type of stent were excluded.

Data Extraction

The following data from articles meeting our inclusion criteria were reviewed and extracted: sample size, deployment success, thromboembolic events, periprocedural intracranial hemorrhage, stent stenosis, permanent morbidity (present at last follow-up), mortality, angiographic aneurysmal occlusion immediately following the procedure and at last follow-up, and recanalization. Thromboembolic events were defined as stroke, transient ischemic attack, or development of asymptomatic thrombus during the procedure. Stent stenosis was defined as "moderate," "severe," or "symptomatic" stenosis, or as $\geq$50% stenosis if quantified (8–10). Angiographic occlusion was defined in accordance with the Raymond–Roy classification and the modified Raymond–Roy classification (11, 12). Recanalization was defined as "recanalization" or "recurrence"; residual aneurysms that increased in size and aneurysms that progressed to a higher Raymond–Roy class were also considered recanalized. All data were reviewed and verified independently by the two authors and entered into the study database using specialized forms. In some outcome analyses, patients from studies with missing data were excluded from the analysis.

Statistical Analysis

Statistical analyses were performed using SPSS software version 26 (IBM Corp., Armonk, NY, USA.). Continuous data are presented as means. Categorical data are presented as frequencies or percentages and were compared using the two-tailed Fischer exact test. $P < 0.05$ was considered significant.

RESULTS

A total of 56 studies comprising 4,373 patients harboring 4,540 aneurysms were included (6, 13–67). Patients were divided into two groups on the basis of stent type: laser-cut stents (2,076 aneurysms in 1991 patients; mean follow-up, 12.99 months) and braided stents (2,464 aneurysms in 2,382 patients; mean follow-up, 18.41 months). Both stents performed equally well, with no significant difference in frequencies of thromboembolic events, stent stenosis events, mortality, recanalization, and class 1 (complete) and class 2 (near-complete) Raymond–Roy angiographic occlusion between groups. Frequency of successful deployment was significantly higher in the laser-cut stent group (98.69 vs. 97.07%, $p = 0.003$), while frequency of periprocedural intracranial hemorrhage was significantly lower (1.13 vs. 1.85%, $p = 0.048$). Frequency of permanent morbidity was significantly lower in the braided stent group (1.58 vs. 2.92%, $p = 0.015$). Rates of clinical complications and class 1 and class 2 angiographic occlusion overall and according to stent type are presented in **Table 1**. Denominators of the analyses vary based on the number of patients with available data.

DISCUSSION

Our comparative analysis of 4,540 aneurysms in 4,373 patients found that SAC of IAs using either laser-cut or braided stents had favorable clinical outcomes and angiographic results. Overall, rates of mortality, permanent morbidity, and recanalization were low, suggesting that SAC is safe and effective.

TABLE 1 | The clinical and angiographic outcomes after stent-assisted coiling of cerebral aneurysms with laser-cut and braided stents.

	Total *N* (%)	Laser engraving stent *N* (%)	Braided stents *N* (%)	*p*-value
Number of patients	4,373	1,991	2,382	N/A
Number of aneurysms	4,540	2,076	2,464	N/A
Deployment success, %	2957/3026 (97.72)	1202/1218 (98.69)	1755/1808 (97.07)	0.003
Thromboembolic events	210/4451 (4.72)	90/2077 (4.33)	120/2374 (5.05)	0.288
In-stent stenosis	83/2887 (2.87)	32/1089 (2.94)	51/1798 (2.84)	0.909
Peri-procedural intracranial hemorrhage	67/4451 (1.51)	23/2077 (1.13)	44/2374 (1.85)	0.048
Initial Raymond 1	2686/4293 (62.57)	1208/1909 (63.28)	1478/2384 (61.70)	0.392
Initial Raymond 2	1009/4293 (23.50)	441/1909 (23.10)	568/2384 (23.82)	0.587
Initial Raymond 3	598/4293 (13.93)	260/1909 (13.61)	338/2384 (14.18)	0.626
Last follow-up Raymond 1	2453/3109 (78.90)	1175/1478 (79.50)	1278/1631 (78.36)	0.454
Last follow-up Raymond 2	401/3109 (12.90)	175/1478 (11.84)	226/1631 (13.86)	0.097
Last follow-up Raymond 3	255/3109 (8.20)	128/1478 (8.66)	127/1631 (7.79)	0.395
Permanent morbidity	65/3040 (2.14)	37/1268 (2.92)	28/1772 (1.58)	0.015
Mortality	38/3274 (1.16)	16/1316 (1.22)	22/1958 (1.12)	0.868
Recanalization	200/3298 (6.06)	91/1325 (6.87)	109/1973 (5.52)	0.056

Laser-cut stents: Enterprise, Neuroform, Neuroform atlas, Solitaire.
Braided Stents: Lvis, Lvis Jr, Leo baby.

Early endovascular coiling studies indicated that low coil density, large aneurysm size, and wide aneurysm neck are recanalization risk factors (68). However, the development of SAC has enabled treatment of wide-neck, complex, and bifurcation intracranial aneurysms. Stent deployment significantly improves outcome by serving as a scaffold to prevent coil prolapse and preserve the parent artery. This promotes thrombosis in the aneurysm lumen as well as re-endothelialization and may explain why SAC has a lower recanalization rate than coil embolization alone. However, stent placement is associated with higher procedural risk and risk of stent thrombosis.

Braided stents in our study were represented by LVIS, LVIS Jr, and LEO Baby. These stents have greater metal surface coverage and provide greater flow diversion, which promotes IA occlusion and results in fewer adverse ischemic events. Laser-cut stents were represented by the Neuroform, Enterprise, and Solitaire series of stents. These stents have the advantages of high vascular compliance, good flexibility, excellent stability, and fewer thromboembolic events in collateral vessels. Our comparative analysis resulted in several significant findings. The rates of successful deployment and periprocedural intracranial hemorrhage favored laser-cut stents; however, permanent morbidity was significantly lower in patients who underwent SAC with braided stents. In addition, rates of angiographic aneurysmal occlusion, thromboembolic events, stent stenosis, mortality, and recanalization did not differ between the two groups. However, several different individual stents were used in each group and the data are representative of multiple device iterations, different operators, and accumulated institutional experience over the past 6 years. Our findings may not be applicable to current practice and should be interpreted with caution.

To be noted, previous studies demonstrated that braided stents have greater metal surface coverage and provide greater flow diversion, which promotes IA occlusion. Feng et al. showed that LVIS stents may achieve lower rate of recanalization and in-stent stenosis than Enterprise (38). Ge et al. reported a higher rate of recanalization associated with enterprise stent than with the LVIS stent (10.7 vs 2.8%) (25). Lim et al. observed in SAC of IAs, laser- cut and braided stent groups produced similar outcomes in follow-up, the difference of recanalization incidence rates between the braided- stent and the laser-cut group was not statistically significant (5).

Unlike previous studies, there are more than one kind of stent in both two groups. Our study finding is similar to that of many previous studies, the recurrence rate of laser-cut stents is higher than braided stents (91/1325 6.87% vs 109/1973 5.52%). Overall, the result was encouraging, with minor difference.

The present studies containing 4,373 aneurysms in more than 4,500 patients in recent 6 years. It is an up-to-date and robust review of this rapidly developing field. This comparative analysis demonstrated that both laser-cut stents and braided stents had good clinical outcomes. Overall, high rate of deployment success (97.72%), initial and final completely and near completely angiographic occlusion was seen in 86.07 and 91.80% of patients, low rate of thromboembolic events (4.72%) and In-stent stenosis (2.87%), low permanent morbidity (2.14%), and mortality (1.16%).

The low clinical complication rate, high deployment success and high degree of occlusion are particularly encouraging, which may result from the increased stenting experience, improvements in stenting technology, and increased IA detection.

The advantages of laser-cut stents characterized by high vascular compliance, good flexibility, excellent stability (24). Besides, the push technique and the release of braided stents

as well as catheter pullback are difficult, especially in tortuous vessels. The above mentioned could account for more favorable deployment and less peri-procedural intracranial hemorrhage in laser-cut stents group.

In this study, we made a comparative analysis between the published results of the laser-cut stents and braided stents demonstrated that both laser- cut and braided stent groups produced similar outcomes in SAC of IAs. The pooled data include studies across multiple device iterations in the recent 6 years, the data do not necessarily represent the procedural device failures, clinical complications, or occlusion of the most modern device iterations or procedural techniques used currently. These results should be interpreted with caution.

This study has significant limitations. First, numerous retrospective studies were analyzed, each with their own biases. Second, heterogeneity between the analyzed studies may weaken the generalizability and validity of our findings. Third, the study data were pooled from previously published studies without stringent inclusion criteria, and the scientific quality of the included studies was not graded. Fourth, we did not consider IA location, number of stents used, stent length, stent cost and availability, and different follow-up durations and did not compare stent morphological characteristics between groups, which may have introduced significant bias. Furthermore, direct comparisons between studies were difficult as data reporting was variable. Finally, the reported 6.06% recanalization rate probably significantly underestimates the true rate (69).

CONCLUSION

This analysis of 4,373 patients harboring 4,540 IAs who underwent SAC with laser-cut or braided stents within the past 6 years found that SAC is safe and effective. Rates of permanent morbidity, mortality, and recanalization were comparable between the devices; however, braided stents were associated with lower permanent morbidity while laser-cut stents were associated with more favorable rates of successful deployment and periprocedural intracranial hemorrhage.

AUTHOR CONTRIBUTIONS

LZ drafted the manuscript and prepared the table. XC, PL, LD, and LJ conducted data collection. ML and YZ conceived and designed this project. All authors reviewed the manuscript.

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STUDY PROTOCOL
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Thrombectomy for Acute Ischemic Stroke With a New Device-Skyflow: Study Protocol for a Prospective, Multicenter, Stratified Randomized, Single-Blinded, Parallel, Positive Controlled, Non-inferiority Clinical Trial

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Background: Stent retriever thrombectomy is the standard treatment for acute ischemic stroke (AIS) with large vessel occlusion (LVO) in anterior circulation. The aim of the trial is to evaluate whether the new thrombectomy device-Skyflow can achieve the same safety and efficacy as Solitaire FR in the treatment.

Method: This study is a prospective, multicenter, stratified randomized, single blind, paralleled, positive controlled, non-inferiority clinical trial. The safety and efficacy of vascular recanalization in AIS patients who are treated with either a new thrombectomy device-Skyflow or with Solitaire FR and within 8 h of symptom onset will be compared. A total of 192 patients will be enrolled, each group with 96 patients. The primary endpoint is successful recanalization rate after the operation. The secondary efficacy endpoints are the time from artery puncture to successful recanalization (mTICI 2b-3), NIHSS scores of 24 h (18–36 h), and 7 ± 2 days after the operation, mRS scores, and the rate of patients with mRS 0–2 scores 90 ± 14 days after the operation, and the success rate of instrument operation. The safety endpoints are the rate of symptomatic intracranial hemorrhage (sICH) and subarachnoid hemorrhage at 24 h (18–36 h) post-operation, incidence of adverse events (AE) and serious adverse events (SAE), all-cause mortality, and incidence of device defects.

Discussion: This trial will provide information on the safety and efficacy of Sky-flow stent retriever in the treatment of AIS patients with anterior circulation LVO. The success of this trial will be the basis for the product to be finally officially listed and applied in China.

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INTRODUCTION

Stroke is one of the main causes of human disability and death. Acute ischemic stroke (AIS) accounts for about 80% of all types of stroke (1). The key to AIS treatment is to recanalize the occluded blood vessel as soon as possible and salvage the ischemic penumbra. Endovascular treatment (EVT) in patients with large vessel occlusion (LVO) has attracted much attention because of many advantages such as rapid recanalization, lower hemorrhagic transformation rate, and extended stroke interventional therapy time window (2–5).

The invention of the stent retriever is a huge advancement of EVT, which has been reported to achieve a higher recanalization and favorable clinical outcome rate (2). The stent retriever uses a temporary stent to capture the thrombus, and restore blood flow by squeezing the peripheral blood vessel wall and moving the thrombus. When the stent is withdrawn, the thrombus is captured in the stent gap and removed together with the stent. The food and drug administration (FDA) of USA approved Solitaire (Medtronic/ev3) and Trevo (Strike) stent retriever to be mainly used for the treatment of large vessel occlusive stroke in 2012. The Solitaire FR With the Intention for Thrombectomy (SWIFT) study (6) and Thrombectomy Revascularization of Large Vessel Occlusions in Acute Ischemic Stroke (TREVO 2) trial (7) declared that MT with the Solitaire FR stent (ev3 Covidien) and the Trevo stent (Stryker Neurovascular) achieved better revascularization than those with the Merci retriever device. And it is recommended to use the stent retriever for acute mechanical thrombectomy (MT) (Class I, Level A) in the treatment of acute anterior circulation LVO stroke in guidelines for the early management of patients with AIS (8).

At present, the China Food and Drug Administration (CFDA) has approved several thrombectomy devices of foreign companies to be listed domestically, including Solitaire FR (Medtronic/ev3), Trevo thrombectomy system (Stryker), and Revive self-expanding intracranial thrombectomy device (Codman). In recent studies, the new mechanical thrombectomy devices, such as EmboTrap, Tigertriever and NeVa^{TM}, have also achieved a high recanalization rate and good clinical outcome (9–12). The safety and efficacy of the domestically-made mechanical thrombectomy devices, such as Tonbridge stent retriever, JRecan stent retriever, and Reco stent retriever, have been verified in animal experiments or clinical trials, but they have not yet been widely used (13–15). In China, stent retrievers are still mainly imported and are expensive, making a lot of patients unable to receive effective treatment.

In order to better meet the domestic AIS patients and the ever-increasing clinical needs, Skynor medical (Shanghai) co. LTD designed a new thrombectomy device-Skyflow which has been approved by CFDA. The thrombectomy device is mainly composed of stent retriever and an introducer sheath, and the stent retriever including a stent and a pushing wire. There are marks of platinum alloy on the stent, which can be seen through DSA or X-ray. The stent can be released and retrieved by pushing and pulling the delivery wire. And the stent retriever is compressed into an introducer sheath, which is designed to facilitate stent loading into the microcatheter. The length of the delivery wire of the device is 185 cm, and the inner diameter of the compatible micro catheter is 0.021″/0.027″. It is divided into different specifications according to stent diameter of 3, 4, or 6 mm (**Figure 1**).

This clinical trial aims to evaluate the safety and efficacy of the new thrombectomy device-Skyflow for patients of AIS with large vessel occlusion in anterior, and provide a basis for the product to be finally officially listed and applied.

METHOD

Objective

The aim of the trial is to evaluate the safety and efficacy of the new thrombectomy device-Skyflow in the treatment of AIS to provide a basis for product registration, listing, and application.

Study Design

This study is a prospective, multicenter, stratified randomized, single blind, paralleled, positive controlled, non-inferiority clinical trial comparing the safety and efficacy of recanalizing occluded vessel for patients with AIS within 8 h of symptom onset treated with either a new thrombectomy device-Skyflow (TD 320, TD420, TD430, TD440, TD620, or TD630) or with Solitaire FR (SFR-4-15, SFR-4-20, SFR-6-20, or SFR-6-30). The study will be conducted in more than 10 clinical trial centers. A total of 192 patients who fulfill the inclusion and exclusion criteria and provide informed consent will be randomized into either a treatment group or a control group in the ratio of one-to-one. The treatment group will receive mechanical thrombectomy with the properly sized new device-Skyflow and the control group with Solitaire FR to restore blood flow of the occluded vessel and improve clinical symptoms. Subjects will be followed up for 5 times after enrollment, respectively, before operation, intraoperation, 24 h after operation, 7 days after operation, and 90 days after operation. If there is an adverse event during the clinical trial, the investigator needs to observe outcome of the adverse event. All assessment indexes were recorded to evaluate the safety and efficacy of the experimental thrombectomy device in the treatment of AIS. **Table 1** is a brief summary of visits and assessment schedule.

Participants

Inclusion Criteria

Patients eligible for inclusion will meet the following criteria (6, 16, 17):

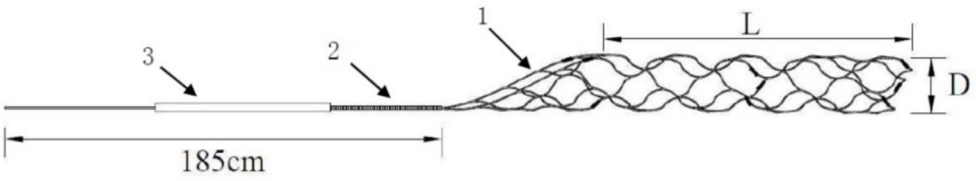

FIGURE 1 | Description of stent composition: there are different sizes of stent retriever, including TD 320, TD420, TD430, and TD440 requiring a compatible microcatheter of 0.021 inch and TD620 and TD630 requiring a compatible microcatheter of 0.027 inch. Stent retriever with double helix structure, partial large mesh and full development design (1), pushing wire 185 cm with a variable-diameter structure coiled with platinum alloy coil in the distal (2), introducer sheath (3), diameter of stent, 3 mm for TD 320, 4 mm for TD420, TD430, and TD440, 6 mm for TD620 and TD630 (D), and stent retriever effective length, 20 mm for TD 320, TD420, and TD620, 30 mm for TD430 and TD630, and 40 mm for TD440 (L).

TABLE 1 | Visits and assessment schedule.

	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5
	−1∼0 day before operation	**During operation**	**24 h after operation (18–36 h)**	**7 ± 2 day after operation**	**7 ± 2 day after operation**
Informed consent	×				
Inclusion/exclusion criteria	×	×			
Random allocation		×			
Demographic data	×				
History of current illness.	×				
Past medical history	×				
Vital signs	×			×	
NIHSS score	×		×	×	
mRS score	×				×
Blood routine test[1]	×			×	
Routine coagulation test[2]	×			×	
Liver function test[3]				×	
Renal function test[4]	×			×	
Random blood glucose	×				
Pregnancy test[5]	×				
12-lead electrocardiogram	×			×	
Brain CT or MR[6]	×		×		
Cerebrovascular DSA[7]		×			
The use of surgical and experimental instruments		×			
Concomitant medication[8]	×	×	×	×	×
Adverse events		×	×	×	×
Device defects		×			

[1]*blood routine test: Hgb, Hemoglobin Content; RBC, Red Blood Cells Count; WBC, White Blood Cell Count; NEUT, Absolute Neutrophil Count; NEUT%, neutrophil ratio; PLT, Platelet Count;* [2]*routine coagulation test: PT, Prothrombin Time; APTT, Activated Partial Thromboplastin Time; INR, the international normalized ratio;* [3]*liver function test: AST, aspartate transaminase; ALT, alanine transaminase; STB, serum total bilirubin; TP, Serum Total Protein; ALB, serum albumin;* [4]*renal function test: Scr, serum creatinine; BUN, Blood Urea Nitrogen;* [5]*pregnancy test: blood HCG or urine pregnant test, Suitable for women of childbearing age;* [6]*brain CT or MR: identify whether there is intracranial hemorrhage, massive cerebral infarction or angiemphraxis before the interventional procedure, and whether there is intracranial hemorrhage after procedure;* [7]*cerebrovascular DSA: identify whether there is initial carotid artery occlusion, carotid artery dissection or arteritis, whether there is a tortuous vessel path that makes it difficult for the test/control device to reach the target position, the target vessel and the diseased segment, the proximal diameter of the occluded vessel, mTICI before, and after the operation;* [8]*record the use of anticoagulant, antiplatelet drugs, and drug for adverse events.*

1. Aged 18–80 years, clinical signs consistent with AIS.
2. Clinical signs consistent with AIS; Subjects who are able to be treated within 8 h of onset of stroke symptoms; NIHSS $\geq$ 6 and $<$ 30 at the time of randomization.
3. Occlusion in the intracranial internal carotid, or M1/M2 segment of the middle cerebral artery (MCA) confirmed by DSA.
4. Prestroke Modified Rankin Score$\leq$2.
5. Informed consent of the patient or family member.

Exclusion Criteria

Patients will be excluded if they meet any of the following criteria:

1. CT or MRI evidence of hemorrhage or infarction involving greater than 1/3 of the MCA territory (or in

other territories, > 70 ml of tissue on presentation, or CT/DWI-ASPECT <6).
2. Bilateral internal carotid artery occlusion detected by DSA.
3. Initial segment of internal carotid artery occlusion or carotid artery dissection detected by DSA.
4. The route artery is too tortuous for test/control equipment to reach the target position.
5. Severe and sustained hypertension (defined as systolic blood pressure >185 mmHg or diastolic blood pressure >110 mm Hg under the treatment of antihypertensive drug).
6. Baseline platelet count <40 × 10*9/L or recent oral anticoagulant therapy with INR>3.
7. Baseline blood glucose <2.8 mmol/L or > 22.20 mmol/L.
8. Having a heart, lung, liver, and kidney function failure or other serious diseases, such as intracranial malignant tumors, intracranial arteriovenous malformation, arteritis, systemic infection, and activity of disseminated intravascular coagulation, with serious disabling stroke within 6 months and severe mental illness.
9. Can't cooperate with interventional surgery or can't tolerate.
10. Life expectancy of less than 90 days.
11. Known serious sensitivity to radiographic contrast agents.
12. Female who is pregnant or lactating or has a positive pregnancy test at time of admission.
13. Involved in other drugs or equipment trials within 3 months before randomization.

Criteria and Procedures for Discontinuing Trial/Trial Treatment

Dropout Criteria

All subjects who sign an informed consent form and are selected to be enrolled in the central randomization system are entitled to withdraw from the clinical trial at any time. As long as they didn't complete the clinical trial observation, it should be considered as dropout cases.

Management of Dropout Cases

When a subject drops out, the researcher must fill in the reason in the CRF, and contact the subject as much as possible to complete the assessment items and record the last follow-up time. The CRF should be reserved for future reference. For cases who drop out due to adverse events, in addition to being recorded in the CRF, they should be also included in the adverse event evaluation. The random number of dropout cases cannot be replaced.

Elimination Criteria

Subjects who meet one of the following criteria should be eliminated: being falsely enrolled or neither using test devices nor control devices.

Management of Eliminated Cases

The researcher must fill in the elimination reason in the CRF and the CRF should be reserved for future reference. The random number of eliminated cases cannot be replaced.

Full Termination Criteria

The experiment should be terminated due to any of the following reasons: there are serious safety issues with the experimental device; the experimental device has a poor effect and there is no need to continue the test; there are major mistakes in the protocol; and there are funding or management problems of sponsor.

Treatment and Intervention

For all the enrolled patients, stent retriever thrombectomy is the first-line approach. Skyflow device is for the trial group and solitaire FR for control group. Patients who are eligible for intravenous thrombolysis according to the guidelines were given 0.9 mg/kg alteplase. General or local anesthesia was chosen based on the patients' clinical condition and heparin was used selectively. Stent retriever thrombectomy can be performed repeatedly and generally no less than 3 times before rescue therapy. If the intracranial occluded blood vessel had significant stenosis or other lesions after mechanical thrombectomy with stent retriever, the researcher should evaluate whether to perform the aspiration thrombectomy, balloon dilatation, stent implantation or other rescue therapy based on the subject's clinical conditions. If adjuvant rescue treatment was performed, DSA should be recorded and mTICI classification should be reevaluated. Follow-up examinations and visits were carried out according to the test procedure.

Management of Concomitant Medication

Drugs and treatments for underlying diseases, comorbidities or adverse events are permitted. But devices with similar effects to the experimental device or the control device are prohibited for all subjects during clinical trials. If the subject used other drugs and treatments for various reasons during the study period, the investigator needed to record this case in details in the original medical record for future reference and evaluate the possible bias in clinical trial results.

Endpoint Measurement

The primary endpoint is successful recanalization rate. It is defined as the proportion of target vessels achieving successful recanalization [modified Thrombolysis in Cerebral Infarction (mTICI) 2b-3].

The secondary efficacy endpoints are the times from artery puncture to successful recanalization (mTICI 2b-3), NIHSS scores 7 ± 2days after the operation, mRS scores and the rate of patients with 0–2 scores 90 ± 14 days after the operation, and the success rate of instrument operation (the rate of instruments being successfully delivered, released, and withdrawn in this group).

The safety endpoints are the rate of symptomatic intracranial hemorrhage (sICH) and subarachnoid hemorrhage at 24 h (18–36 h) post-operation, incidence of adverse events (AE)

and serious adverse events (SAE), all-cause mortality and device defects.

sICH is defined as any ICH associated with neurological deterioration assessed by 4 or more points increase on the NIHSS score within 18–36 h. Adverse events are unfavorable medical events that occur during clinical trials, whether related to the test device or not, including hematoma or hemorrhage at the site of puncture, air embolism, infection, distal embolization, vascular spasm, thrombosis, vascular dissection and perforation, embolism, acute occlusion, ischemia, intracranial hemorrhage, pseudoaneurysm formation, neurological deficits including stroke, and death, and device deformation, fracture and malfunction. Serious adverse events are defined as any events which can cause deaths or serious health deterioration that occur during clinical trials, including fatal diseases or injuries, permanent defects of body structure or function, events that need hospitalization or can prolonged hospitalization, events that need medical or surgical intervention in order to avoid permanent defects in body structure or function, and events that can cause fetal distress, fetal death, or congenital anomalies and congenital defects. Device defects refer to the unreasonable risks of medical devices under normal use that may endanger human health and life safety during the clinical trials, such as incorrect identification and device breakage.

Management of Adverse Events

All adverse events that occurred during the trial must be faithfully recorded. Researchers should give targeted treatment and follow-up for adverse events until the symptoms disappear or become stable.

For serious adverse events in the clinical trial, the investigator should immediately take appropriate treatment measures to the subject, and at the same time report to the medical device clinical trial management department in writing and notify the sponsor in writing through the department. The medical device clinical trial management department should report to the relevant ethics committee, the Food and Drug Administration and the health and family planning department of the province, autonomous region, and municipality in writing within 24 h. For deaths, clinical trial institutions and researchers should provide all necessary information to the ethics committee and sponsors.

When device defect occurs, replace it with the same device or take conventional treatment. For device defects that cause or may cause serious adverse events, the sponsor should report to the registered FDA and the health and family planning authority at the same level within 5 working days. At the same time, it should notify other clinical trial institutions and researchers participating in the trial and timely informs the ethics committee of the clinical trial institution through the medical device clinical trials management department.

Randomization

Immediately after DSA and prior to mechanical thrombectomy, 192 patients are randomly allocated in a one-to-one ratio to either experimental or control group using an Internet-based Central Random System (IWRS). When grouping the patients, stratification will be performed to control key indicators by the clinical trial center and the baseline NIHSS score (divided by NIHSS score $\leq$ 17 points or $>$ 17 points) (2).

Reduction and Avoidance of Bias

The following measures have been taken to reduce and avoid bias:

NIHSS and mRS score were assessed by physician independent of the operator in each clinical trial center. The images are reviewed by the core laboratory to assess time of successful recanalization and the grade of the blood flow of the target vessel before and after the operation. When the result is different from the clinician's judgment, the core laboratory result shall prevail.

Sponsors, clinical trial supervisors, and researchers took corresponding measures to reduce the bias on results during the trial, including training for investigators before the start of the study to make sure they are familiar with research procedure and device operation, selecting skilled and experienced surgeons who has completed more than 30 mechanical thrombectomy operations, ensuring that the experimental protocol is strictly followed, following the requirements of relevant treatment guidelines, and data verification after the completion of clinical trials.

Monitoring Plan

The sponsor should select qualified supervisors to perform supervisory duties on all participating institutions. Before the trial, supervisors should confirm the clinical trial institution has the appropriate conditions including the staffing and training meeting the requirements, well-equipped laboratory, good working condition, sufficient number of subjects, and the researchers are familiar with the test requirements. They should also supervise whether the clinical trial institutions and researchers comply with relevant regulations, and supervise medical device samples and related equipment during the trial. And supervisors must confirm that each subject signs an informed consent before participating in the clinical trial and all case report forms are filled correctly and consistent with the original data, and ensure that all clinical trial related documents received by investigators are new versions. Detailed information must be recorded for patients who withdrew from the experiment, don't follow the informed consent form, and are not followed up completely, as well as all adverse events, complications, and other device defects.

Ethical Considerations and Informed Consent

This clinical trial comply with the Declaration of Helsinki, Medical Device Clinical Trial Quality Management Regulations and Chinese relevant laws and regulations. Before the start of the trial, the protocol must be approved by the ethics committee of each research center. The investigators should provide the subjects or their guardians complete information about the trial and should not compel or induce subjects to participate in the trial in improper ways. If the subjects have a disturbance of consciousness or have a difficulty in understanding language, the

investigator should fully explain the details of the clinical trial to their guardian, and the guardian and investigators shall sign their name and date on the written informed consent prior to enrollment and keep it in the research files.

Sample Size

The calculation of the sample size is based on the successful recanalization rate evaluated during the operation. Based on the results of the North American Solitaire post-marketing study (18), the meta-analysis of thrombectomy devices (2), and a multi-center registered clinical trial (EAST) led by Professor Miao Zhongrong of Tiantan Hospital, it is expected that the test group can reach the same efficiency when the sponsor and clinicians assumed the rate of successful recanalization after treatment was about 90% in the control group. Eventually, a total of 192 patients were enrolled according to calculation based on statistical principles, 96 cases in each group with a 12.5% non-inferiority margin, a 5% significance level (two-tailed), an 80% statistical power and a 5% dropout rate.

Statistical Analysis

For descriptive analysis, enumeration data will be expressed by frequency and composition ratio, and the measurement data will be expressed by the mean, standard deviation, maximum, minimum, median, 25th and 75th quantile.

For baseline demographics, all date will be analyzed based on full analysis set. Continuous calibration Chi-square tests or Fisher's exact tests will be used for comparison of enumeration data between groups. Group *t*-test will be used for comparison of normally distributed measurement data between groups, and Wilcoxon Rank Sum test for non-normally distributed measurement data.

For the primary outcome, the successful recanalization rate of blood vessels, the CMH chi-square analysis with adjusted center effect will be used for comparison between groups based on full analysis set and per protocol set. In addition to the success rate, the difference in the success rate between the experimental group and the control group and the 95% confidence interval with the lower bound greater than −12.5% will be also estimated.

Other efficacy indicators comparation between groups will be the same as the baseline analysis. The paired *t*-test will be used for the intra-group comparison of normally distributed measurement data and the Wilcoxon Sign Rank test for the intra-group comparison of non-normally distributed measurement data.

For safety evaluation, the number and proportion will be used to describe cases that were normal before treatment and abnormal after treatment in the full analysis set. Adverse events will be described by number and incidence, and this incidence will be tested by continuous calibration Chi-square tests or Fisher's exact tests. At the same time, the specific manifestations and extent of all adverse events in each group and their relationship with the research products will be described in detail.

For missing data, only the missing primary endpoint indicators will be carried forward during analysis, while other indicators will be not. Incorrect and unreasonable data will be checked by the electronic data capture (Electronic Data Capture, EDC) system and the question will be answered by the researcher before statistical analysis. For patients withdrawing from the trial, the information will still be included in the final statistical analysis.

All data will be analyzed using SAS9.4 software and all statistical analysis will be performed at the two-sided 0.05 significance level (except for special instructions).

Date Management

The data management will be in the charge of the Medical Statistics Department of the National Cardiovascular Disease Center, and the data collection will be performed by them using EDC system. Researchers are responsible for the quality of the data entry, and should ensure the authenticity and completeness of the data. Data verification is completed by both the EDC system and the data administrator. The modification and locking of data need to be approved by the sponsor, the person in charge of data management, and the person in charge of statistics.

DISCUSSION

Stent retriever has recently been widely used for thrombectomy, and has been reported to be associated with faster reperfusion and higher rate of successful recanalization in endovascular treatment of intracranial LVO (19). However, the research and development of domestic stent retrievers is relatively slow and few devices have been verified by clinical trials (15), which greatly hinders the progress of endovascular treatment in China. The purpose of this trial is to verify whether the new thrombectomy device-Skyflow has similar safety and efficacy compared with Solitaire FR in the treatment of acute LVO.

Compared with other stent retriever, the device-Skyflow has some unique structural features (15, 20, 21). The double helix structure makes stent have excellent flexibility and adhesion, which improve the thrombus removal rate, while avoid excessive damage for intracranial blood vessels. Partial large mesh design and the wall thickness greater than the rod width can effectively embed and remove the thrombus. Full development design helps the doctor to determine the position and length of the stent and its unfolding shape which can improve the success rate of the operation. The pushing wire of the thrombectomy device is made of nickel-titanium material, and the distal end is designed as a variable-diameter structure coiled with platinum alloy coil, which improves the pushability and visualization of the product. And the device has different models and specifications, which can meet the requirements of occluded vessel with different diameters. All these features provide theoretical basis for the safety and efficacy of the test product. But relative to the reel overlap design and multi-target combination with thrombus of solitaire FR, the Skyflow has a weaker cutting and grasping ability for thrombus. In addition, compared to solitaire FR, the delivering catheter of Skyflow device is larger, which may make it difficult to pass the Atherosclerotic stenosis.

The Solitaire FR is a representative of stent retriever and the technology is mature. The main structure, action principle, treatment method, indications, etc. are similar to the test product (20). Therefore, it is reasonable to choose Solitaire FR device as a control product in our trial. In addition, this trial has strict inclusion and exclusion criteria. DSA is used to identify the occlusion site, and CT or MRI to exclude patients with preoperative intracranial hemorrhage and large core infarct. And the trial adopted a stratified random approach to avoid the influence on the results of preoperative NIHSS score and different research centers. A series of other measures have also been taken to ensure the quality of research, including the supervision of the experimental equipment of clinical trial institutions and relevant training for the investigators, quality control and monitoring, and data management and check after the research etc. These can make the trial results more convincing. But this is a single-blind clinical trial. The researchers cannot be blinded due to the difference of appearance between the test device and the control device, which can cause an impact on the trial results.

In conclusion, results of this trial will provide information on the safety and efficacy of Skyflow stent retriever. The success of this trial will provide a new option for the treatment for patients of AIS with LVO in China.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Ethics Committee of Drugs (Devices) Clinical Experiment in Henan provincial People's Hospital and other research centers participating in the clinical trial. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

TL and YH conceived of the study. ZL and LZ designed the study. HL contributed to the draft of the manuscript. TZ, QW, YH, and XS contributed to the revision of the manuscript. All authors read and approved the final manuscript.

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Increased Postoperative Fasting Glucose Is Associated With Unfavorable Outcomes in Patients Treated With Mechanical Thrombectomy Treatment

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Background and objective: Hyperglycemia on admission was associated with worse clinical outcomes after mechanical thrombectomy (MT) of acute ischemic stroke (AIS). We evaluated whether increased postoperative fasting glucose (PFG) was also related to poor clinical outcomes in patients who underwent MT treatment.

Methods: Consecutive patients with large vessel occlusion underwent MT in our center were included. Admission glucose and fasting glucose levels after MT treatment were evaluated. Primary outcome was 90-day unfavorable outcomes (modified Rankin Scale score of 3–6). Secondary outcome was the rate of symptomatic intracranial hemorrhage (sICH) after MT treatment. The association of PFG and 90-day clinical outcome after MT treatment was determined using logistic regression analyses.

Results: One hundred twenty seven patients were collected. The median postoperative fasting glucose level was 6.27 mmol/L (IQR 5.59–7.62). Fourteen patients (11.02%) had sICH, and fifty-eight patients (45.67%) had unfavorable outcomes at 90-day after MT. After adjustment for potential confounding factors, PFG level was an independent predictor of 90-day unfavorable outcome (OR 1.265; 95% CI 1.017–1.575; $p = 0.035$) and sICH (OR 1.523; 95% CI 1.056–2.195; $p = 0.024$) after MT. In addition, older age, higher baseline NIHSS score, and higher postoperative NLR were also associated with unfavorable outcomes at 90-day after MT treatment.

Conclusions: Increased PFG is associated with unfavorable outcomes at 90-day and an increased risk of sICH in patients underwent MT treatment.

Keywords: stroke, fasting glucose, mechanical thrombectomy, outcome, stent

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INTRODUCTION

Endovascular mechanical thrombectomy (MT) therapy is now accepted as standard treatment for stroke patients caused by large vessel occlusions in anterior circulation (1). However, about 54% of patients still have a poor prognosis, even after urgent and successful reperfusion (2).

Hyperglycemia is common and independently associated with worse clinical outcomes in AIS patients (3). The potential effects of hyperglycemia include increased

lactic acidosis resulting in increasing cytotoxic edema and impairment of the penumbra, reduced cerebral vasomotor reactivity and damage collateral circulation, disruption of the blood-brain barrier and increased risk of sICH (4–8). Several studies found that hyperglycemia on admission or fasting hyperglycemia were associated with worse outcomes in patients treated with intravenous alteplase (9, 10). However, whether disturbed glucose metabolism is related to clinical outcome in patients after MT is unknown. Recently, several studies have focused on the influence of admission glucose on outcomes for endovascular therapy. Huo et al. showed that higher admission blood glucose was independently associated with poor clinical outcome at 3 months in patients experienced MT (11). Goyal et al. showed that higher admission glucose and hyperglycemia were independent predictors of worse functional outcomes in patients treated with MT (12).

Previous research has mainly focused on the effects of admission glucose or hyperglycemia and clinical outcomes after MT, but the correlation between PFG and prognosis remains unclear. In this study, we explored the potential association between PFG level and 90-day clinical outcomes in patients treated with MT.

METHODS

Study Population

We retrospectively collected a consecutive group of patients who treated with MT at Zhejiang Provincial People's Hospital between August 2015 and April 2017. The inclusion criteria were (1) Patients with AIS and admission within 6 h after symptom onset; (2) Proximal large vessel occlusion in the intracranial internal carotid artery, the middle cerebral artery M1 or M2; and (3) treatment with MT and successful reperfusion. Patients were excluded if they (1) had posterior circulation large vessel occlusion or (2) lacked integral laboratory data, such as glucose levels at different time points or subsequent CT/MRI scans.

This study was authorized by the Ethics Committee of Zhejiang Provincial People's Hospital (2017KY021).

Data Collection and Clinical Assessment

Demographics, medical history, clinical and laboratory data, and procedural characteristics were collected for analysis. Stroke severity was measured by National Institutes of Health Stroke Scale (NIHSS). Stroke etiology was classified by the criteria of the Trial of ORG 10172 in Acute Stroke Treatment (13). Successful reperfusion was defifined as a modifified Thrombolysis in Cerebral Infarction (mTICI) score of 2b or 3 (14). Symptomatic intracranial hemorrhage (sICH) was diagnosed according to Heidelberg Bleeding Classification criteria (15): (1) neurological deterioration $\geq$4 total points on NIHSS; (2) NIHSS increase of $\geq$2 points in any subcategory; (3) led to intubation, hemicraniectomy, external ventricular drain placement; (4) absence of other explanation for deterioration. The mRS at 90-day was obtained by outpatient or telephone follow-up. Clinical outcomes at 90-day after MT was divided into a favorable outcome (mRS 0–2) and an unfavorable outcome (mRS 3–6).

Statistical Analysis

Kolmogorov-Smirnov test was performed to examine the normality of distribution. Continuous variables were presented as the mean $\pm$ standard deviation (SD, normal distribution) and the median with IQR (skewed distribution). Differences between patients with and without favorable outcomes were explored using Student's t test or Mann-Whitney U test for continuous variables and Fisher's exact test or $\chi 2$ test for categorical variables. Clinically variables with $p < 0.05$ from the results of the univariate analyses were included in logistic regression. Adjustments were performed for age, baseline NIHSS, post-operation NIR (neutrophil-lymphocyte ratio, NLR), a multivariate logistic regression was used to analyze the postoperative fasting glucose on 90-day clinical outcomes. After adjusting for baseline ASPECTS, platelet count, IV-tpa, hypertension, admission glucose, a multivariate logistic regression was used to analyze the postoperative fasting glucose on sICH after MT. A two-tailed $P < 0.05$ was deemed statistically signifificant. Statistical analysis was conducted using IBM SPSS (version 25).

RESULTS

Overall, 127 patients were included in the current analysis. The mean age was 70.95 years, and 51.2% were men. The median baseline NIHSS score was 20 (IQR 16–25), and the median time from stroke onset to treatment was 305 min (IQR 236–366). Median PFG levels were 6.27 mmol/L (IQR 5.59–7.62). Fourteen patients (11.02%) had sICH. A total of fifty-eight patients (45.67%) had unfavorable outcomes at 90 days. The main characteristics of the patients are summarized in **Table 1**.

Compared to patients without favorable outcomes, patients with favorable outcomes tended to be younger (67.38 vs. 75.21 years old, $p = 0.001$). Moreover, patients with favorable outcomes had lower baseline NIHSS scores (median, 18 vs. 24; $P = 0.001$), lower postoperative fasting glucose levels (median, 6.12 vs. 7.03; $P = 0.001$), lower postoperative NLR (7.2 vs. 9.33; $p = 0.001$), and higher baseline ASPECTS (median, 8 vs. 7; $P = 0.001$). The prevalence of sICH was lower in patients with favorable outcomes (2.9% vs. 20.7%; $P = 0.001$) (**Table 1**).

After adjusting for confounding factors (age, baseline NIHSS score, postoperative NLR) in multivariate logistic analyses, PFG level remained an independent predictor of 90-day unfavorable outcome after MT (OR 1.265; 95% CI 1.017–1.57); p =0.035). We also found that older age, higher baseline NIHSS score, and higher postoperative NLR were also associated with unfavorable outcomes at 90-day after MT (**Table 2**).

After adjusting for aseline ASPECTS, platelet count, IV-tpa, hypertension, admission glucose, multivariate regression analyses showed that PFG (OR 1.523; 95% CI 1.056–2.195; p = 0.024) was an independent risk factor for sICH after MT (**Table 3**).

TABLE 1 | Comparison of characteristics between patients with favorable and unfavorable outcome.

	All patients (*n* = 127)	**Favorable outcome (*n* = 69)**	**Unfavorable outcome (*n* = 58)**	***P***
Age (y), mean ± SD	70.95 ± 12.24	67.38 ± 13.04	75.21 ± 9.73	0.001
Male, *n* (%)	65 (51.2)	40 (58)	25 (43.1)	0.095
Baseline NIHSS, median (IQR)	20 (16–25)	18 (16–24)	24 (20–28)	0.001
Preexisting conditions, *n* (%)				
Smoking	19 (15)	10 (52.6)	9 (15.5)	0.872
Hypertension	86 (67.7)	44 (63.8)	42 (72.4)	0.299
Diabetes mellitus	16 (12.6)	7 (10.1)	9 (15.5)	0.363
Atrial fibrillation	90 (70.9)	44 (63.8)	46 (79.3)	0.055
Vital signs (mm Hg), median (IQR)				
Baseline SBP	146 (132–160)	146 (131.5–158)	147.5 (135.5–165.5)	0.262
Baseline DBP	85 (75–96)	85 (74–95.5)	84.5 (76–96)	0.521
Post-operation SBP	127 (112–140)	128 (114.5–140)	125 (110–144.5)	0.545
Post-operation DBP	75 (65–83)	76 (64–86)	74.5 (65–81.25)	0.764
Laboratory finding, median (IQR)				
Platelet count(*10^9/L)	159 (126–191)	163 (128–191)	155 (124.75–191.5)	0.474
Admission glucose (mmol/L)	6.77 (6.21–8.32)	6.85 (6.11–8.07)	6.77 (6.29–8.71)	0.289
Postoperative fasting glucose (mmol/L)	6.27 (5.59–7.62)	6.12 (5.28–6.95)	7.03 (6.02–9.17)	0.001
Baseline NLR	5.87 (3.43–9.48)	6.29 (3.58–9.06)	5.35 (3.33–10.04)	0.742
Post-operation NLR	7.89 (5.77–12.38)	7.2 (4.95–9.29)	9.33 (6.51–15.75)	0.001
Uric acid (μmol/L)	281 (236–340)	287 (239.5–356.5)	276 (231.7–337.75)	0.487
Creatinine (μmol/L)	65 (55.4–77)	63 (52.75–75.75)	68.39 (57.4–77.73)	0.392
Procedure time(min), median (IQR)				
Onset to door	210 (141–274)	211 (109.5–298.5)	207 (143.25–265.5)	0.713
Onset to puncture	305 (236–366)	321 (229–376.5)	289 (236.75–343.5)	0.239
Door to puncture	99 (64–122)	102 (80.5–124.5)	89 (58.75–114)	0.057
Onset to reperfusion	360 (295–418)	383 (286.5–431)	349 (312.75–404.75)	0.335
IV tPA administration, *n* (%)	53 (41.7)	30 (43.5)	23 (39.7)	0.663
General anesthesia, *n* (%)	76 (59.8)	37 (53.6)	39 (67.2)	0.183
Baseline ASPECTS, median (IQR)	8 (6–10)	8 (7–10)	7 (5–8)	0.001
Location of occlusion site, *n* (%)				0.091
ICA	42 (33.1)	19 (27.5)	23 (39.7)	
M1-MCA	74 (58.3)	41 (59.4)	33 (56.9)	
M2-MCA	11 (8.7)	9 (13)	2 (3.4)	
TOAST classification, *n* (%)				0.092
Large arterial atherosclerosis	15 (11.8)	12 (17.4)	3 (5.2)	
Cardioembolism	98 (77.2)	49 (71)	49 (84.5)	
Undetermined etiology	14 (11)	8 (11.6)	6 (10.3)	
SICH, *n* (%)	14 (11)	2 (2.9)	12 (20.7)	0.001

Mean ± SD, mean (standard deviation, SD); n (%), number(percent); IQR, interquartile range; NIHSS, National Institutes of Health Stroke Scale; SBP, systolic blood pressure; DBP, diastolic blood pressure; NLR, neutrophil-lymphocyte ratio; IV tPA, intravenous tissue-type plasminogen activator; ASPECTS, indicates Alberta Stroke Program Early CT Score; ICA, internal carotid artery; M1-MCA, M1 segment of middle cerebral artery; M2-MCA, M2 segment of middle cerebral artery; TOAST, the trial of Org 10172 in acute stroke treatment; SICH, symptomatic intracerebral hemorrhage.

DISCUSSION

In this study, we found that increased postoperative fasting glucose level was independently associated with unfavorable outcomes at 90-day and an increased risk of sICH in patients treated with mechanical thrombectomy. We speculated that hyperglycemia should be managed more aggressively after MT.

Previous research has demonstrated that hyperglycemia was independently associated with adverse clinical outcomes in AIS, and a J-shaped association between admission glucose and clinical outcomes has been reported in patients with AIS before the endovascular treatment era (16). Compared to previous therapy, MT has significantly improved the recanalization rate and clinical prognosis, and the impact of hyperglycemia on

TABLE 2 | Association between postoperative fasting glucose and 90-day unfavorable outcomes after mechanical thrombectomy.

	OR (95%CI)			
	Unadjusted	***p***	**Adjusted**	***p***
Age	1.062 (1.026–1.100)	0.001	1.053 (1.011–1.096)	0.013
Baseline NIHSS	1.136 (1.063–1.215)	0.001	1.112 (1.035–1.195)	0.004
Post-operation NLR	1.156 (1.068–1.251)	0.001	1.128 (1.038–1.225)	0.004
Post-operative fasting glucose	1.421 (1.159–1.741)	0.001	1.265 (1.017–1.575)	0.035

NIHSS, National Institutes of Health Stroke Scale; NLR, neutrophil-lymphocyte ratio.

TABLE 3 | Association between postoperative fasting glucose and sICH after mechanical thrombectomy.

	OR (95%CI)			
	Unadjusted	***p***	**Adjusted**	***p***
Baseline ASPECTS	0.657 (0.481–0.897)	0.008	0.712 (0.472–1.074)	0.105
Platelet count	0.981 (0.968–0.995)	0.010	0.978 (0.959–0.998)	0.035
IV tPA	4.070 (1.201–13.787)	0.024	6.253 (1.309–29.870)	0.022
Hypertension	0.219 (0.068–0.705)	0.011	0.198 (0.041–0.951)	0.043
Admission glucose	1.308 (1.013–1.689)	0.040	1.127 (0.790–1.609)	0.509
Postoperative fasting glucose	1.563 (1.229–1.988)	0.000	1.523 (1.056–2.195)	0.024

ASPECTS, indicates Alberta Stroke Program Early CT Score; IV tPA, intravenous tissue-type plasminogen activator.

clinical outcomes in patients underwent MT requires further research. Observational study shown that hyperglycemia maybe an adverse prognostic factor in patients treated with MT (17). Borggrefe et al. showed that admission hyperglycemia, age, and NIHSS score were main factors for an unfavorable outcome after MT (18). Rinkel et al. showed that increased admission glucose was associated with worse outcome and increased risk of sICH (19). Broocks G and colleagues found that elevated admission blood glucose levels were associated with aggravation brain edema and adverse clinical outcomes (20). The impact of blood glucose levels on outcome depended on collateral status, and higher glucose levels reduced the likelihood of a favorable outcome among patients with good collaterals but less significantly for patients with poor collaterals (21). However, the influence of admission hyperglycemia on clinical outcomes have shown contradictory results. In MR CLEAN pretrial cohort, there were no association between admission blood glucose level and 90-day functional outcome was found (22).

To date, the association of admission hyperglycemia and poor outcome in patients with AIS after MT has been well-studied. However, only a few studies have evaluated the role of impaired fasting glucose on outcomes in patients treated with MT. Our study findings are consistent with recently published studies that found that increasing PFG levels were independently associated with unfavorable outcomes at 90-day and an increased risk of sICH after MT. Osei et al. reported that fasting glucose after MT was an independent risk factor for worse outcomes in patients experienced MT (23). Li et al. reported that postoperative glucose levels might be an independent risk factor for sICH in patients with acute large vessel occlusion who are treated with MT (24). Increased fasting glucose levels are a result of stress hyperglycemia, which is caused by the interplay of hormones, with concomitant insulin resistance during acute illness (25). Therefore, fasting glucose, which reflects stress hyperglycemia, may be more reliable in predicting clinical outcomes. One study found that higher fasting glucose levels after intravenous alteplase predicted poor outcome or death better than admission glucose; moreover, the association of fasting glucose with unfavorable outcome was independent of HBA1c levels and the presence of diabetes (26). Another study supported than fasting glucose was a more important predictor of long-term clinical outcome in patients treated with MT compared with glucose on admission (27).

The impact of dysfunctional glucose metabolism on clinical outcomes after MT could be explained by several pathophysiological mechanisms. Hyperglycemia may affect mitochondrial function in ischemic penumbra. Altered mitochondrial function leads to acidosis and cell death (5); impairs cerebrovascular reactivity in the microvasculature, which may disturb reperfusion after recanalization (28); and alters blood barrier permeability and induces blood barrier disruption, which may aggravate brain edema formation and lead to hemorrhagic transformation (4).

In addition, consistent with prior research, we confirmed that a higher postoperative NLR was also associated with unfavorable outcomes at 90-day after MT. Moustafa Aly et al. showed that a lower NLR at 3–7 days was an independent predictor of favorable outcomes and reduced risk for sICH (29). Semerano et al. found

that the follow-up higher NLR in MT patients was associated with an increased risk of sICH (30). The underlying mechanism may involve the activation of neutrophils and the suppression of lymphocytes by systemic stress, resulting in an increased risk of reperfusion injury, malignant edema, and/or hemorrhagic transformation (31, 32).

Our study has several limitations. First, the study design was retrospective with all inherent limitations, and we adjusted the variables using multivariate logistic regression analysis to exclude possible bias. Second, this study only includes data from this period, as the cohort is relatively small, a longer time frame and thus more patients would increase the power of the statistical findings. Third, the effect of blood glucose level on outcome depended on collateral status, and collateral grades were not evaluated in our data. Fourth, glucose levels are a dynamic condition, and one isolated value at one point seems to be insufficient.

CONCLUSION

In conclusion, our study revealed that increased postoperative fasting glucose seems to be associated with unfavorable outcomes at 90-day and an increased risk of sICH in AIS patients treated with MT. These findings indicate the importance of optimal management of serum glucose after MT in AIS patients with large vessel occlusion.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding authors.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by this study was approved by the Ethics Committee of Zhejiang Provincial People's Hospital (Approval No: 2017KY021). The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

ZS: substantial contributions to study design, data collection for the whole trial, data analysis and interpretation of data, drafting and revising the manuscript for intellectual content, and wrote the statistical analysis plan. CX: substantial contributions to study design, cleaned and analyzed the data, revising the manuscript for intellectual content, image data collection for the whole trial, and revising the manuscript for intellectual content. SG and JP: data acquisition, interpretation of data, and revising the manuscript for intellectual content. SZ and YG: study concept and design, study supervision, interpretation of data, revising the manuscript critically for intellectual content, and final approval of the version to be published. All authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Efficacy and Safety of Endovascular Treatment for Acute Large-Vessel Ischemic Stroke Beyond 6 h After Symptom Onset: A Meta-Analysis

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Background: There is considerable evidence on the benefits of endovascular thrombectomy (EVT) for acute ischemic stroke (AIS) within 6 h after symptom onset. However, uncertainties remain regarding EVT efficacy beyond 6 h after symptom onset. We undertook a meta-analysis to assess the efficacy and safety of EVT in patients with AIS >6 h after symptom onset.

Methods: We searched PubMed, EMBASE, and Chinese Biomedical through July 2019. We included studies involving early (≤6 h) vs. delayed (>6 h) EVT in selected patients with AIS, based on radiological evaluation criteria. Functional independence, successful recanalization, mortality, and symptomatic intracranial hemorrhage (sICH) rates were assessed.

Results: Eight articles, with 3,265 patients who had undergone early EVT and 1,078 patients who had received delayed EVT, were included in the meta-analysis. Patients treated with early EVT showed a similar proportion of functional independence at 90 days [odds ratio (OR) = 1.14, 95% confidence interval (CI) = 0.926–1.397, $P = 0.219$; $I^2 = 36.2\%$, $P = 0.128$] as those treated with delayed EVT. Delayed EVT was also associated with no significant difference in mortality (OR = 1.015, 95% CI = 0.852–1.209; $P = 0.871$; $I^2 = 0.0\%$, $P = 0.527$), successful recanalization (OR = 1.255, 95% CI = 0.923–1.705; $P = 0.147$; $I^2 = 60.5\%$, $P = 0.009$), and sICH (OR = 0.976, 95% CI = 0.737–1.293; $P = 0.871$; $I^2 = 0.0\%$, $P = 0.742$) rates compared with early EVT.

Conclusions: Among selected patients with AIS, delayed EVT showed comparable outcomes in functional independence, recanalization, mortality, and sICH rates compared with early EVT.

Keywords: delayed presentation, endovascular treatment, ischemic stroke, time-to-treatment, meta-analysis

INTRODUCTION

Acute ischemic stroke (AIS) is one of the leading causes of mortality and long-term disability globally (1). In recent years, overwhelming evidence has demonstrated the benefits of endovascular thrombectomy (EVT) for AIS within 6 h after symptom onset (2). Six randomized controlled trials (RCTs) (MR CLEAN, ESCAPE, EXTEND-IA, REVASCAT, SWIFT-PRIME, and THRACE) concerning EVT for large vessel occlusion (LVO) in the anterior circulation established this therapy as a new standard for AIS treatment (1–3). However, uncertainties remain regarding the efficacy and safety of EVT for patients with AIS and LVO when performed >6 h after symptom onset (4). Recent American Heart Association/American Stroke Association (AHA/ASA) and European Stroke Organization (ESO) guidelines have recommended that EVT should be performed within 6 h of symptom onset for patients with AIS (5, 6).

However, notably, two recent RCTs, namely, the DAWN trial and the DEFUSE trial, have challenged previous understandings. In patients with a mismatch between deficit and infarct, the DAWN trial demonstrated that EVT was beneficial 6–24 h after symptom onset when compared with standard medical care only (7). Perfusion or advanced computed tomography (CT) perfusion was also a criterion for patient selection in the DEFUSE-3 trial (8). The results indicated that EVT plus standard medical care for patients with AIS 6–16 h after symptom onset was associated with more favorable efficacy and safety than standard medical therapy alone (8). The aforementioned two RCTs emphasized the importance of the tissue window in saving potentially salvageable brain tissue. Hacke (9) reported that the usual 6-h time window for EVT should be replaced with a "tissue window." These findings would appear to indicate that the current time window needs to be reconsidered.

Furthermore, prior to these RCTs, several studies had challenged the 6-h time window. Some retrospective studies have shown that patients with AIS who had been treated with delayed EVT (>6 h after symptom onset) showed comparable efficacy and safety compared with patients with AIS who had been treated with early EVT (within 6 h after symptom onset) (10, 11). These studies provided further evidence for delayed EVT in patients with AIS that needs consideration. Therefore, we undertook a meta-analysis to assess the efficacy and safety of EVT for patients with AIS who had been treated >6 h after symptom onset.

METHODS

The protocol for this meta-analysis followed the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines (12).

Search Strategy

We searched PubMed, EMBASE, and Chinese Biomedical (CBM) databases for relevant articles up until July 2019, using the following search terms: "reperfusion OR recanalization OR mechanical thrombectomy OR endovascular thrombectomy OR endovascular treatment" AND "stroke OR acute ischemic stroke OR ischemic stroke OR cerebrovascular accident" AND "extend OR delay OR beyond OR more than 6." In addition, references within included studies and relevant review articles were also screened to avoid missing potentially eligible studies.

Eligibility Criteria

Study inclusion criteria were as follows: (1) studies concerning early EVT (within 6 h after symptom onset) vs. delayed (>6 h after symptom onset); (2) studies concerning non-contrast CT, CT angiography (CTA), CT perfusion, or perfusion–diffusion magnetic resonance imaging (MRI) used to select patients (aged ≥18 years) regardless of the time window; (3) studies in which the stroke location of the included patients comprised anterior and posterior circulation occlusion; and (4) studies that included the following data: (i) functional outcomes using the modified Rankin scale (mRS) at 90 days, (ii) mortality at 90 days, (iii) successful recanalization (modified thrombolysis in cerebral infarction and the modified treatment in cerebral infarction (mTICI) score, ≥2b), and (iv) symptomatic intracranial hemorrhage (sICH) at 90 days.

Study Selection

Two investigators (ZXY and JJW) independently screened the study titles and abstracts. After the initial screening and selection, the full texts of the remaining articles were assessed for further processing. Disagreements were discussed and resolved with the help of the senior investigator (FL).

Data Extraction

ZQL, QC, JFZ, and CQW independently extracted data from the primary text of the included studies and **Supplementary Materials**. These data included author name, year of publication, number of patients (including cases and controls), mechanical thrombectomy devices, cutoff interval (early EVT vs. delayed EVT), mean age, number of EVT combined with intravenous tissue plasminogen activator, stroke location, efficacy outcomes (functional independence, mRS score 0–2; successful recanalization, mTICI score 2b−3), and safety outcomes (sICH and mortality).

Outcome Measures

The primary efficacy outcome was the proportion of patients with functional independence (mRS score, 0–2) at 90 days. The secondary efficacy outcome was the proportion of patients who achieved successful recanalization (mTICI score, 2b−3). The primary safety outcome was all-cause mortality at 90 days. The secondary safety outcome was the ratio of patients with sICH at 90 days.

Statistical Analysis

Statistical analysis was performed using STATA 12 software to establish a random-effects model (because of possible heterogeneity among studies) for each outcome. The pooled odds ratios (ORs) with corresponding 95% confidence intervals (CIs) were calculated. Primary and secondary outcomes were then assessed via the pooled ORs weighted using inverse variance. The heterogeneity among studies was measured using the I^2-value (significance set at >50%) (13). Sensitivity and subgroup analyses

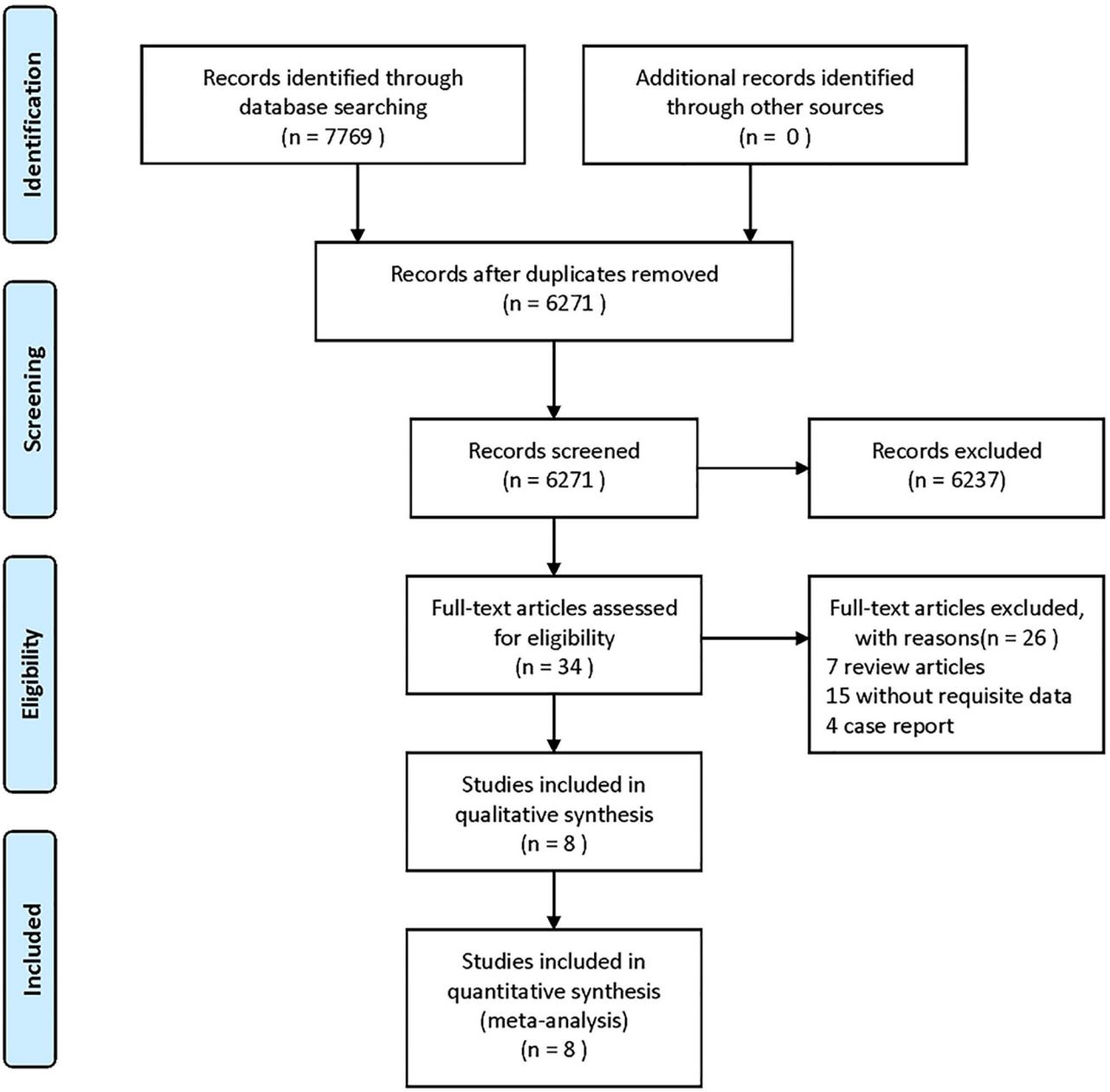

FIGURE 1 | Flow diagram of the study selection process.

were used to determine potential influencing factors. Begg's funnel plot analysis and Egger's test were used to estimate publication bias (significance set at $P < 0.1$).

RESULTS

Search Results and Study Characteristics

Figure 1 shows the search and selection process used in this meta-analysis. Our search identified 7,769 studies from PubMed, Web of Science, and CBM databases (**Figure 1**). After removing duplicates and ineligible articles, 34 articles were eligible for further assessment. After a full-text review, 26 articles were excluded. Data were extracted from eight eligible articles [including nine studies; the same data analyzed with different cutoff intervals were considered as different studies, namely, Mokin et al. (14), Meinel et al. (11), Motyer et al. (10), Motyer et al.* (10), Millán et al. (15), Turk et al. (16), Turk et al. (17), Jung et al. (18), and Abou-Chebl et al. (19)].

In these nine studies, a total of 4,343 patients (mean age, 59.4–74 years) were included in the meta-analysis. Of these, 3,265 patients with AIS had undergone early EVT, and 1,078 patients

TABLE 1 | Characteristics of studies included in the meta-analysis.

References	No. of patients	Devices	Cut-off interval	Early EVT, NO (%)				Delayed EVT, NO (%)			
				Age (mean ± SD)	No. of patients	IV t-PA No. (%)	Stroke location	Age (mean ± SD)	No. of patients	IV t-PA	Stroke location
Mokin et al. (14)	807	Solitaire FR Trevo device	6 h	67.4 ± 14.9	559	150 (26.9%)	MCA M1&M2: 295 (53.1%) MCA M3: 128 (23%) ACA: 3 (0.5%) ICA: 130 (23.4%)	66.1 ± 14.6	248	48 (19.4%)	MCA M1&M2: 144 (58.3%) MCA M3: 56 (22.7%) ACA: 0 (0%) ICA: 47 (19%)
Meinel et al. (11)	1,461	Solitaire FR	6 h	73.8	1,068	614 (57.5%)	MCA M1: 644 (60.2%) MCA M2: 138 (12.9%) Carotid-T/L: 244 (22.8%) Intracranial ICA: 34 (3.2%)	74	393	130 (33.1%)	MCA M1: 229 (58.3%) MCA M2: 51 (13%) Carotid-T/L: 95 (24.2%) Intracranial ICA: 18 (4.6%)
Motyer et al. (10)	355	Stent retrievers	6 h	68 ± 14	281	177 (63%)	Anterior circulation	68 ± 14	74	32 (43%)	Anterior circulation
Motyer* et al. (10)	355	Stent retrievers	7.3 h	NA	317	NA	Anterior circulation	NA	38	NA	Anterior circulation
Millán et al. (15)	141	Solitaire FR Trevo device Merci retriever	6 h 10 min	66.5 ± 12.1	109	68 (62.4%)	MCA M1: 63 (57.8%) MCA M2: 9 (8.3%) TICA: 18 (16.5%) ICA: 4 (3.7%) TANDEM: 15 (13.8%)	64.7 ± 13.1	32	3 (9.4%)	MCA M1: 13 (40.6%) MCA M2: 2 (6.3%) TICA: 7 (21.9%) ICA: 2 (6.3%) TANDEM: 8 (25%)
Turk et al. (16)	140	Penumbra Balloon angioplasty Merci retrieval system	7 h	68	70	33 (46.5%)	ICA: 18 (25.4%) MCA: 45 (64.8%) Posterior circulation: 7 (9.9%)	64.9	70	21 (30.4%)	ICA: 11 (15.9%) MCA: 46 (65.2%) Posterior circulation: 13 (18.8%)
Turk et al. (17)	247	Penumbra aspiration system.	8 h	67	173	95 (55.2%)	Anterior circulation: 158 (92.4%) Posterior circulation: 15 (8.6%)	64	74	20 (27%)	Anterior circulation: 61 (83.6%) Posterior circulation: 13 (16.4%)
Jung et al. (18)	782	Aspiration Solitaire stent PTA Other retriever	6 h	63.3 ± 13.5	654	547 (83.7%)	Carotid artery: 160 (24.5%) MCA: 419 (64.1%) Posterior cerebral artery: 9 (1.4%) Anterior cerebral artery: 5 (0.8%) Basilar/vertebral artery: 61 (9.3%)	61.1 ± 15.1	128	97 (75.8%)	Carotid artery: 36 (28.1%) MCA: 43 (33.6%) Posterior cerebral artery: 5 (3.9%) Anterior cerebral artery: 1 (0.8%) Basilar / vertebral artery: 43 (33.6%)
Abou-Chebl (19)	55	Merci Retriever	6 h	63.4 ± 16.2	34	20 (58.8%)	MCA: 15 (44.1%) ICA: 4 (11.8%) TANDEM: 11 (32.4%) Vertebrobasilar: 4 (11.8%)	59.4 ± 17.2	21	5 (23.8%)	MCA: 8 (38.1%) ICA: 4 (19%) TANDEM: 11 (9.5%) Vertebrobasilar: 7 (33.3%)

IV t-PA, *intravenous thrombolysis with tissue plasminogen activator;* ***EVT***, *endovascular treatment;* ***ICA***, *internal carotid artery;* ***ACA***, *anterior cerebral artery;* ***MCA***, *middle cerebral artery;* ***TICA***, *terminal internal carotid artery;* ***PTA***, *percutan transluminal angioplasty.*

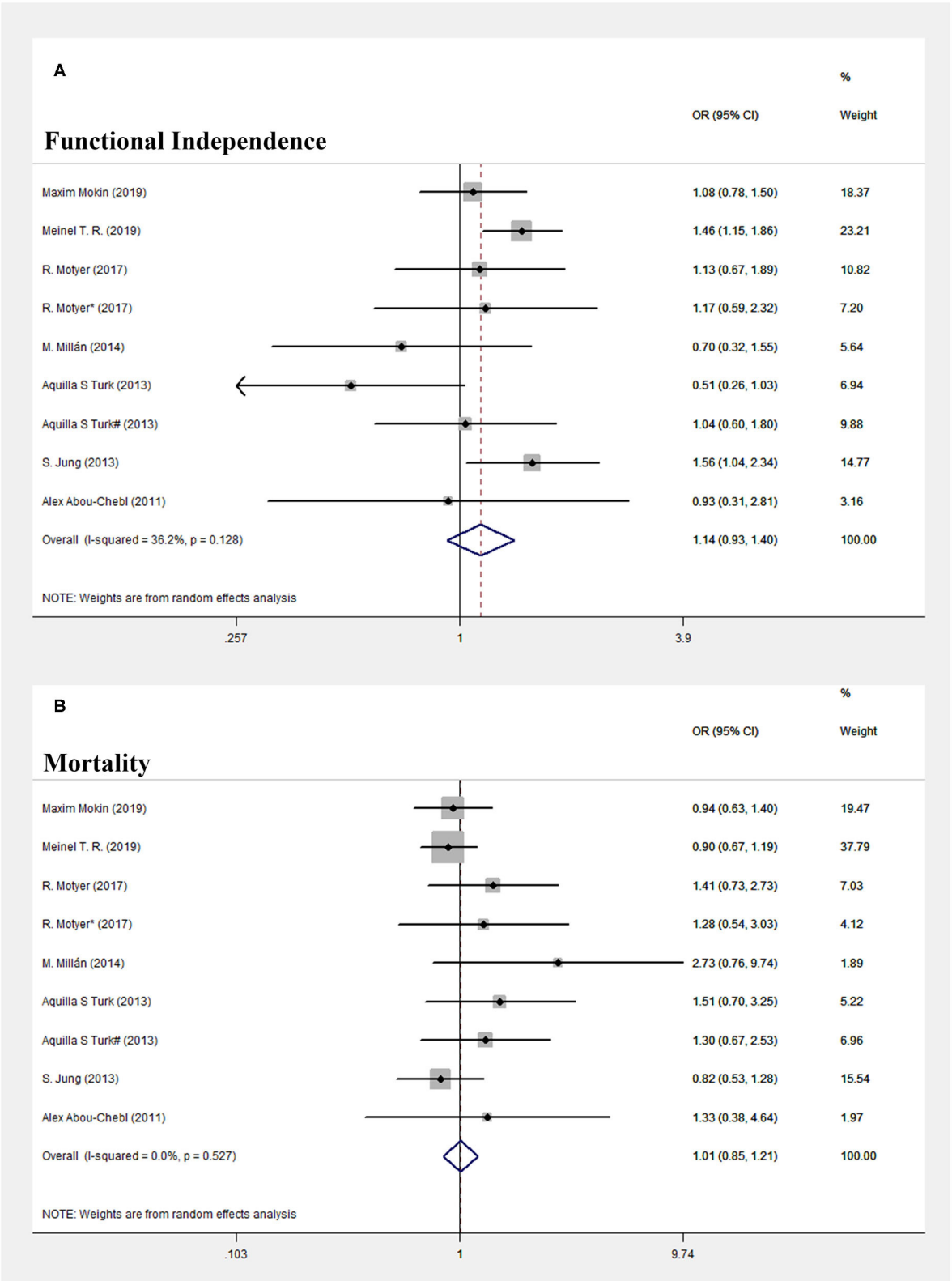

FIGURE 2 | Forest plot of comparison. **(A)** Functional independence. **(B)** Mortality.

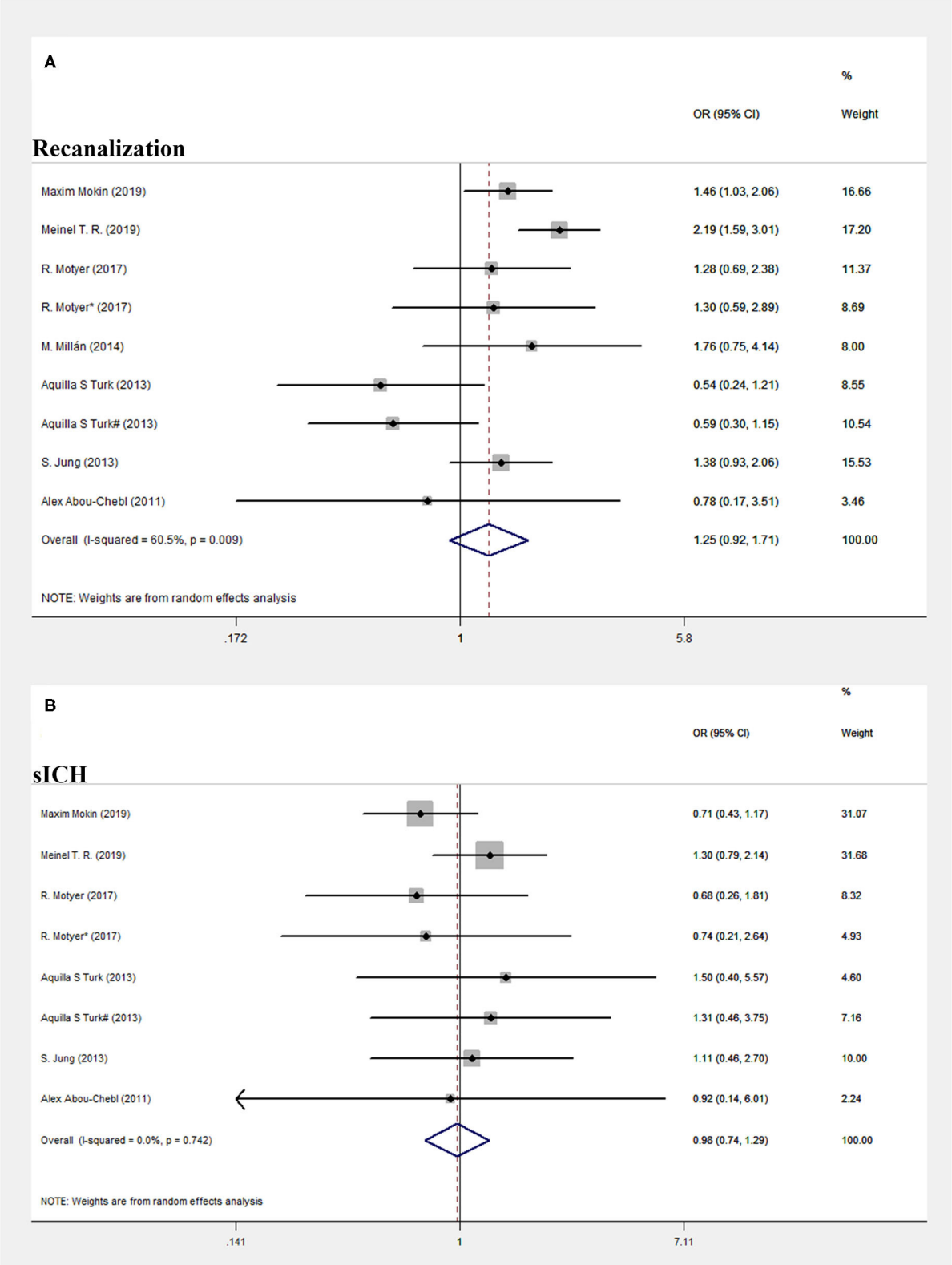

FIGURE 3 | Forest plot of comparison. **(A)** Successful recanalization. **(B)** Systematic intracranial hemorrhage.

with AIS had received delayed EVT. Detailed data concerning the study patients' characteristics are summarized in **Table 1**.

Quantitative Synthesis

In terms of primary efficacy outcomes, patients treated with early EVT showed a similar proportion of favorable functional outcome at 90 days compared with those treated with delayed EVT (OR = 1.14, 95% CI = 0.926–1.397, $P = 0.219$; $I^2 = 36.2\%$, $P = 0.128$, respectively, **Figure 2A**).

In terms of primary safety outcomes, no significant difference in mortality rates within 90 days was found between the early and delayed EVT patient groups (OR = 1.015, 95% CI = 0.852–1.209, $P = 0.871$; $I^2 = 0.0\%$, $P = 0.527$, respectively, **Figure 2B**).

In terms of secondary efficacy outcomes, the rates of successful recanalization (mTICI score, 2b−3) were 2,645/3,265 (81%) and 821/1,077 (76.2%) in the early and delayed EVT patient groups, respectively (OR = 1.255, 95% CI = 0.923–1.705, $P = 0.147$; $I^2 = 60.5\%$, $P = 0.009$, respectively; **Figure 3A**), but the differences between the groups were not statistically significant. However, there was significant heterogeneity in the secondary efficacy outcomes ($I^2 = 60.5\%$, $P = 0.009$). Thus, we performed subgroup analysis to find out the potential influencing factors. As statistical heterogeneity was revealed in the forest plot showing non-overlapping CIs for all the included studies, the eligible studies were divided into "overlapping CI" and "non-overlapping CI" group. As shown in **Supplementary Figure 1**, $I^2 = 36.0\%$, $P = 0.154$, in the "overlapping" group, and $I^2 = 65.0\%$, $P = 0.091$, in the "non-overlapping" group. The heterogeneity was decreased after grouping. Interestingly, we found a common feature in these two studies (Maxim Mokin-2019 and Meinel T. R.-2019) in "non-overlapping CI" group. Both studies performed all thrombectomies by using Solitaire FR Revascularization Device with or without Trevo device. As we know, devices for mechanical thrombectomy were important factors associated with improved functional outcomes and rate of recanalization (2). Hence, the devices for thrombectomy may be one of the potential influencing factors of heterogeneity.

In terms of secondary safety outcomes, there was also no significant difference in the rates of sICH within 90 days between the patient groups: 6.67% for early EVT and 7.09% for delayed EVT (OR = 0.976, 95% CI = 0.737–1.293, $P = 0.871$; $I^2 = 0.0\%$, $P = 0.742$, respectively, **Figure 3B**). Detailed data concerning efficacy and safety outcomes are summarized in **Table 2**.

Publication Bias

Publication bias was assessed using Egger's test and Begg's funnel plot. However, Begg's test ($P = 0.144$) and Egger's test ($P = 0.042$) showed opposite results, with Begg's funnel plot (**Figure 4**) indicating that publication bias might exist (funnel plot asymmetry). Therefore, we applied the trim-and-fill method to further assess whether publication bias existed (20, 21). The results indicated no significant difference before and after four iterations (**Supplementary Figure 2**, $Z = 4.048$, $P < 0.001$, vs. Z = 2.584, $P = 0.01$).

TABLE 2 | The detailed date of efficacy and safety outcome.

References	mRS0-2				Mortality				Successful recanalization				Symptomatic ICH			
	Eevent	Enon-event	Devent	Dnon-event	Eevent	Enon-event	Devent	Dnon-event	Eevent	Enon-event	Devent	Dnon-event	Eevent	Enon-event	Devent	Dnon-event
Mokin et al. (14)	234	252	96	112	100	386	45	163	444	115	180	68	44	507	27	220
Meinel et al. (11)	463	605	135	258	209	859	84	309	961	107	316	77	73	995	21	372
Motyer et al. (10)	130	151	32	42	65	216	13	61	228	53	57	17	16	265	6	68
Motyer et al.* (10)	146	171	16	22	71	246	7	31	256	61	29	9	19	298	3	35
Millán et al. (15)	45	64	16	16	24	85	3	29	84	25	21	11	11	98	0	32
Turk et al. (16)	21	50	31	38	21	50	15	54	51	20	57	12	6	65	4	65
Turk et al. (17)	74	99	31	43	43	130	15	59	124	49	60	14	15	158	5	69
Jung et al. (18)	294	346	43	79	145	495	32	90	469	184	83	45	34	618	6	121
Abou-Chebl (19)	14	20	9	12	10	24	5	16	28	6	18	3	3	31	2	19

*These data were reanalyzed using the 7.3-h threshold. Eevent, Early EVT events; Enon-event, Early EVT non-event; Devent, Delayed EVT event; Dnon-event, Delayed EVT non-event.

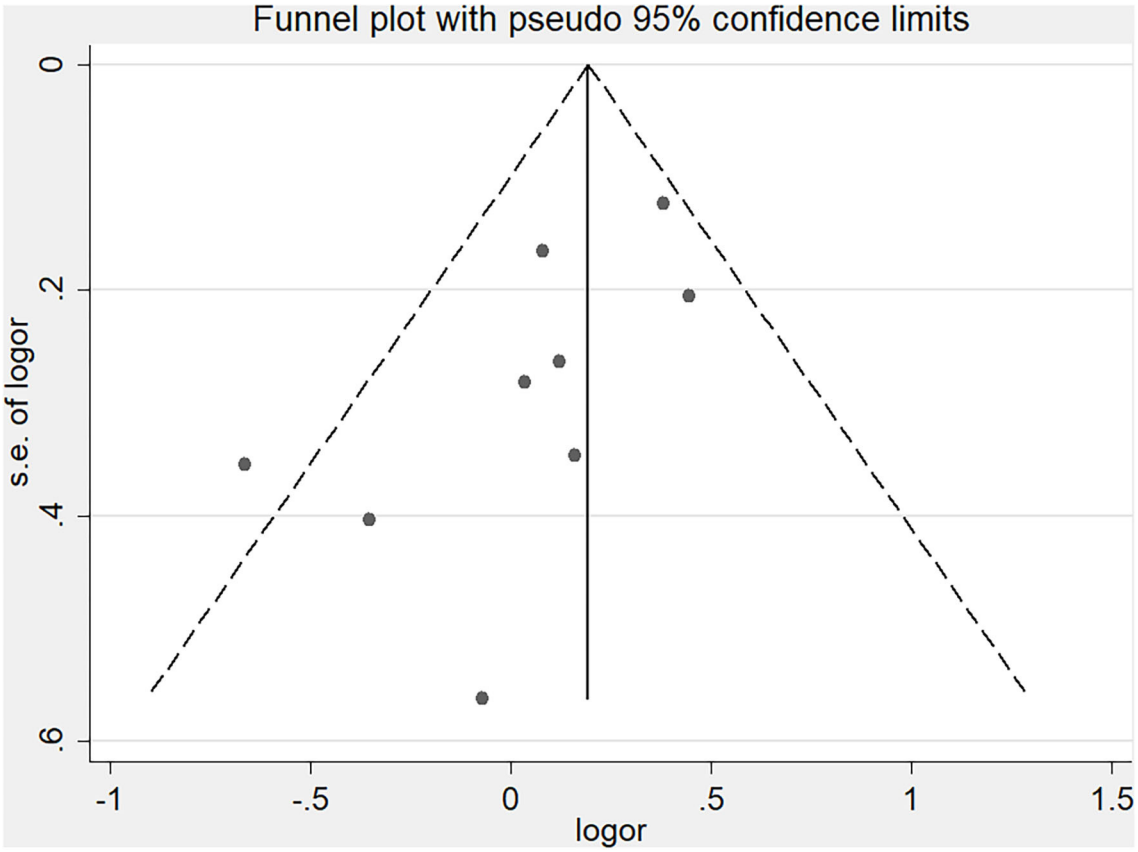

FIGURE 4 | Funnel plot of included studies.

DISCUSSION

The present meta-analysis of pooled data indicated that patients with AIS who had delayed EVT treatment (>6 h) had similar rates of functional outcomes when compared with patients who received early EVT treatment (>6 h). All patients underwent imaging selection rather than guided time selection. There were no significant differences in mortality, recanalization, and sICH rates between the early and delayed EVT patient groups.

Six previous RCTs, namely, MR CLEAN, ESCAPE, EXTEND-IA, REVASCAT, SWIFT-PRIME, and THRACE, involving EVT for LVO in the anterior circulation established this therapy as a new standard of AIS treatment (1–3, 22). These RCTs showed that EVT treatment was associated with improved functional outcomes within 6 h after symptom onset when compared with standard medical care in patients with AIS. Following this "revolution" in stroke treatment, AHA/ASA, and ESO guidelines recommended that EVT should be performed within 6 h of symptom onset for patients with AIS (5, 6). However, this specific therapeutic window has been contested. The HERMES study found that EVT therapy was effective within 7.3 h after stroke onset and less effective beyond 7.3 h (4). The DAWN and DEFUSE-3 trials showed that EVT is beneficial 6–24 h after symptom onset in selected patients with proximal vessel occlusion in the anterior circulation (7, 8). These results indicate that a firm time window for stroke treatment may be obsolete and that the role of the time window needs to be reexamined (23). Time may not be a less critical factor than previously thought in independently affecting the prognosis of patients with AIS. Nogueira et al. reported that time (to treatment or to reperfusion) was one of many variables that may influence the outcomes of proximal vessel occlusion for patients with stroke and that it appeared to show a more modest effect during the later phases of stroke evolution (24). Nathan et al. reported that EVT for patients with AIS >24 h from symptom onset was safe and effective; however, further evidence-based trials to evaluate benefits vs. risks using prolonged time windows are required (25).

In contrast to the DAWN and DEFUSE-3 trials, we pooled data from several retrospective studies that had directly compared early and delayed EVT. In terms of primary efficacy outcomes, patients treated with early EVT showed a comparable proportion of favorable functional outcomes at 90 days compared with those treated with delayed EVT. Furthermore, primary safety outcomes also showed no significant difference in 90-day mortality rates between the early and delayed EVT patient groups. These results indicated comparable outcomes in both groups in terms of effectiveness and safety. Our findings provided further evidence supporting delayed EVT as being a

beneficial intervention in appropriately selected patients with AIS. Therefore, it is vital to identify patients with salvageable brain tissue, and aggressive endovascular treatment should be encouraged.

Our study has several limitations. The criteria for patient selection were heterogeneous (based on nonc-ontrast CT, CTA, CT perfusion, or perfusion–diffusion MRI). The studies in our meta-analysis included patients with both anterior and posterior circulation occlusion. The original study data were not available; therefore, more subgroup analyses could not be performed, which led to the possibility of data heterogeneity. Although the present study showed a comparable result in functional independence between early and delayed EVT group, mild heterogeneity still existed ($I^2 = 36.2\%$, $P = 0.128$). As shown in **Supplementary Figure 3**, the heterogeneity was eliminated after stratification ($I^2 = 0.0\%$, $P = 0.785$; $I^2 = 0.0\%$, $P = 0.553$). We found that these two studies (Meinel T. R.-2019 and S. Jung-2013) included several unclear-onset stroke or wake-up stroke patients. For this part of patients, the time from stroke onset to recanalization may be much longer than 6 h. As the time to treatment may have an important effect on the efficacy of EVT. Longer EVT procedures lead to lower rates of functional independence and higher rates of sICH 2. That may partly explain the reason of heterogeneity. However, the present study cannot exclude all the relevant affecting causes. Moreover, time to treatment may have had an important effect on the efficacy of EVT. Longer ET procedures are known to lead to lower rates of functional independence and higher rates of sICH (26). In this meta-analysis, we could not exclude relevant affecting causes. In addition, the retrospective nature of the included studies was a notable limitation in that criteria used in the selection of patients who received EVT in the early and late windows may not have been comparable, which may have affected our study findings. Hence, these results require further evaluation prior to any implementation in clinical practice.

CONCLUSION

Among patients with AIS, those in the delayed EVT group (>6 h) showed comparable outcomes in functional independence and recanalization rates compared with those in the early EVT group (>6 h). There were no significant differences in mortality rates and sICH between the early and delayed EVT patient groups. These data support delayed EVT as a beneficial intervention for appropriately selected patients with AIS.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/**Supplementary Material**, further inquiries can be directed to the corresponding author/s.

AUTHOR CONTRIBUTIONS

YZ, LZ, and WJ developed the study protocol and drafted the manuscript. CQ, ZJ, and WC analyzed the data and performed a meta-analysis. LF revised the manuscript and edited the language. All authors contributed to the article and approved the submitted version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2021.654816/full#supplementary-material

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Use of a Smartphone Application to Speed Up Interhospital Transfer of Acute Ischemic Stroke Patients for Thrombectomy

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Background: In most countries, large cerebral artery occlusion is identified as the leading cause of disability. In 2015, five large-scale clinical trials confirmed the benefit of intra-arterial thrombectomy. However, thrombectomy is a highly technical and facility-dependent procedure. Primary stroke centers need to transfer patients to comprehensive stroke centers to perform thrombectomy. The time-lapse during interhospital transfer would decrease the chance of the patient's proper recovery. Communication barriers also contribute to this delay.

Aims: We used a smartphone application to overcome communication barriers between hospitals. We aimed to shorten the door-to-puncture time of interhospital transfer patients.

Methods: We began using a smartphone application, "LINE," to facilitate interhospital communication on May 01, 2018. We carried out retrospective data analyses for all the transfer patients ($n = 351$), with the primary outcome being the door-to-puncture time in our comprehensive stroke center (China Medical University Hospital). We compared the three periods: May 01 to Dec 31, 2017 (before the use of the smartphone application); May 01 to Dec 31, 2018 (the 1st year of using the smartphone application); and May 01 to Dec 31, 2019 (the 2nd year of using the smartphone application). We also compared the transfer data with non-transfer thrombectomies in the same period.

Results: We compared 2017, 2018, and 2019 data. The total number of transfer patients increased over the years: 63, 113, 175, respectively. The mean door-to-puncture time decreased significantly, going from 109, through 102, to 92 min. Meanwhile, the

mean door-to-puncture time in non-transfer patients were 140.3, 122.1, and 129.3 min. The main reason of time saving was the change of the way of communication, from point-to-point interhospital communication to hub-to-spoke interhospital communication.

Conclusions: We used this smartphone application to enhance interhospital communication, changed from the point-to-point to hub-to-spoke method. It made us overcome the communication barrier and build up interhospital connection, thus shortening the door-to-puncture time. Our experience demonstrated the importance of close communication and teamwork in hyperacute stroke care, especially in interhospital transfer for thrombectomy.

Keywords: stroke, thrombectomy, interhospital transfer, door-to-puncture time, communication, smartphone, application, hub-to-spoke

INTRODUCTION

Stroke has been identified as one of the leading causes of morbidity and mortality around the world (1). Large vessel occlusion (LVO) is the most devastating form of stroke (2, 3). About the definition of LVO, we used the broad definition that included internal carotid artery (ICA), the first segment of the middle cerebral artery (M1), the second segment of the middle cerebral artery (M2), the basilar artery (BA), anterior cerebral artery (ACA), posterior cerebral artery (PCA), and vertebral artery (VA) occlusions (4). Every 1-min delay of recanalization will lead to the death of 1.9 million neurons (5). Thus, it is crucial to save the brain immediately (6–8). The most modifiable factor in salvaging the brain is door-to-puncture (DTP) time (9).

In 2015, five large-scale clinical trials confirmed the benefits of intra-arterial thrombectomy (10–14). However, thrombectomy is deemed as a highly technical and facility-dependent procedure (15). Thrombectomy capabilities are not exclusive to comprehensive stroke centers. The time-lapse during interhospital transfer would then decrease the chance of adequate recovery of patients (16–18).

There are many factors affecting the timeliness of interhospital transfer of patients for thrombectomy (19). Previous research reported that interhospital communication barriers are a major cause of time delay (20). Several teams have developed smartphone applications in order to facilitate communication (20, 21).

In Taiwan, the most popular smartphone application for social communication is "LINE." In 2019, "LINE" had over 21 million users in Taiwan (89% of the total population, 23.6 million) (22), with each user spending more than 1 h on it per day (23).

As a result, after several interhospital transfer meetings with primary stroke centers, we created an encrypted group in "LINE" in order to overcome communication barriers and speed up the workflow of thrombectomy.

AIMS AND/OR HYPOTHESIS

We aimed to decrease the DTP time in the comprehensive stroke center (China Medical University Hospital) by using this smartphone application called "LINE" to facilitate communication between doctors. We also supposed that the percentage of patients with good outcomes would increase (modified Rankin Scale = 0, 1, or 2 at 3 months) (24).

Methods

Hospital Setting

The China Medical University Hospital (CMUH) is a Medical Center in central Taiwan, with a total of 2,054 beds. The stroke center had 21 attending physicians, 16 residents, and 3 nurse practitioners. We had 55 ordinary beds and 10 intensive care unit beds. Our stroke center got the Joint Commission International accreditation in 2010. Each year, we had around 1,300 acute ischemic stroke patients, 90 tissue plasminogen activator thrombolyses, and 120 intra-arterial thrombectomies. We are a tertiary referral center in central Taiwan, receiving transfer patients from 38 primary stroke centers, with the distance of transfer ranging from 1.8 to 126 km (**Supplementary Table 1** and **Figure 1**).

Smartphone Application

"LINE" has been determined to be the most commonly used social smartphone application in Taiwan. The application used LINE Event Delivery Gateway (LEGY) to encrypt messages and protect the privacy of its users. The LINE company got the International Organization for Standardization (ISO) ISO 27001 accreditation for information security in 2007. They also got the accreditation of Service Organization Controls (SOC) SOC2, SOC3, and SysTrust (25).

The neurologists at the CMUH created an encrypted group for interhospital transfer and invited the neurologists, emergency department doctors, or nurse practitioners in the primary stroke centers. Patients' identification details such as name and chart number have to be deleted during communication. A screenshot of one real communication was taken from the "LINE" smartphone application as an example (**Figure 2**).

Thrombectomy Workflow

CMUH set up the comprehensive stroke center in February 2007. We provided thrombolysis and thrombectomy services 365 days

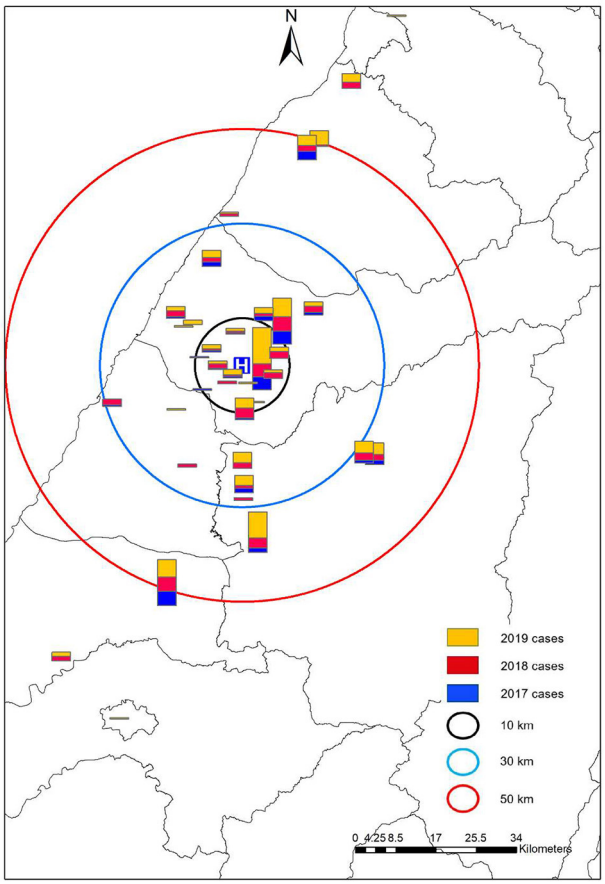

FIGURE 1 | The geographic distribution of primary stroke centers and the interhospital transfer cases. We found an increasing number of transfers in almost all the hospitals, irrespective of the distance.

FIGURE 2 | A real communication on the "LINE" smartphone application. "A 67-year-old hypertensive male who took aspirin every day. He developed sudden-onset weakness of the left limbs and slurred speech, with NIHSS = 12. The EKG revealed atrial fibrillation. Ask for transfer".

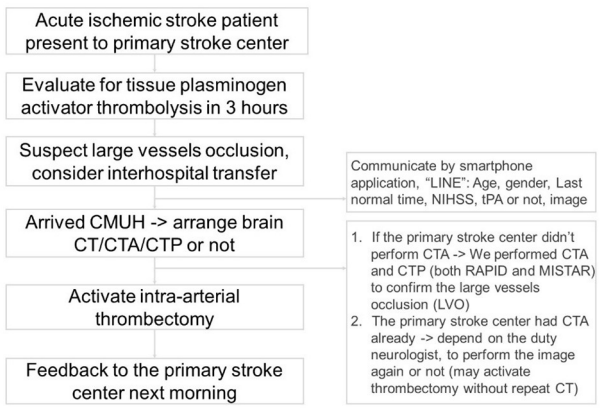

FIGURE 3 | The workflow of interhospital transfer of patients for intra-arterial thrombectomy.

a year, 24 h a day. We followed the treatment guidelines of the Taiwan Stroke Society (26, 27). Our workflow for interhospital transfer of patients has been summarized in **Figure 3**.

Study Design

We began using the smartphone application known as "LINE" to facilitate interhospital communication on May 01, 2018. We then performed retrospective data analysis for all transfer patients (n = 351) during the study period, with the primary outcome being the DTP time at CMUH. The three periods are then compared: May 01 to Dec 31, 2017 (before the use of the smartphone application); May 01 to Dec 31, 2018 (the 1st year of using the smartphone application); and May 01 to Dec 31, 2019 (the 2nd year of using the smartphone application). We chose the same period of comparison to eliminate other confounding factors such as weather [especially atmospheric pressure (28)] and the experience of first-line residents (our resident started visiting acute ischemic stroke patients at the emergency department after 16 months training in the neurology department, often started in January; they might attain minimal time-lapses in the first 3 to 4 months).

We also collected the similar data for the "non-transfer" (or "front door arrival") thrombectomies in the same three periods, that means the patients were directly presented to our emergency department without an interhospital transfer. By comparison, we could eliminate other factors such as overall improvement in the thrombectomy workflow, or the gain of more experience over time in the thrombectomy team members.

This study was able to secure an ethical approval from CMUH, CMUH109-REC3-099.

Outcome Measures

The primary outcome in this study is the DTP of interhospital transfer and non-transfer thrombectomy cases. We have also calculated the total number of transfers, total thrombectomies, successful recanalization rate (modified TICI score (29) = 2b, 2c, and 3), symptomatic intracerebral hemorrhage rate, and the

TABLE 1 | Characteristics of transfer cases of the three periods.

	Overall	2017-05-12	2018-05-12	2019-05-12	*P*-value	*P* for trend
Total transfer patients	351	63 (17.9)	113 (32.2)	175 (49.9)		
The distance between referral hospital and CMUH[a]					0.527	NA
< 10 km	119	22 (34.9%)	39 (34.5%)	58 (33.1%)		
10–50 km	94	16 (25.4%)	36 (31.9%)	42 (24.0%)		
> 50 km	138	25 (39.7%)	38 (33.6%)	75 (42.9%)		
Total thrombectomies	154	35 (55.6%)	50 (44.3%)	69 (39.4%)		
Age (year) in IAT patients	154	70.9 (13.7)	69.2 (12.7)	66.7 (13.7)	0.278	0.111
Female in IAT patients	63	18 (51.4%)	18 (36.0%)	27 (39.1%)	0.334	0.309
NIHSS in IAT patients	154	20.5 (7.6)	19.1 (6.6)	19.6 (6.6)	0.627	0.635
Work hour thrombectomy in IAT patients[b]	54	14 (40.0%)	20 (40.0%)	20 (29.0%)	0.363	0.206
Door-to-puncture time	154	109.3 (53.3)	102.4 (33.9)	92 (20.9)	**0.045**	**0.013**
DTP < 90 min	69	13 (37.1%)	21 (42.0%)	35 (50.7%)	0.374	0.166
Successful reperfusion[c]	139	30 (85.7%)	43 (86.0%)	66 (97.1%)	**0.039**	**0.033**
Symptomatic intracerebral hemorrhage	17	5 (14.3%)	4 (8.0%)	7 (10.1%)	0.644	0.609
Good outcome[d]	26	5 (14.3%)	7 (14.0%)	14 (20.3%)	0.547	0.280

CMUH, China Medical University Hospital; km, kilometer; IAT, intra-arterial thrombectomy; NIHSS, the NIH Stroke Scale; DTP, door-to-puncture time; mTICI, modified thrombolysis in cerebral infarction grade; mRS, modified Rankin Scale.

[a]The distance is the fastest route in time between primary stroke center and our hospital by ambulance transfer. [b]Work hours definition: 08:00 A.M. to 05:00 P.M., Monday to Friday. [c]Successful reperfusion was defined as mTICI= 2b-3. [d]Good outcome was defined as mRS = 0, 1, 2.

The bold values means the P value < 0.05.

percentage of good outcomes (modified Rankin scale (30) = 0, 1, or 2 at 3 months).

Statistical Analyses

The characteristics of this study population have been expressed as the mean (standard deviation [SD]) for continuous variables and frequency (percentage) for categorical variables. We used the one-way ANOVA and χ^2 tests to calculate p-values for continuous and categorical variables, respectively. Moreover, p-values for trends (31) were calculated using Pearson's correlation for continuous variables and Cochran-Armitage trend test for dichotomous variables. All statistical analyses were performed using SAS (SAS Institute, Cary, NC, USA), version 9.4. The threshold for statistical significance was set at $P = 0.05$ based on a two-sided test.

RESULTS

We summarized the main results in **Tables 1**, **2**. After the introduction of the "LINE" smartphone application, the total number of transfer cases increased from 63 to 113 and then to 175. We stratified by the distance of transfer and found consistently increasing numbers (**Figure 1**). The total number of thrombectomies has also increased. Between the three periods, the basic characteristics of transfer patients, including age, gender, initial NIH Stroke Scale (NIHSS), and time of arrival at work hour (8:00 A.M. to 5:00 P.M., Monday to Friday) were similar. The primary outcome was the DTP time, which decreased from 109.3 to 102.4 min and then 92 min ($p = 0.045$), showing a significant decreasing trend ($P = 0.013$). We also observed that the rate of successful reperfusion exhibited a significant increasing trend through the years ($P = 0.033$) (**Table 1**). However, there was no significant difference between the symptomatic intracerebral hemorrhage and the percentage of good outcomes over the years.

We put the data of non-transfer patients in **Table 2**, and the DTP times were 140.3, 122.1, and 129.3 min, respectively, with P-value of 0.391. It did not have the similar decreasing trend as the transfer patients. We could also find a trend of increased successful reperfusion rate in 2019, but the data did not reach statistical significance ($P = 0.098$).

The distance during our interhospital transfer ranges from 1.8 to 126 km. We did the subgroup analysis between short and long transfer distance, divided by the mean transfer distance, 35 km (**Table 3**). The result didn't show significant difference between these two groups, including DTP time, successful reperfusion, symptomatic intracerebral hemorrhage, and good functional outcome.

DISCUSSION

In large artery ischemic stroke, every 10-min delay of recanalization can decrease one's chance of functional independence per 100 patients treated (32). It is very important to treat the stroke patient immediately.

We used the smartphone application called "LINE" to shorten the DTP time. The main benefit is to overcome the communication barriers between hospitals and our stroke team members (20). The biggest change was the way of communication, from phone-base-point-to-point to LINE-base-hub-to-spoke (**Figure 4**). Before the introduction of smartphone

TABLE 2 | Characteristics of non-transfer cases with intra-arterial thrombectomy of the three periods.

	Overall	2017.05-12	2018.05-12	2019.05-12	*P*-value	*P* for trend
IAT patients[a]						
Total thrombectomies	115	29 (25.2%)	56 (48.7%)	30 (26.1%)		
Age (year)	115	68.6 (11)	68.1 (12.7)	70.4 (11.7)	0.698	0.567
Female	46	12 (41.4%)	18 (32.1%)	16 (53.3%)	0.158	0.339
NIHSS	115	20.7 (19.9)	19.2 (7.5)	17.1 (6.7)	0.505	0.246
Work hour thrombectomies[b]	50	13 (46.4)	28 (50)	9 (31)	0.240	0.236
Door to puncture time (minute)	115	140.3 (68)	122.1 (49.2)	129.3 (62.2)	0.391	0.475
DTP < 90 min	21	3 (10.3%)	14 (25%)	4 (13.3%)	0.182	0.783
Successful reperfusion[c]	98	24 (82.8%)	45 (80.4%)	29 (96.7%)	0.098	0.128
Symptomatic intracerebral hemorrhage	7	1 (3.5%)	5 (8.9%)	1 (3.3%)	0.680	0.974
Good outcome[d]	29	6 (20.7%)	13 (23.2%)	10 (33.3%)	0.506	0.261

IAT, intra-arterial thrombectomy; NIHSS, The NIH Stroke Scale; DTP, Door to puncture time; mTICI, modified thrombolysis in cerebral infarction grade; mRS, modified Rankin Scale; SD, standard deviation.

[a]Categorical variables are presented as frequency (%) and continuous variables are presented as mean (SD). [b]Work hour definition: 08:00 A.M. to 05:00 P.M., Monday to Friday. [c]Successful reperfusion was defined as mTICI= 2b-3. [d]Good outcome was defined as mRS = 0, 1, 2.

TABLE 3 | Characteristics of study population stratified by transfer distance.

Characteristic[a]	Overall	Transfer		*P* value
		<35 km	≥ 35 km	
Total transfer patients	351	202 (57.6%)	149 (42.5%)	
IA patients				
Total thrombectomies	154	97 (48.0%)	57 (38.3%)	0.068
Age (year)	154	68.2 (13.6)	69 (13.2)	0.701
Female	63	35 (36.1%)	28 (49.1%)	0.112
NIHSS	154	19.7 (7.1)	19.5 (6.3)	0.814
Work hour thrombectomies[c]	54	32 (33.0%)	22 (38.6%)	0.481
Door to puncture time (minute)	154	100.7 (39.8)	96.9 (25.9)	0.466
DTP < 90 min	69	51 (52.6%)	34 (59.7%)	0.394
Successful reperfusion[d]	139	88 (91.7%)	51 (89.5%)	0.649
Symptomatic intracerebral hemorrhage	16	9 (9.3%)	7 (12.3%)	0.556
Good outcome[e]	26	16 (16.4%)	10 (17.5%)	0.793

We divided our patients into two groups according to the mean distance between primary stroke center to our hospital (35 km).

[a]Categorical variables are presented as frequency (%) and continuous variables are presented as mean (SD). [c]Work hour definition: 08:00 A.M. to 05:00 P.M., Monday to Friday. [d]Successful reperfusion was defined as mTICI = 2b-3. [e]Good outcome was defined as mRS = 0, 1, 2.

application, the neurologists in primary stroke centers needed to present their situation to the emergency department doctor or nurse practitioner. Then the doctor or nurse practitioner repeated the words and made a phone call to our emergency department. Our emergency staff then made a phone call to our neurologist, repeated the same message (onset time, NIHSS, age, etc.) and asked for availability of thrombectomy. Then our nurse practitioner called back to reply to the emergency department of the primary stroke center. And during these processes, no one could see the patient's image; they only got messages by oral dictation. If our neurologists or intervention radiologist needed more information (such as comorbidities, lab data), then the process would repeat again and waste more time. After we introduced this smartphone application, we invited the neurologists in primary stroke centers, the doctor or nurse practitioner in emergency departments, our neurologists, and intervention radiologists to the encrypted group. All the related people could see the first-hand message delivered by the primary stroke center neurologists. Our team could respond or ask questions immediately. A rapid review of brain images is also available via the application. Then we delivered the final decision to all the members. Meanwhile, every related staff member could start to prepare for the interhospital transfer for thrombectomy. Moreover, we have invited the neurologists in other comprehensive stroke centers into the group so that we can pass a transfer request message to them; that is, we ask directly if any other comprehensive stroke center is available for thrombectomy in case our hospital is full to receive a second transfer patients or there are simultaneous stoke activations in two different primary

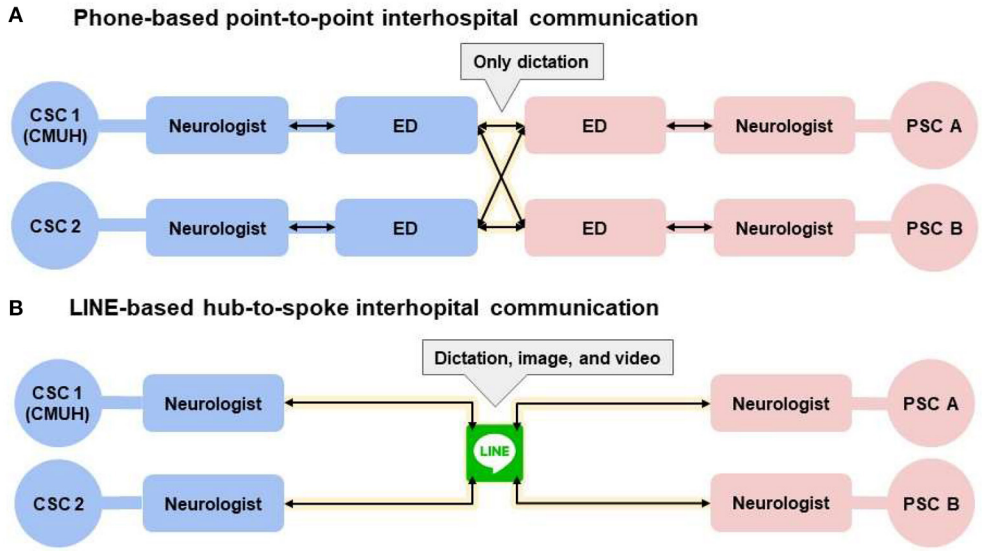

FIGURE 4 | The way of communication changed by smartphone application, LINE. **(A)** Indicates the original way of communication. Doctor or nurse practitioner in each hospital needed to communicate by phone call. **(B)** Indicates the novel way of communication. All the related staff could see the message at the same time, including the dictation, image, or video. We put the circle of CSC2, because sometimes our hospital could not receive the transfer patients. For example, we are doing another thrombectomy or stoke activations in two different primary stroke centers. We invited the neurologists in CSC2 to let them know the need of transfer immediately if we could not receive the PSC patients. CSC, comprehensive stroke center; ED, emergency department; PSC, primary stroke center.

stroke centers (**Figure 5**). Because the patient's information is posted on the same group, it is not necessary to be repeated by the primary stroke center and thus prevents time wasting.

A team member at Massachusetts General Hospital Telestroke Network found a frequent contact as this hub-to-spoke method is associated with improved stroke care (33). The hub-to-spoke organization design was used in the healthcare industry to serve patients better (34). And in the hospitals' perspectives, hub-to-spoke telestroke networks are cost-effective in acute stroke management (35, 36).

In addition, it has decreased the time needed to obtain informed consent from the family of the patient, because we sent the important message of thrombectomy to the primary stroke center through a smartphone application. The procedure could then be explained while the patient is waiting for the transfer. In the previous thrombolysis research in south Taiwan, obtaining informed consent was identified as one of the most important factors causing delay (37). In addition, failure to obtain informed consent was the reason why 21.1% of the eligible patients did not receive tissue plasminogen thrombolysis (38).

In 2007, our hospital set up the stroke center and further organized the emergency department, neurology department, and radiology department to improve the quality of thrombolysis and thrombectomy. We performed the first thrombectomy in 2008. After the five large-scale clinical trials in 2015, we started to have annual training of the NIHSS and hold monthly interdepartmental committee meetings to discuss the thrombectomy cases and try to reduce the DTP time (39). However, the reduction of DTP time remains to be limited. The DTP time at the same three periods in the non-transfer patients was 140.3 min in 2017, 122.1 min in 2018, and 129.3 min in 2019 (**Table 2**). The data convinced us that the significant improvement meant that the DTP time in transfer patients is different from that of the non-transfer [or "front door arrival" (40)] patients. This improvement might then be accounted for by the smartphone application use in interhospital communication, rather than the overall improvement in the thrombectomy workflow, or the gain of more experience over time in the thrombectomy team members.

We also found the rate of successful reperfusion (mTICI = 2b-3) was 97.1% (in transfer patients) and 96.7% (non-transfer patients) in 2019, which might have contributed to the introduction of novel thrombectomy techniques and devices. That is "a direct aspiration first pass technique (ADAPT)" (41) by contact aspiration (42) catheters, such as ACE 068, and Sofia Plus.

Although we had a shorter DTP time and a higher percentage of successful reperfusion, the percentage of good outcomes did not significantly increase. The reason for this could be the relatively small sample we used.

The major limitation of our study was the use of a commercially available smartphone application "LINE." Although the company passed the accreditation for information security (ISO 27001, SOC2, SOC3, and SysTrust) (25), it is not an application designed solely for medical information transfer. We then used the encrypted function of the application but still did not have full control of the data. We will develop novel

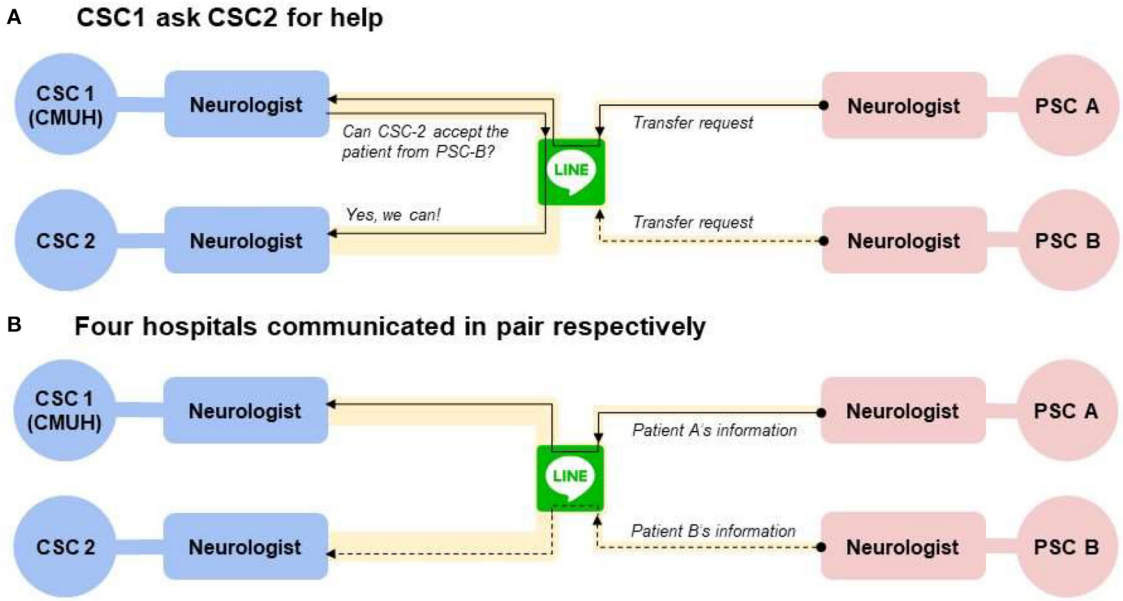

FIGURE 5 | The way of communication if there are simultaneous stoke activations in two different primary stroke centers. **(A)** Indicates the way CSC1 (our hospital) asked CSC2 for help. If CSC2 was available for thrombectomy, they would send the message on "Line" and both the CSC1 and PSC B could see it. Then the process moved to the **(B)**, that PSC A communicated with CSC1, and PSC B communicated with CSC2, respectively. CSC, comprehensive stroke center; ED, emergency department; PSC, primary stroke center.

smartphone applications for interhospital transfer in the future to overcome this hindrance.

Another limitation is the lack of exact transfer time, because we didn't collect the data recorded in the emergent medical service system. But a previous study (43) demonstrated that the transfer time was directly correlated with the hospital-to-hospital distance. We did the subgroup analysis according to short and long transfer distance (divided by the mean transfer distance, as 35 km), and we found the distance of interhospital transfer did not confound our results (**Table 3**).

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/**Supplementary Material**, further inquiries can be directed to the corresponding author/s.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by China Medical University Hospital, CMUH109-REC3-099. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

S-TT, W-CW, and W-SH: study conception and design. Y-TL and C-CK: analysis and interpretation of data. S-TT and W-CW: drafting the article. H-YH, C-JW, E-ZL, W-LK, P-SY, W-LC, and Y-LT: substantial acquisition of data for the study. Y-CG, K-HL, and M-KL: revising the article. D-YC, C-CC, and C-HT: general supervision of the research project. All authors contributed to the article and approved the submitted version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2021.606673/full#supplementary-material

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The Impact of Post-contrast Acute Kidney Injury on In-hospital Mortality After Endovascular Thrombectomy in Patients With Acute Ischemic Stroke

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Background and Purpose: Clinical outcome and mortality after endovascular thrombectomy (EVT) in patients with ischemic stroke are commonly assessed after 3 months. In patients with acute kidney injury (AKI), unfavorable results for 3-month mortality have been reported. However, data on the in-hospital mortality after EVT in this population are sparse. In the present study, we assessed whether AKI impacts in-hospital and 3-month mortality in patients undergoing EVT.

Materials and Methods: From a prospectively recruiting database, consecutive acute ischemic stroke patients receiving EVT between 2010 and 2018 due to acute large vessel occlusion were included. Post-contrast AKI (PC-AKI) was defined as an increase of baseline creatinine of $\geq$0.5 mg/dL or >25% within 48 h after the first measurement at admission. Adjusting for potential confounders, associations between PC-AKI and mortality after stroke were tested in univariate and multivariate logistic regression models.

Results: One thousand one hundred sixty-nine patients were included; 166 of them (14.2%) died during the acute hospital stay. Criteria for PC-AKI were met by 29 patients (2.5%). Presence of PC-AKI was associated with a significantly higher risk of in-hospital mortality in multivariate analysis [odds ratio (OR) = 2.87, 95% confidence interval (CI) = 1.16–7.13, $p = 0.023$]. Furthermore, factors associated with in-hospital mortality encompassed higher age (OR = 1.03, 95% CI = 1.01–1.04, $p = 0.002$), stroke severity (OR = 1.05, 95% CI = 1.03–1.08, $p < 0.001$), symptomatic intracerebral hemorrhage (OR = 3.20, 95% CI = 1.69–6.04, $p < 0.001$), posterior circulation stroke (OR = 2.85, 95% CI = 1.72–4.71, $p < 0.001$), and failed recanalization (OR = 2.00, 95% CI = 1.35–3.00, $p = 0.001$).

Conclusion: PC-AKI is rare after EVT but represents an important risk factor for in-hospital mortality and for mortality within 3 months after hospital discharge. Preventing PC-AKI after EVT may represent an important and potentially lifesaving effort in future daily clinical practice.

Keywords: endovascular thrombectomy, ischemic stroke, post-contrast acute kidney injury, renal impairment, in-hospital mortality

INTRODUCTION

Mortality after 3 months is an important outcome parameter in most observational and clinical stroke trials, including the most recent studies on endovascular stroke treatment [endovascular thrombectomy (EVT)] (1, 2). Well-established factors known to influence midterm to long-term mortality after EVT encompass older age (3–6), higher stroke severity at admission (3–8), larger infarct size (3, 5), lower reperfusion results (3, 5, 7, 8), symptom onset to groin times of more than 6 h (3), and absence of intravenous thrombolysis (3, 5). In addition, comorbid baseline renal impairment has been identified to be associated with mortality after 3 months (8, 9).

A better knowledge on factors influencing, in particular, early mortality would be of high interest for treatment decisions and for predicting short-term prognosis in these seriously affected patients. Nonetheless, only few studies have evaluated early in-hospital mortality in stroke patients irrespective of recanalization treatments (1, 10–14), and even fewer reports are available with regard to the in-hospital mortality after EVT (7, 15). By now, initial stroke severity and increasing age were reported to represent strong predictors of in-hospital mortality after EVT in one single study (7). This study also included information on kidney function, and a higher in-hospital mortality rate in patients with acute kidney injury (AKI) was reported (7). AKI represents an acute and complex renal function disorder that can be observed in up to 50% of patients treated on intensive care units (16–19). The contrast agents applied for computed tomography angiography (CTA) and cerebral angiography have been discussed to precede post-contrast AKI (PC-AKI) (20).

PC-AKI in ischemic stroke patients undergoing EVT appears to particularly affect patients with preexisting renal dysfunction (7, 21), but the role of acute renal disease for short-term outcome after EVT remains largely unknown. Therefore, we here explored whether PC-AKI after EVT has an impact particularly on in-hospital mortality in acute ischemic stroke patients.

PATIENTS AND METHODS

Acute ischemic stroke patients 18 years or older who underwent CTA and subsequent EVT between October 2010 and August 2018 at the Neurological Department of Heidelberg University Hospital were included into a prospective and consecutively recruiting database. Patients were either presented directly to our center or transferred by collaborating smaller hospitals of a regional stroke network. Clinical baseline characteristics of all patients were recorded, including patient's age, the premorbid modified Rankin Scale score (pmRS), stroke severity measured by the National Institutes of Health Stroke Scale (NIHSS) at admission and upon discharge or the last value available, the hospital stay length, and important cardiovascular risk factors, e.g., hypertension, diabetes, hypercholesterolemia, and coronary heart disease. Concordant to previous work (3, 4), the pmRS was dichotomized at a scale of 1 (0–1 and 2–5) to reflect preexisting functional disability. Information of baseline renal impairment, including renal replacement therapy, was extracted from medical records. According to current guidelines (22), we classified estimated glomerular filtration rate (eGFR) values < 60 mL/min per 1.73 m^2 at admission as presence of an abnormality of kidney function and presumed baseline renal impairment. The Alberta Stroke Program Early CT Score (ASPECTS) and posterior circulation (pc-)ASPECTS were calculated for all patients.

For CTA, a standardized dose of 65 mL of iodinated contrast dye iobitridol (Xenetix® 350, 38.39 g/50 mL iobitridol; Guerbet, Sulzbach, Germany) was administered intravenously. For cerebral angiography, iopamidol (Solutrast® 300, 30.62 g/50 mL iopamidol; Bracco Imaging Deutschland GmbH, Germany) was administered in 50-mL steps intra-arterially. An approximate median amount of 215 mL contrast dye per patient was applied. EVT was performed by experienced board-certified neuroradiologists, and recanalization results were recorded in each patient according to the Thrombolysis In Cerebral Infarction (TICI) grading system by the treating neuroradiologist. TICI scores of 0–2a were defined as failed recanalization. A subsequent control computed tomography (CT) or magnetic resonance imaging was performed within 20–36 h or earlier in case of clinical deterioration to assess intracerebral hemorrhage (ICH). Symptomatic ICH (sICH) was defined as an intracranial hemorrhage associated with an increase in the NIHSS score of $\geq$4 points or leading to death (23). An early neurological deterioration was defined as an increase of the NIHSS score $\geq$ 4. We also documented whether there were decisions to restrict medical treatment and to follow a best-supportive care strategy during the acute hospital stay.

For the present analysis, we included all patients in which information on renal function before and up to 48 h after EVT was available [creatinine, eGFR]. Following the previous recommendation for reporting contrast-associated AKI, PC-AKI was defined as a >25% increase of the baseline serum creatinine value or an absolute increase of serum creatinine of $\geq$0.5 mg/dL within 48 h after EVT (20). All patients who received renal replacement therapy prior to stroke defined as chronic hemodialysis or peritoneal dialysis were excluded from final analysis, because for them, assessment of PC-AKI was unreasonable. In-hospital mortality as well as the mRS at 3 months were recorded via chart review or telephone interview. The local ethics committee of the Medical Faculty of Heidelberg University approved the study. Because of the study character, patients' consent was waived.

Statistical Analysis

SPSS, IBM, version 25.0 (IBM, Armonk, NY), was used for all statistical analyses. The primary binary outcome was in-hospital mortality. Our secondary binary outcomes were 3-month mortality, including only patients who survived the acute hospital stay, the development of PC-AKI, unfavorable functional outcomes (dichotomized at a mRS scale at 3 months of 1 and 2), early neurological deterioration, and sICH. We performed a separate analysis of in-hospital mortality and 3-month mortality for anterior circulation stroke and after excluding patients with baseline renal impairment. Differences among groups regarding were compared using the Mann–Whitney U-test, the independent t-test, and the χ^2 test according to the scale of variables. Repeated measurements of eGFR

values were compared with the paired samples *t*-test. For multivariable logistic regression analyses, we selected variables formerly described to be associated with mortality and PC-AKI (2, 4, 7, 24, 25).

To evaluate whether the relationship between the PC-AKI and in-hospital mortality may depend on other important variables reported to be associated with mortality in patients undergoing EVT (age, NIHSS, pmRS > 1, baseline renal impairment, posterior circulation stroke, failed recanalization, and sICH), a moderation analysis was performed by using the PROCESS macro version 3.5 for SPSS, model 1 according to Hayes (26). All tests were two-sided, and $p \leq 0.05$ was considered significant.

RESULTS

Characteristics of Included Patients

A total of 1,205 patients who were treated with EVT due to acute ischemic stroke were included into the database. Of these, 36 patients had to be excluded because of missing creatinine values at baseline or within 48 h ($n = 24$, 2.0%) or because of long-term renal replacement therapy ($n = 12$, 1.0%), respectively. Hence, 1,169 patients entered the final analysis. As summarized in **Table 1**, the median age of included patients was 76 years [interquartile range (IQR) = 66–82 years], and the majority were female ($n = 608$, 52.0%).

The mean initial NIHSS score was 17 (IQR = 11–21). A total of 1,053 patients (90.1%) suffered an anterior circulation stroke. As shown in **Table 1**, in 384 patients (36.4%), occlusions of the internal carotid artery (ICA), including carotid-T, were detected. One hundred thirty of these 384 patients (33.9%) suffered both ICA and middle cerebral artery (MCA) occlusions. Furthermore, 652 patients (61.9%) suffered isolated occlusions of the MCA (M1 or M2 segment); 17 patients (1.6%) had other anterior circulation vessel occlusions. Posterior circulation strokes were present in 116 patients (9.9%); the majority of these ($n = 111$, 95.7%) occurred because of occlusions of the basilar artery. The median ASPECTS was 9 (IQR = 7–10).

Most patients had no or no relevant disabilities before onset of stroke (pmRS of 0 or 1: $n = 751$, 64.2%). A total of 206 patients (17.6%) had a pmRS of 2; 166 had a pmRS of 3 (14.2%). Moderately severe disability before stroke (pmRS 4) was present in 3.3% of patients ($n = 39$), and in 0.4% ($n = 5$), severe disability (pmRS 5) was present.

Renal Function

At admission, in 32.4% ($n = 379$ patients), an eGFR < 60 mL/min per 1.73 m^2 was observed, indicating baseline renal impairment. The mean initial eGFR was 70.4 ± 29.0 mL/min per 1.73 m^2, and eGFR follow-up within 48 h was in mean 76.8 ± 24.0 mL/min per 1.73 m^2 ($p < 0.001$). Within 48 h, an increase of creatinine of ≥0.5 mg/dL or an increase of baseline serum creatinine of >25% was detected in 29 patients (2.5%), thus fulfilling criteria of PC-AKI after EVT.

Age of PC-AKI patients [median age = 72 years (IQR = 58–82 years)] did not differ from non–PC-AKI patients [median age = 76 years (IQR = 66–82 years), $p = 0.342$; cf. **Supplementary Table 1**]. Also, the prevalence of cardiovascular risk factors among patients with and without PC-AKI did not differ (cf. **Supplementary Table 1**). Overall, only 10% of PC-AKI patients ($n = 3$) had already baseline renal impairment at admission (e.g., GFR < 60 mL/min per 1.73 m^2). These were 3 of a total of 379 patients with baseline renal impairment who developed PC-AKI (0.8%) As presented in the **Supplementary Table 1**, PC-AKI patients had a median length of stay of 5 days (3–13 days) vs. 4 days (3–7 days) in patients without PC-AKI ($p = 0.253$). There was no significant association between PC-AKI and the duration of inpatient treatment in univariable analysis. In multivariable logistic regression analysis, as shown in **Supplementary Table 2**, PC-AKI patients were significantly less likely to present with baseline renal impairment compared to patients who did not develop PC-AKI [odds ratio (OR), 0.23, 95% confidence interval (CI) = 0.07–0.76, $p = 0.016$]. Patients who had received additional thrombolysis seemed to be at a significantly higher risk to develop PC-AKI (OR = 3.47, 95% CI = 1.56–7.71, $p = 0.002$). Factors that may have contributed to AKI development in addition to contrast agents are shown in the **Supplementary Table 3**. As most frequent competing reasons for PC-AKI, we identified pneumonia and/or sepsis in 35% ($n = 10$).

In-hospital Mortality

During the acute hospital stay, 166 patients undergoing EVT died (14.2%; **Table 1**). The median duration between admission and death was 2 days (IQR = 2–4 days). These patients were older than patients surviving the acute post-EVT phase ($p = 0.001$) and had more severe strokes as measured by the NIHSS score at admission ($p < 0.001$), and they more often suffered posterior circulation strokes ($p < 0.001$). Clinical and treatment-specific variables in patients with in-hospital mortality and patients surviving the acute hospital stay are given in **Table 1**, as are the results of univariate correlation analyses.

In multivariable analysis (**Table 2**), the presence of PC-AKI was independently associated with a higher risk of in-hospital mortality (OR = 2.87, 95% CI = 1.16–7.13, $p = 0.023$). Expectedly, further factors independently associated with in-hospital mortality encompassed posterior circulation stroke (OR = 2.85, 95% CI = 1.72–4.71, $p < 0.001$), sICH (OR = 3.20, 95% CI = 1.69–6.04, $p < 0.001$), and failed recanalization procedures (OR = 2.00, 95% CI = 1.35–3.00, $p = 0.001$). Moreover, increasing age (OR = 1.03, 95% CI = 1.01–1.04, $p = 0.002$) and higher stroke severity were associated with a higher risk of in-hospital mortality in multivariable analysis (OR = 1.05, 95% CI = 1.03–1.08, $p < 0.001$). In-hospital deaths without PC-AKI received significantly more often additional thrombolysis compared to those with PC-AKI (52.5 vs. 25%, $p = 0.027$), c.f. **Supplementary Table 4**.

Moderation analysis indicated that there was no moderating effect of age ($p = 0.167$), stroke severity (NIHSS, $p = 0.945$), preexisting functional impairment ($p = 0.484$), baseline renal impairment ($p = 0.985$), posterior circulation stroke ($p = 0.569$), failed recanalization ($p = 0.400$), or sICH ($p = 0.987$) on the relationship between PC-AKI and in-hospital mortality.

TABLE 1 | Clinical characteristics concerning in-hospital mortality vs. survivors of the acute hospital stay.

	All (n = 1,169)	In-hospital mortality (n = 166)	Survivors of acute hospital stay (n = 1,003)	p-value
Female sex, *n* (%)	608 (52.0)	80 (48.2)	528 (52.6)	0.288#
Age, median (IQR)	76 (66–82)	79 (71–83)	75 (65–82)	**0.001**§
Hospital stay length (days), median (IQR), *n* = 1,169	4 (3–7)	—	5 (4–7)	—
Functional impairment				
NIHSS score at admission, median (IQR), *n* = 1,169	17 (11–21)	20 (14–26)	16 (11–21)	**<0.001**§
pmRS, median, IQR, *n* = 1,167	1 (0–2)	1 (0–2)	1 (0–2)	0.055§
Preexisting functional impairment (pmRS > 1), *n* (%), *n* = 1,167	416 (35.6)	67 (40.4)	349 (34.8)	0.151#
3-month mRS, median, IQR, *n* = 1,002	—	—	3 (1–4)	—
Switch to best supportive care, *n* (%), *n* = 1,169	150 (12.8)	142 (85.5)	8 (0.8)	**<0.001**§
Comorbidities				
Hypertension, *n* (%), *n* = 1,136	878 (75.1)	126 (75.9)	752 (75.0)	0.879#
Diabetes, *n* (%), *n* = 1,138	259 (22.2)	44 (26.5)	215 (21.4)	0.179#
Hypercholesterolemia, *n* (%), *n* = 1,158	392 (33.5)	49 (29.5)	343 (34.2)	0.323#
Coronary heart disease, *n* (%), *n* = 1,147	315 (26.9)	54 (32.5)	261 (26.0)	0.090#
AF, *n* (%), *n* = 1,142	569 (48.7)	82 (49.4)	487 (48.6)	0.961#
Previous stroke, *n* (%), *n* = 1,134	243 (20.8)	42 (25.3)	201 (20.0)	0.145#
BP systolic, mean, SD, *n* = 1,037	143 (72)	158 (27)	160 (27)	0.577*
Medical treatment				
Antiplatelets at baseline, *n* (%), *n* = 1,136	389 (33.3)	69 (41.6)	320 (31.9)	**0.006#**
OAC at baseline, *n* (%), *n* = 1,125	210 (18.0)	25 (15.1)	185 (18.4)	0.342#
Statin at baseline, *n* (%), *n* = 1,094	330 (28.2)	38 (22.9)	292 (29.1)	0.182#
Additional thrombolysis, *n* (%), *n* = 1,169	697 (59.6)	84 (50.6)	613 (61.1)	**0.011#**
Renal function				
Baseline creatinine, mean (SD), *n* = 1,169	1.01 (0.38)	0.98 (0.44)	1.00 (0.37)	**0.016***
Baseline eGFR, mean (SD), *n* = 1,169	70.4 (29.0)	65.8 (22.8)	71.2 (29.9)	**0.026***
Baseline renal impairment (eGFR < 60 at admission), *n* (%), *n* = 1,169	379 (32.4)	64 (38.6)	315 (31.4)	0.068#
PC-AKI, *n* (%), *n* = 1,169	29 (2.5)	8 (4.8)	21 (2.1)	0.037#
Neuroradiological parameters				
Anterior circulation stroke, *n* (%), *n* = 1,169	1,053 (90.1)	127 (76.5)	926 (92.3)	**<0.001#**
Posterior circulation stroke, *n* (%), *n* = 1,169	116 (9.9)	39 (23.5)	77 (7.7)	
Vessel occlusion, n = 1,169				
MCA, *n* (%)	652 (55.8)	53 (31.9)	599 (59.7)	**<0.001#**
Carotid-T, *n* (%)	199 (17.1)	35 (21.1)	164 (16.4)	
ICA and MCA, *n* (%)	130 (11.1)	24 (14.5)	106 (10.6)	
ICA, *n* (%)	55 (4.7)	10 (6.0)	45 (4.5)	
BA, *n* (%)	111 (9.5)	37 (22.3)	74 (7.4)	
VA, *n* (%)	2 (0.2)	1 (0.6)	1 (0.1)	
Other, *n* (%)	20 (1.7)	6 (3.6)	14 (1.4)	
ASPECTS, median, IQR, *n* = 1,093	9 (7–10)	9 (7–10)	9 (7–10)	0.364§
TICI 2b−3 recanalization, *n* (%), *n* = 1,169	938 (80.2)	117 (70.5)	822 (81.9)	**0.001#**
Failed recanalization (TICI 0–2a), *n* (%), *n* = 1,169	231 (19.8)	49 (29.5)	182 (18.1)	
Any ICH after treatment, *n* (%), *n* = 1,132	355 (30.4)	55 (33.1)	300 (29.9)	0.403#
sICH after treatment, *n* (%), *n* = 1,132	55 (4.7)	17 (10.2)	38 (3.8)	**<0.001#**

*IQR, interquartile range; SD, standard deviation; (p)mRS, (premorbid) modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; BP, blood pressure; OAC, oral anticoagulation; eGFR, estimated glomerular filtration rate; PC-AKI, postcontrast acute kidney injury; MCA, middle cerebral artery; ICA, internal cerebral artery; BA, basilar artery; VA, vertebral artery; ASPECTS, Alberta Stroke Program Early CT Score (restricted to anterior circulation stroke patients); TICI, Thrombolysis In Cerebral Infarction; (s)ICH, (symptomatic) interacerebral hemorrhage. *Unpaired t-test, §Mann–Whitney U-test, # χ^2-test. P ≤ 0.5 are displayed in bold font.*

Mortality at 3 Months

For the analysis of mortality at 3 months, we subsequently included patients who survived the acute hospital stay only (n = 1,003). Three-month outcome data in these patients were available in 99.8% (n = 1,001); mortality at 3 months was 14.6% (146/1,001).

TABLE 2 | Multivariable logistic regression analysis for in-hospital mortality.

	In-hospital mortality, $n = 166$ of 1,169 patients		
	Multivariable logistic regression analysis		
	OR	**95% CI**	***P***
Age (per year increasing)	1.03	1.01–1.04	**0.002**
NIHSS score at admission (per point increasing)	1.05	1.03–1.08	**<0.001**
Preexisting functional impairment (pmRS > 1 vs. ≤1)	0.86	0.59–1.25	0.415
Baseline renal impairment (eGFR < 60 vs. ≥60 at admission)	1.23	0.84–1.80	0.286
PC-AKI (vs. no PC-AKI)	2.87	1.16–7.13	**0.023**
Posterior circulation stroke (vs. anterior circulation stroke)	2.85	1.72–4.71	**<0.001**
Failed recanalization (TICI 0–2a vs. 2b−3)	2.00	1.35–3.00	**0.001**
sICH vs. no sICH	3.20	1.69–6.04	**<0.001**

NIHSS, National Institutes of Health Stroke Scale; eGFR, estimated glomerular filtration rate; PC-AKI, postcontrast acute kidney injury; TICI, Thrombolysis In Cerebral Infarction; sICH, symptomatic intracerebral hemorrhage. P ≤ 0.5 are displayed in bold font.

A considerably higher 3-month mortality rate was observed in case of PC-AKI compared to patients without PC-AKI (33.3% vs. 14.2%; $p = 0.014$, **Supplementary Table 1**). Results of univariate correlation analyses between patients who died between hospital discharge and follow-up, and those surviving 3 months are summarized in **Supplementary Table 5**.

In multivariable logistic regression (**Table 3**), again, patients with PC-AKI had a substantially higher risk of death (OR = 3.70, 95% CI = 1.19–11.53, $p = 0.024$). In addition, increasing age (OR = 1.04, 95% CI = 1.02–1.06, $p < 0.001$), stroke severity (OR = 1.08, 95% CI = 1.05–1.11, $p < 0.001$), preexisting functional impairment (OR = 2.44, 95% CI = 1.64–3.63, $p < 0.001$), failed recanalization (OR = 2.69, 95% CI = 1.74–4.17, $p < 0.001$), and sICH (OR = 2.94, 95% CI = 1.30–6.65, $p = 0.009$) were significant risk factors for mortality within 3 months.

The main results of multivariable regression analyses regarding in-hospital mortality remained unchanged when only patients without baseline renal impairment were considered (c.f. **Supplementary Table 6**), but PC-AKI no longer was associated with 3-month mortality.

Functional Outcome

PC-AKI had no impact on the risk of an unfavorable functional outcome (mRS > 1 and mRS > 2), early neurological deterioration, or sICH, as shown in the **Supplementary Table 7**. As illustrated by **Figure 1**, the rate of functional dependence (mRS > 2) after 3 months with PC-AKI and without PC-AKI was 72.4 vs. 64.2% and did not differ significantly ($p = 0.369$).

Anterior Circulation Stroke

As shown in the **Supplementary Table 8**, the same factors had a significant impact on 3-month mortality in anterior large vessel occlusion (LVO) alone as it was the case for the whole cohort. These were PC-AKI, increasing age, increasing NIHSS values at admission, a preexisting functional impairment, failed recanalization, and sICH. However, with regard to in-hospital mortality in anterior LVO exclusively, the impact of a PC-AKI on in-house mortality was not significant (c.f. **Supplementary Table 8**).

DISCUSSION

The main findings of our study are that PC-AKI after EVT in patients with acute ischemic stroke is strongly associated both with mortality in-hospital and 3 months after hospital discharge.

It is a matter of current discussion whether AKI in hospitalized patients represents a surrogate of general illness or whether its development during the hospital stay is caused by specific medical procedures (27). Previous work suggests that the contrast agent may contribute to PC-AKI in some patients, as creatinine values > 1.6 mg/dL were found to make individuals more prone to develop PC-AKI during hospitalization (28). Other recent reports did not observe associations between amounts of applied contrast agent and a risk of AKI after EVT (7, 21) and after contrast-enhanced CT imaging (29). Besides contrast-induced nephropathy (30), further reported important mechanisms for the development of AKI in acute ischemic stroke patients also encompass hemodynamic changes following blood pressure variations (31), acute tubular lesions (32), intravasal volume deficiency (30), and inflammatory conditions (20, 32). In our cohort, all of these mechanisms may apply to some extent as general anesthesia during EVT in example frequently involves drops in systolic blood pressure < 140 mmHg (33) and all patients received contrast dye two times (for CTA and for EVT). In addition, acute infections, i.e., pneumonia or urinary tract infections, are common complications in the post–acute phase after stroke (34).

Compared to previous studies evaluating the incidence of PC-AKI in ischemic stroke patients undergoing EVT (7, 21, 35–37), our overall rate of PC-AKI was within the lower range of previously reported incidences [2.5 vs. 1.5% (35) to 7.3% (7, 21, 36, 37)], although no pre-specified hydration protocol was used. Differences of the AKI incidence may be explained by a varying post-admission observation period of 48 h (35, 36) vs. 72 h (7, 21, 37) and up to 5 days (7) and dissimilar criteria used for AKI detection (7, 21, 35). PC-AKI in ischemic stroke patients who undergo EVT has been reported to particularly affect patients with baseline renal impairment (7, 21). In contrast, and unlike previous studies in which approximately one-third of AKI patients had the preexisting

TABLE 3 | Multivariable logistic regression analysis for 3-month mortality.

	3-month mortality (n = 146, only survivors of the acute hospital stay were considered) Multivariable logistic regression analysis		
	OR	**95% CI**	***P***
Age (per year increasing)	1.04	1.02–1.06	**<0.001**
NIHSS score at admission (per point increasing)	1.08	1.05–1.11	**<0.001**
Preexisting functional impairment (pmRS > 1 vs. ≤1)	2.44	1.64–3.63	**<0.001**
Baseline renal impairment (eGFR < 60 vs. ≥60 at admission)	1.14	0.76–1.71	0.535
PC-AKI (vs. no PC-AKI)	3.70	1.19–11.53	**0.024**
Posterior circulation stroke (vs. anterior circulation stroke)	0.32	0.14–0.76	**0.010**
Failed recanalization (TICI 0–2a vs. 2b−3)	2.69	1.74–4.17	**<0.001**
sICH vs. no sICH	2.94	1.30–6.65	**0.009**

NIHSS, National Institutes of Health Stroke Scale; pmRS, premorbid modified Rankin Scale; eGFR, estimated glomerular filtration rate; PC-AKI, post-contrast-AKI, TICI, Thrombolysis In Cerebral Infarction; sICH, symptomatic intracerebral hemorrhage. P ≤ 0.5 are displayed in bold font.

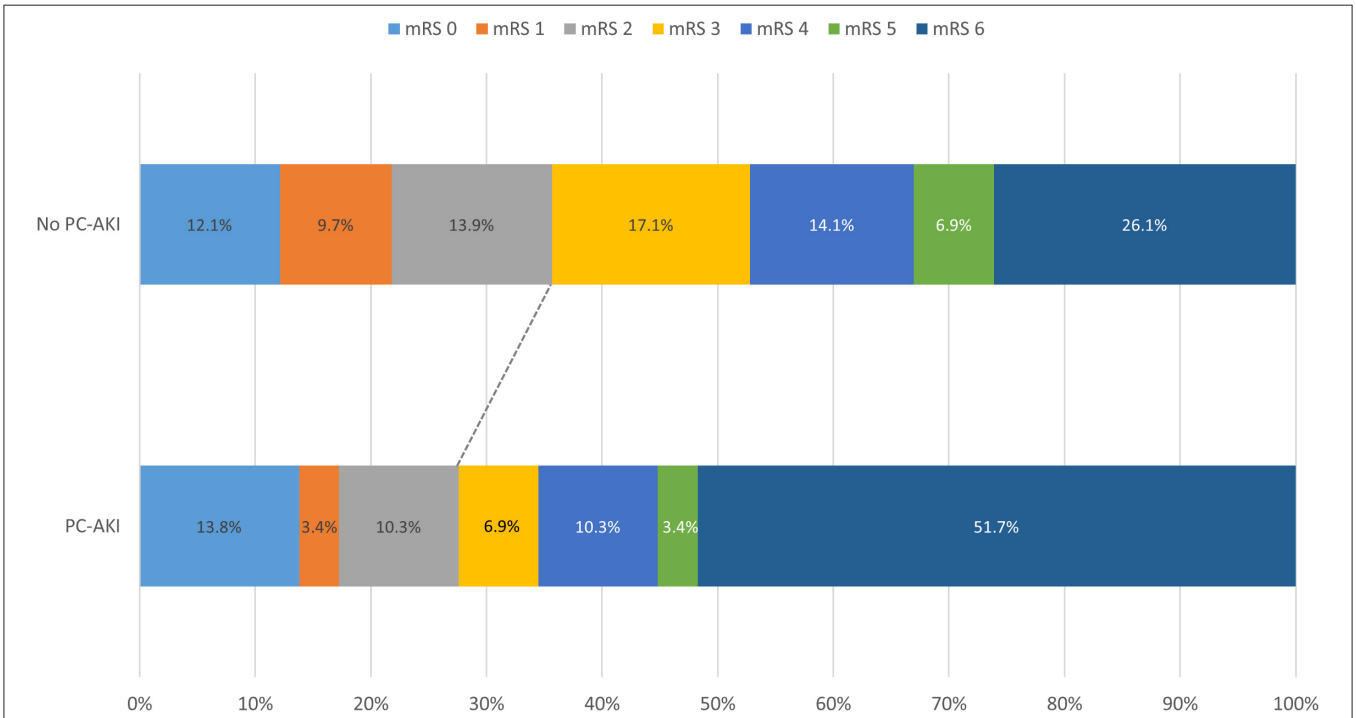

FIGURE 1 | Clinical outcomes of patients with and without PC-AKI. All 1,169 patients were considered. The cutt-off for functional dependence was set at a mRS of >2.

comorbidity of a chronic kidney disease (38, 39), we observed that baseline renal impairment was numerically less common in patients with PC-AKI compared to patients without PC-AKI (10.3 vs. 33.0%). Also, decreasing eGFR values did not correlate with the risk of PC-AKI, as described previously for a level < 30 mL/min per 1.73 m^2 (21), and baseline renal impairment was a risk neither of short-term nor of long-term mortality in multivariate analysis. Possible reasons for this observation are differing triggers underlying AKI development (38) as baseline renal impairment is only one of various known predisposing factors for AKI. In addition, different approaches were used to define baseline renal impairment across studies (7, 21).

On the other hand, in-hospital mortality in our patients with PC-AKI (28%) is comparable to the mortality rate of the report by Weber et al. [20% (7)]. Of note, adjusted for important confounders, PC-AKI more than doubled the risk of in-hospital death in our patients. This corresponds well to the results of the aforementioned study (7). Importantly, the additional moderation analysis performed in the present study did not reveal that PC-AKI and in-hospital mortality depended on other known factors associated with mortality in our large cohort of patients undergoing EVT. This hence indicates that PC-AKI appears to represent an independent risk factor for short-term and midterm mortality after EVT.

Neither the previously proposed PREMISE risk model (10) to assess the risk of early mortality after acute ischemic stroke nor the American Get With The Guidelines Stroke Program mortality score (40) did consider AKI or renal function. On the other hand, the IScore to predict poor functional outcomes early after hospitalization for an acute ischemic stroke included severe kidney dysfunction requiring renal replacement therapy (41). Here, renal dialysis was observed to be independently associated with 30-day mortality risk (41). Adding the findings of the recent study, our data indicate that acute renal dysfunction (i.e., PC-AKI) represents an important but so far often neglected risk factor for early mortality and 3-month mortality after EVT. Therefore, PC-AKI should be considered for future clinical scores to facilitate treatment decisions in this group of frequently seriously affected acute ischemic stroke patients.

The consecutive recruitment of all EVT patients admitted to our high-volume primary stroke center, thorough collection of laboratory parameters, and assessment of in-hospital mortality as well as outcome assessment after 3 months represent obvious strengths of our analysis. Limitations include that, similar to most other stroke registries, stroke volumetry was not performed. Moreover, some potential factors, including exact amounts of contrast dye that may have contributed to PC-AKI, could have been missed, and we did not include data on infectious diseases after EVT. In addition, decisions to limit medical care may have influenced the numbers of in-hospital deaths, and although acute stroke treatments are highly standardized within the regional network, we cannot completely exclude a selection bias.

CONCLUSIONS

To conclude, our results indicate that PC-AKI, although rare, represents an important but so far often neglected risk factor for in-hospital mortality and for mortality within 3 months after hospital discharge in acute ischemic stroke patients undergoing EVT. Hence, preventing AKI in these patients appears to represent an important and potentially lifesaving effort in future daily clinical practice.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Ethics Committee of the Medical Faculty of Heidelberg University, Alte Glockengießerei 11/1, 69115 Heidelberg, Germany. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

ML: study design, data collection, statistical analysis, data interpretation, manuscript drafting, critical revision, and final approval of the manuscript. EJ: statistical analysis, data interpretation, critical review of the manuscript. MM: performance of EVT, data collection, and critical review of the manuscript. MB: supervision and performance of EVT and data collection, critical review of the manuscript. PR: data collection, critical review of the manuscript. TR: concept and study design, statistical analysis, manuscript drafting, critical revision, and final approval of the manuscript. All authors contributed to the article and approved the submitted version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2021.665614/full#supplementary-material

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Treatment of Unruptured Vertebral Artery Aneurysm Involving Posterior Inferior Cerebellar Artery With Pipeline Embolization Device

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Background: Treatment of unruptured vertebral artery aneurysm involving posterior inferior cerebellar artery (PICA) is challenging. The experience of pipeline embolization device (PED) therapy for these lesions is still limited.

Objective: To evaluate the safety and efficacy of the PED for unruptured vertebral artery aneurysm involving PICA.

Methods: Thirty-two patients with unruptured vertebral artery aneurysm involving PICA underwent treatment with PED were retrospectively identified. Procedure-related complications, PICA patency, clinical, and angiographic outcomes were analyzed.

Results: Thirty-two aneurysms were successfully treated without any procedure-related complications. Images were available in 30 patients (93.8%) during a period of 3–26 months follow-up (average 8.4 months), which confirmed complete occlusion in 17 patients (56.5%), near-complete occlusion in 9 patients (30%), and incomplete occlusion in one patient (3.3%). Parent artery occlusion (PAO) was occurred in 3 patients (10%). Twenty-eight of 30 PICA remained patent. The two occlusions of PICA were secondary to PAO. At a mean of 20.7 months (range 7–50 months) clinical follow-up, all the patients achieved a favorable outcome without any new neurological deficit.

Conclusion: PED seems to be a safe and effective alternative endovascular option for patients with unruptured vertebral artery aneurysm involving PICA.

Keywords: pipeline embolization device, vertebral artery, posterior circulation aneurysms, dissecting aneurysms, pica

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INTRODUCTION

Vertebral artery aneurysm account for 11% of posterior circulation aneurysms and 3–5% of subarachnoid hemorrhage (SAH) (1–3). The outcome of ruptured vertebral artery aneurysm is dismay with a high mortality rate of up to 50% (4). Therefore, it is necessary to take more aggressive treatment for the unruptured vertebral artery aneurysm considering the risk of progression and rupture, especially vertebral artery aneurysm involving posterior inferior cerebellar artery (PICA). Previous study reported that PICA involvement is risk factor of progression (5),

and it has the highest morbidity among the ruptured vertebral artery aneurysm (6). However, Treatment of vertebral artery aneurysm involving PICA is challenging. The major consideration including preservation of the PICA and complete occlusion of the aneurysm (7). Selection of appropriate treatment modalities for these lesions remains controversial, the most acceptable conventional endovascular methods include internal coil trapping with revascularization of PICA and stent-assisted coiling. However, each method has its own drawback and limitation in terms of retaining the patency of PICA (8). PED has emerged as a popular treatment option for intracranial aneurysms and achieved promising results (9). This device can preserve parent vessels as well as major side branches while excluding aneurysm from circulation by disrupting flow within the aneurysm and remodeling vessel (10). These characteristics may be suitable for the treatment for vertebral artery aneurysm involving PICA. However, few articles have been published describing patient outcome following PED in treatment of these lesions. In this study, we report our experience regarding the efficacy and safety of the treatment of unruptured vertebral artery aneurysm involving PICA with PED.

METHODS

Patients

In accordance with our institutional review board, a retrospective study by extracting patient data from a prospectively maintained database was performed. Three hundred and twenty-four patients with vertebral artery aneurysms treated with endovascular methods in our institution between January 2016 and October 2019 were reviewed. Cases were excluded if the aneurysm did not involve PICA, the patients presented with subarachnoid hemorrhage, or the aneurysms were not treated with PED. Thirty-two patients with unruptured vertebral artery aneurysm involving PICA and using PED as treatment modality were included. Every patient was discussed by at least 3 experienced senior interventional radiologists for indications, which include high risk of rupture and uncontrolled progressive clinical symptoms (headache, dizziness, ataxia, vomiting, dysphagia; **Table 1**). All the patients provided written informed content and the study was approved by ethics committee of our institution.

TABLE 1 | Basic information and aneurysm characteristics.

Characteristics	No./Ave (range)	%/SD
Patients	32	
Aneurysms	32	32
Genders (males)	23	71.9%
Age (years)	52 (17–67)	±9.37
Risk factors		
Hypertension	14	43.8%
Diabetes	4	12.5%
Smoking	7	21.9%
Presentation		
Headache	14	43.8%
Dizziness	6	18.8%
Ataxia	2	6.3%
Dysphagia	2	6.3%
Vomiting	2	6.3%
Incidence	6	18.8%
Aneurysm morphology		
Fusiform	23	71.9%
Saccular	9	28.1%
Length (mm)	13.9 (7–27)	±5.18
Width (mm)	8.9 (4-18)	±3.67
VA dominance		
Co-dominant	20	62.5%
Right	9	28.1%
Left	3	9.4%
Baseline MRS number (%)		
MRS (0–2)	32	100%
MRS (3–5)	0	0

SD, Standard deviation; Ave, Average; VA, Vertebral artery; MRS, Modified Rankin Scale.

Procedure

All endovascular procedures were performed under general anesthesia and systemic heparinization was administered after placement of the sheath, a 6-F guiding catheter (Codman, Raynham, Massachusetts, USA) was placed in the distal V2 segment. Using a coaxial system, Marksman (EV3, Irvine, California, USA) was navigated over a 0.014-inch microwire in the target artery beyond the aneurysm. Once the PED reached scheduled position, it was released carefully by a combination of withdrawing the Marksman catheter and advancing the delivery wire. For the aneurysms with necessity of adjunctive coil embolization, additional coiling was conducted through a pre-jailed Echelon-10 catheter (EV3, Plymouth, Minnesota, USA) to loosely pack the aneurysmal sac. Coil embolization was performed to facilitate the thrombosis of the aneurysm, instead of completely occlude the aneurysm. A final angiogram was obtained after deployment to assess stent placement and vessel patency. Cone-beam CT was performed to ascertain the wall apposition of the device.

Antiplatelet and Anticoagulation Treatment

Patients were pre-medicated with a dual antiplatelet regimen (75 mg of clopidogrel and 100 mg of aspirin daily) for at least 5 days before treatment. During the procedure, we administered an intravenous bolus dose of heparin (70 IU/kg) and continued heparinization to maintain an activated clotting time throughout the procedure of two to three times greater than the baseline value. Dual antiplatelet therapy was continued for 6 months after the procedure, and aspirin was continued indefinitely to prevent thrombi forming in the stents.

Outcome Management

Clinical outcome was measured by the Modified Rankin Scale (MRS) at the latest available follow-up. Angiographic outcomes were determined by digital subtraction angiography (DSA)or computed tomographic angiography (CTA) which was scheduled

at 3–6 months and 1–2 years postoperatively. A follow-up MRS scores of 0–2 were defined as a favorable outcome; MRS scores of 3–6 were considered a poor outcome. Aneurysms occlusion at follow- up was categorized as complete (100%), near-complete (≥90%) or incomplete (<90%). Follow-up angiographic images were also reviewed for patency of PICA and parent vessels.

Statistical Analysis

Since the number of patients is relatively small and there is no sub-group analysis in the study, the data were presented in descriptive methods. For continuous variables, data that obeyed normal distribution are presented as mean and standard deviation. Data that did not obey normal distribution are presented as median and inter-quartile range. For categorical variables, data are presented as the absolute value followed by percentage.

RESULTS

Patient and Aneurysm Characteristics

A total 32 patients with vertebral artery aneurysm involving PICA were included in the present study. The mean age was 52 years old (range 17–67 years old). This study had greater proportion of males (71.9%) compared with that of females (28.1%). Patients risk factors include hypertension (43.8%), diabetes (12.5%) and smoking (21.9%). Of the 32 patients, twenty-six presents various clinical symptoms including headache (43.8%), dizziness (18.8%), ataxia (6.3%), dysphagia (6.3%), and vomiting (6.3%). The other six were incidentally identified without any symptoms.

The mean length and diameters of aneurysms were 13.94mm (Ranges from 7 to 27 mm) and 8.88 mm (Ranges from 4 to 18 mm), respectively. In terms of morphology, the majority of cases were fusiform (71.9%) compared to saccular (28.1 %). In terms of VA dominance, the majority of cases were codominant (62.5%) compared to single dominant (37.5%). All patients and aneurysm characteristics were summarized in **Table 1**.

Aneurysm Management

Patients with aneurysms of an irregular morphology and clinical symptoms (headache, dizziness, ataxia, vomiting, and dysphagia) were defined as having indications for treatment. All aneurysms were treated successfully with endovascular reconstruction including PED alone ($n = 28$) and pipeline-assisted coiling ($n = 4$). Thirty-three PEDs were used in 32 procedures. Thirty-one cases were treated with one PED, and double PEDs were used in one patient. Balloon angioplasty was used in one patient with parent artery stenosis. The time of contrast within aneurysms increased moderately in all the patients after PED placement. The aneurysm, parent artery and stent details are listed in **Table 2**.

Complications

There was no intra-procedural complication. Three patients developed delayed complication (parent artery occlusion PAO) during follow up which did not lead to any neurological symptoms or neurological deficits.

Angiographic and Clinical Follow-Up Outcome

Of the 32 patients, follow-up DSA or CTA was available in 30 patients. The average angiographic time was 8.3 months (3–26 months) after procedure. Seventeen (56.7%) of follow-up cases were completely occluded angiographically including four patients with adjunctive coiling (**Figure 1**). Nine (30%) cases were near completely occluded, and one case (3.3%) was incompletely occluded (**Figure 2**). Parent artery occlusion occurred in 3 (10%) cases. Involved PICA remained patency in 28 of 30 patients including one of PAO with retrograde filling from contralateral VA (**Figure 3**). The other two patients with PAO showed PICA occlusion. Clinical follow-ups were available in all 32 patients. the mean time of follow-up was 20.7 months (7–50 months). All patients achieved favorable outcome at the last follow-up. There were no morbidity and mortality. All follow-up outcomes were summarized in **Table 3**.

DISCUSSION

PICA is an important branch originate from intracranial VA, which supplies part of cerebellum and medulla. The sacrifice of PICA will result in severe ischemic stroke and poor clinical outcome. Studies have shown that ischemic complications happened in 21.7% cases in which the PICA is sacrificed (8). When vertebral artery aneurysm involves the ostium of PICA, the treatment become complicated and challenging and the options are also limited (11). One consideration is to maintain the PICA patency. Various techniques were utilized for this purpose including loosely filling aneurysm, stent placement from VA to PICA, and surgical bypass using an occipital artery (OA)-to-PICA, PICA side-to-side anastomosis or PICA transposition. However, each approach has its own limitation and is unable to be an ideal and routine method. Loosely filling when using stent-assisted coiling result in high rate of incomplete occlusion which is thought to be an important factor to predict the postprocedural recurrence. A previous study for vertebral artery aneurysm treated with stent assisted coiling found 18% vertebral artery aneurysm involving PCIA experienced recurrence, whereas only 5% occurred in those without PICA involvement (12). The uncertainty of releasing a stent in a vessel <2 mm diameter and the difficulty of introducing a catheter into PICA due to the disadvantaged angel made the using of stent placement from VA to PICA only for a few selective patients (13, 14). Surgical bypass in posterior circulation is technically challenging and may require a lengthy operative time. Furthermore, bypass associated with various of surgical complications such as lower cranial nerve palsy and anastomosis failure (15). A review conducted by Chen et al. (16) noted two graft occlusion and three infarction occurred in 19 patients with vertebral artery aneurysm involving PICA treated by bypass, suggesting this method has been typically reserved for the cases not amendable to endovascular treatment. In the present study, all the PEDs were successfully deployed without technical events. one PED was used in thirty-one patients (96.9%) and the exceptional case (3.1%) using two devices harbored a giant vertebral artery aneurysm extending to basilar

TABLE 2 | Patients, aneurysm and stent details.

Patients	Gender/Age (years)	Morphology of AN	Size of AN (mm)	Diameter of parent artery (Proximal/Distal of AN, mm)	Size of stent (mm)
1	Male/58	Fusiform	11*20 mm	3.7/3.2 mm	4.0*35
2	Male/51	Fusiform	9*12 mm	3.3/3.1 mm	3.5*30
3	Female/54	Fusiform	6*15 mm	3.4/3.3 mm	3.5*20
4	Male/55	Fusiform	8*15 mm	3.3/2.8 mm	3.75*35
5	Male/54	Fusiform	6*11 mm	3.2/3.1 mm	3.5*30
6	Male/52	Saccular	18*17 mm	4.3/3.9 mm	4.5*35
7	Female/47	Fusiform	8*12 mm	3.4/3.1 mm	3.5*30
8	Male/55	Fusiform	8*12 mm	3.3/2.9 mm	3.5*30
9	Female/54	Saccular	15*17 mm	3.6/3.3 mm	4.0*35
10	Female/30	Saccular	5*7 mm	3.3/3.0 mm	3.5*20
11	Female/55	Saccular	11*12 mm	3.6/3.1 mm	3.75*25
12	Female/67	Saccular	7*9 mm	3.3/3.0 mm	3.5*30
13	Female/44	Saccular	8*10 mm	3.2/3.1 mm	3.5*30
14	Female/54	Fusiform	4*8 mm	3.8/3.1 mm	4.0*25
15	Male/52	Saccular	8*10 mm	4.1/3.5 mm	4.5*25
16	Male/53	Fusiform	9*13 mm	4.3/3.8 mm	4.5*25
17	Male/51	Fusiform	20*27 mm	4.8/3.7 mm	5.0*35
18	Male/61	Fusiform	7*14 mm	3.5/3.2 mm	3.75*35
19	Female/53	Fusiform	5*8 mm	3.3/3.2 mm	3.5*25
20	Male/67	Fusiform	7*12 mm	3.7/3.5 mm	4.0*35
21	Male/64	Fusiform	9*17 mm	3.7/3.2 mm	4.0*35
23	Male/56	Fusiform	5*12 mm	4.1/3.7 mm	4.25*25
24	Female/56	Fusiform	8*15 mm	3.4/3.1 mm	3.5*30
25	Male/17	Fusiform	9*12 mm	3.5/3.1 mm	3.75*35
26	Male/54	Fusiform	9*21 mm	3.3/3.1 mm	3.5*25
27	Male/46	Fusiform	7*18 mm	4.0/3.5 mm	4.25*35
28	Male/46	Saccular	6*8 mm	3.1/2.9 mm	3.25*35
29	Male/55	Saccular	6*8 mm	4.1/4.2 mm	4.25*35
30	Male/55	Fusiform	10*21 mm	4.3/4.0 mm	4.5*35/4.0*30
31	Male/53	Fusiform	11*17 mm	3.3/2.9 mm	3.5*25
31	Male/46	Fusiform	12*18 mm	3.9/4.5 mm	4.75*30
32	Male/52	Fusiform	7*14 mm	3.4/3.1 mm	3.5*30

AN, Aneurysm.

artery. For the four large saccular aneurysms, one or two coils were used to facilitate the thrombosis of the aneurysm instead of intensely coiling. Of the 30 patients with follow-up imaging, 28 remained the patency of PICA and two occurred PICA occlusions secondary to PAO. Mazur et al. (17) reported that all the PICA with origin covered by PED remained patency in eight patients and suggested when appropriately sized to the vessel wall and positioned in the VA, the device may cover the origin of PICA without impairing flow through the branching artery. Levitt et al. (18) reported that all the PICA maintained patency in six cases with vertebral artery aneurysms involving PICA treated by flow diverting stent. Similar results were reported by Adeeb et al. (19) and Wu et al. (20). These data suggested that the PICA can be effectively and safely preserved when using PED in treatment of these lesions. Additionally, in terms of conserving PICA, PED appears to be more convenient than conventional endovascular methods.

Nearly 86.7% of patients with angiographic follow-up achieved complete or nearly complete occlusion at mean 7.8 months follow-up without recurrence and retreatment. The only one incomplete occlusion (3.3%) was occurred in a patient with a giant vertebral artery aneurysm extending to basilar artery which was substantially attenuated. In addition, complete occlusion also occurred in three PAOs without any recanalization and recurrence. Likewise, Zhang et al. (21) report 93.3% nearly complete and complete occlusion rate of unruptured vertebral no-saccular aneurysm after PED placement in 32 cases series (21). Kuhn et al. (10) reported 100% nearly complete and complete occlusion rate in six patients with unruptured vertebral aneurysms. The similar results were reported by Yeung et al. (22). These data suggested that unruptured vertebral artery aneurysm may be effectively managed with PED. On the other hand, Stent assisted coiling is associated with high risk of incomplete occlusion and recurrence. Zhao et al. (12)

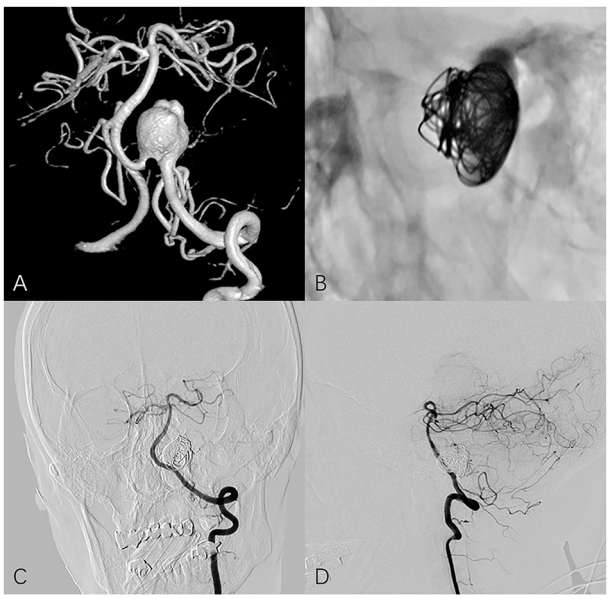

FIGURE 1 | Fifty four year-old female with left vertebral artery aneurysm. **(A)** A 3-dimensional reconstruction image of a vertebral angiogram shows an irregular aneurysm involving PICA. **(B)** Non-subtracted oblique view shows PED in place and loosely filling coils. Follow-up frontal **(C)** and lateral **(D)** angiography shows the aneurysm is completely occluded and PICA remains patency.

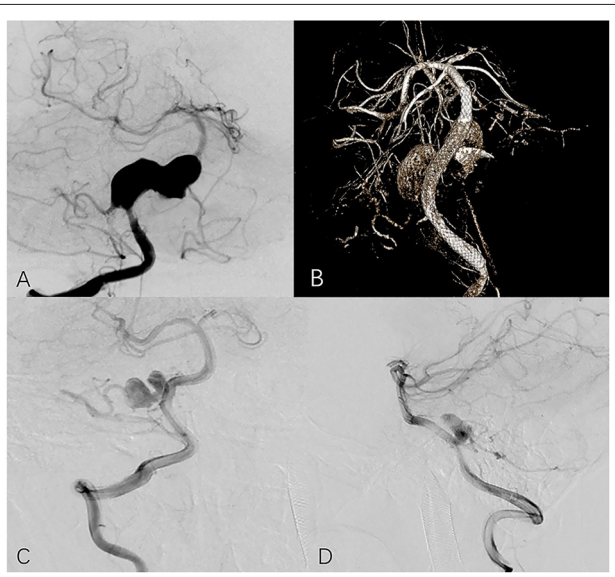

FIGURE 2 | Seventeen year-old male with right vertebral aneurysm extending to basilar artery. **(A)** Preoperative frontal angiogram shows a giant vertebrobasilar aneurysm involving PICA. **(B)** Postoperative DynaCT indicates good opening of the PED and apposition. The 13-month follow-up frontal **(C)** and lateral **(D)** angiogram shows the aneurysm is incompletely occluded and the PICA is preserved.

reported 52.7% partial obliteration rate and 10.3% recurrence in 97 patients with vertebral artery aneurysm treated by stent assisted coiling, suggesting recurrence is closely associated with

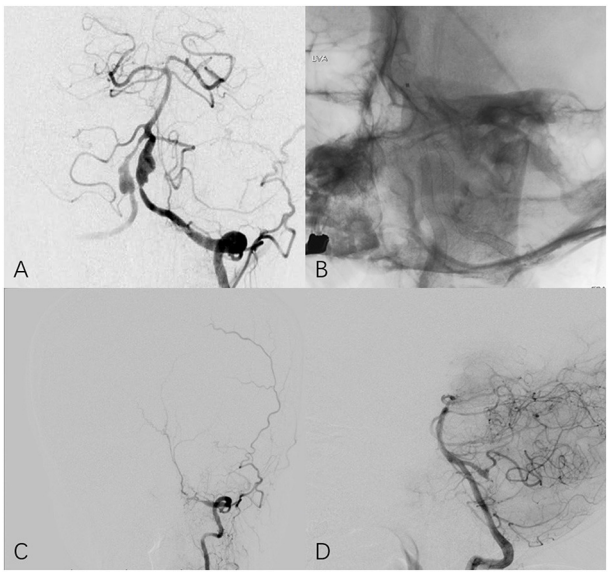

FIGURE 3 | Fifty four year-old female with bilateral vertebral aneurysm. **(A)** Frontal angiogram of the left vertebral artery shows bilateral dissecting aneurysm and the left involved PCIA. **(B)** Non-subtracted frontal view shows bilateral PED in place. **(C)** The 25-month follow-up left **(C)** and right **(D)** angiogram indicates left vertebral artery is occluded at V3 segment and PICA remains patency through contralateral circulation.

TABLE 3 | Procedural details and follow-up outcomes.

Items	Number (100%)
Procedural success	32 (100%)
PED numbers	33
1	31 (96.9%)
2	1 (3.1%)
Adjunct coil deployment	4 (12.5%)
Balloon angioplasty	1 (3.1%)
Imaging follow-up available	30 (93.8%)
Follow-up modality	
Digital subtraction angiography (DSA)	20 (66.7%)
Computed tomographic angiography (CTA)	10 (33.3%)
Follow-up occlusion rate	
Complete occlusion	17 (56.7%)
Near-complete occlusion	9 (30%)
Incomplete occlusion	1 (3.3%)
Patency of PICA	28 (93.3%)
Delay complications	
PAO	3 (10%)
Clinical follow-up available	32 (100%)
Follow-up MRS	
0–2	32 (100%)
3–6	0 (0%)

PED, Pipeline embolization device; PICA, Posterior inferior cerebellar artery; PAO, Parent artery occlusion; MRS, Modified Rankin Scale.

PICA involvement and immediate occlusion degree. Kim et al. (23) also reported 13% recurrence rate after conventional endovascular treatment of vertebrobasilar dissecting aneurysms, and concluded PICA involvement was the independent risk factor for recurrence. Despite the promising results in the present study, long-term angiographic follow-up and large study are needed to assess the efficacy of the PED in unruptured vertebral artery aneurysm involved PICA.

PAO is one of serious complications related to PED. Becsek et al. (24) reported 5 cases of PAO in their study for PED and concluded that non-compliance or resistance to antiplatelet therapy and severe in-stent stenosis might lead to PAO and evaluating antiplatelet effectiveness might be useful to reduce this complication. Oishi et al. (25) reported a patient who developed PAO during the 28 months follow-up after treatment with PED and found thrombus development at the non-covered part with endothelium due to discontinuation of antiplatelet and incomplete occlusion of the aneurysm. In the present study, PAO were developed in three cases during the follow-up. One patient developed PAO at 5 months due to the stenosis of the parent artery, another patient occurred PAO at 11 months attribute to discontinuation of antiplatelet at 6 months after procedure. We are not sure the mechanism of the last patient. There is no *in-situ* stenosis in the parent artery, the antiplatelet therapy was continued, and the deployment of PED was successful. A reasonable explanation might be the resistance of the antiplatelet medication. It might be useful to decline this complication with *in-situ* stenosis angioplasty, longer antiplatelet treatment and routinely monitoring antiplatelet effectiveness. Three PAOs resulted in obliteration of two involving PICA, fortunately, these patients did not develop any new neurological deficit, and there were no postoperative strokes in the treated PICA territory. This may due to slow progress and sufficient time for the establishment of collateral circulation.

The limitations of the current study include the retrospective property and variable follow-up intervals, which may cause selection bias of patients and add difficulties for replication. This study will provide some initial experience for the treatment of such lesions, while the result needs to be consolidated by large multi-center prospective studies.

CONCLUSION

Our preliminary experience of using PED in the treatment of unruptured vertebral artery aneurysm involving PICA demonstrated that this method is effective and safe with favorable angiographic and clinical outcomes.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Medical Ethics Committee of Beijing Tiantan Hospital. Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin.

AUTHOR CONTRIBUTIONS

WF, HJ, and YL designed, conceptualized the study, and analyzed and interpreted the data. WF, HJ, HG, GL, XM, and JW collected the data. WF drafted the manuscript. HJ, HG, GL, XM, JW, and YL revised the manuscript for intellectual content. All authors agreed and approved the publication.

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CASE REPORT
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Case Report: Ruptured Middle Cerebral Artery Aneurysm With Intrasylvian Hematoma Successfully Treated by Coil Embolization and Minimally Invasive Puncture and Drainage

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Up to one-third (12–35%) of patients with aneurysmal subarachnoid hemorrhage experience intracerebral hematoma. Ruptured middle cerebral artery (MCA) aneurysm with hematoma is usually accompanied by progressive cerebral swelling with poor outcomes; however, it can be successfully treated by coil embolization and minimally invasive puncture and drainage. From February 2012 to March 2019, six surgeries for ruptured MCA aneurysms with intrasylvian hematoma were performed at our clinic. All patients had intracranial hematomas of <30 ml and GCS scores >8. The patients were treated by coil embolization and minimally invasive puncture and drainage. The aneurysms in all patients were completely embolized and the hematomas were mostly removed by minimally invasive puncture. The Glasgow outcome scale (GOS) scores of all patients were more than 4 at discharge when they discharged. Coil embolization and minimally invasive puncture and drainage are viable treatments for ruptured MCA aneurysms with hematomas, especially if the patient is too old, in a complicated state to undergo craniotomy, is unwilling to undergo craniotomy, or is at a greater risk of bleeding 3 days after surgery.

Keywords: ruptured middle cerebral artery aneurysm, hematoma, coil embolization, minimally invasive puncture and drainage, outcomes

INTRODUCTION

Intracerebral hematoma (ICH) due to rupture of intracranial aneurysm (IA) occurs in 10–38% of cases with subarachnoid hemorrhage (SAH) (1). Aneurysmal ICH complicates the natural course of the disease and is associated with increased morbidity and mortality (2). Middle cerebral artery (MCA) aneurysms are most likely to result in an intracerebral and intrasylvian hematoma after their rupture (3, 4). About 30-37.5% of ruptured middle cerebral artery aneurysms can lead to intracranial hematoma. Most neurosurgeons prefer microsurgical clipping for treatment of such patients. Smith et al., through a systematic review and meta-analysis, recommended surgical clipping for unruptured MCA aneurysms (5). Along with the publication of International

TABLE 1 | Characteristics of six patients with middle cerebral artery aneurysms.

	Sex	Age	GCS	Hunt-hess	GOS	Antiplatelet	Stent
Case 1	Male	42	11	3	5	NO	NO
Case 2	Male	48	9	4	4	NO	NO
Case 3	Female	69	10	2	5	YES	YES
Case 4	Female	44	12	2	5	NO	NO
Case 5	Female	76	10	3	4	NO	NO
Case 6	Male	50	13	2	5	YES	YES

GCS, Glasgow coma scale; GOS, Glasgow outcome scale.

Subarachnoid Aneurysm Trial (ISAT) and the improvement of neurointervention techniques, more neurosurgical centers have been opting for endovascular coiling (6, 7). However, for ruptured MCA aneurysms with hematomas, most patients still prefer craniotomy clipping. In China, some scholars believe that endovascular coiling is effective in patients with ruptured MCAs (8). Whether interventional embolization can be performed for ruptured middle cerebral artery aneurysms with hematoma is still uncertain. We have reported six cases with ruptured MCA aneurysm and intrasylvian hematoma that were successfully treated by coil embolization and minimally invasive puncture and drainage.

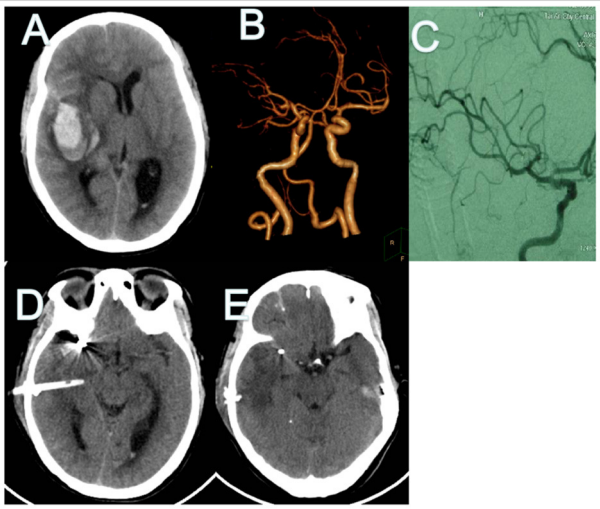

FIGURE 1 | CT and CT angiography in case 1. **(A,B)** Initial CT scans reveal characteristic findings of ruptured MCA aneurysm with intrasylvian hematoma. Hematoma volume was calculated as 28.8 ml. **(C)** Post-operative angiography shows the aneurysm is completely occluded and parent artery is unimpeded. **(D)** Immediate post-operative CT finding the drainage tube was in good position. **(E)** CT finding Hematoma's almost drained clean on POD 2. CT, computed tomography; MCA, middle cerebral artery; POD, post-operative day.

SUBJECTS AND METHODS

Patient Population

From February 2012 to March 2019, six patients (total of six MCA aneurysms) underwent endovascular coiling and minimally invasive puncture and drainage in our institution. The clinical condition at admission was classified according to the Hunt–Hess grade. Post-operative CT scans were obtained for all patients, and the hematoma volume was calculated using the formula a × b × c/2. The clinical outcomes were graded according to the Glasgow Outcome Scale (GOS). MCA aneurysms were confirmed by DSA and treated by an endovascular approach. All the intracranial hematomas were confirmed by CT and treated by minimally invasive puncture and drainage (**Table 1**).

The outcomes of patients were evaluated by GOS. Patients with GOS score 1–3 were defined as having poor outcomes and those with GOS scores 4–5 were defined as having good outcomes. Informed consent was obtained from patients and the study was approved by our institutional review board.

RESULTS

Baseline Characteristics

The clinical characteristics and treatment details of the six patients are shown in **Table 1**. The sample comprised two men and four women with a mean age of 58.7 (range 42–76) years. All patients had a GLS score >8 before the surgery. The GOS scores of all patients were more than 4 at discharge.

Illustrative Cases

Case One

A 48-year-old man presented to the emergency room with a severe headache after sudden loss of consciousness. Initial consciousness level was deep drowsy (Hunt–Hess 4). Brain CT showed a typical SAH from MCA aneurysmal rupture, in which the SAH was mainly dispersed prominently along the left Sylvian fissure. Hematoma volume was calculated as 28.7 ml using the formula a × b × c/2 (**Figures 1A,B**). Coil embolization surgery was performed 6 h after admission. Minimally invasive puncture and drainage were performed immediately after the operation. Surgery was performed successfully on the ruptured aneurysm and no complication was observed during the procedure (**Figures 1C,D**). On the two day after the operation, CT showed that the hematoma had disappeared (**Figure 1E**).

Case Two

A 42-year-old man was transferred to our hospital 3 days after the onset of symptoms (a severe headache) (Hunt-Hess 2). Brain CT and CT angiography revealed SAH from ruptured MCA aneurysm and large amounts of intrasylvian hematoma (about 16.5 ml; **Figures 2A,B**). Coil embolization surgery was performed 5 h after admission. Minimally invasive puncture and drainage were performed immediately after the operation. Surgery was performed successfully on the ruptured aneurysm and there was no complication during the procedure (**Figures 2C,D**). On the third day after the operation, CT showed that the hematoma had almost disappeared (**Figure 2E**).

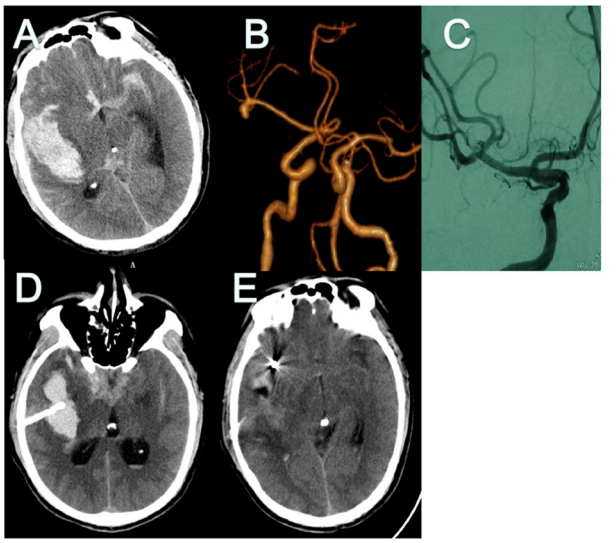

FIGURE 2 | CT and CT angiography in case 1. **(A,B)** Initial CT scans reveal characteristic findings of ruptured MCA aneurysm with intrasylvian hematoma. Hematoma volume was calculated as 16.5 ml. **(C)** Post-operative angiography shows the aneurysm is completely occluded and parent artery is unimpeded. **(D)** Immediate post-operative CT finding the drainage tube was in good position. **(E)** CT finding Hematoma's almost drained clean on POD 3. CT, computed tomography; MCA, middle cerebral artery; POD, post-operative day.

DISCUSSION

The MCA has a complex anatomical structure, which contains multiple ventral perforating arteries. It is widely distributed, with branches lacking collagen circulation. Ruptured aneurysms in the brain can lead to neurological disorders, such as hemiplegia, aphasia, and paresthesia. MCA aneurysms account for 20% of intracranial aneurysms (1). Ruptured intracranial aneurysms are often accompanied by large intracranial hematomas, as compared to other intracranial aneurysms. Hence, the Hunt–Hess grade is worse in such cases. About 30% of ruptured middle cerebral artery aneurysms can lead to intracranial hematoma (7). Zhao et al. reported that 37.3% of the patients had intracranial hematomas, and that inappropriate treatment may affect branch blood flow causing chemical syndrome or cerebral infarction (8).

Currently, the treatment methods for ruptured aneurysms mainly include microsurgical clipping and endovascular embolization. With the publication of ISAT, more neurosurgical centers begun to choose endovascular embolization. However, they have not elaborated on the best treatment for aneurysms, which remains controversial. The complex anatomical structure of the MCA, such as bifurcation and multiple branches, increases the difficulty of performing an interventional surgery. For ruptured wide-necked aneurysms, early stent placement can lead to thrombosis (5, 9). However, for some patients who are not suitable for craniotomy (such as old age, long-term anticoagulant therapy, etc.) there is still no good treatment plan.

With the improvement of interventional techniques and the application of new interventional materials, endovascular embolization techniques, especially three-dimensional rotary angiography, and stent-assisted embolization, can be used to treat more complex large aneurysms. Three-dimensional rotational angiography can clearly show the anatomical features of the MCA and its branches. Stenting reduces the recurrence rate of MCA aneurysms by changing the cerebral hemodynamics and endothelialization of the stent. The effect of stent network on the parent artery branch remains minor. Many studies have confirmed the safety and efficacy of endovascular embolization and have obtained comparable results to that of surgical clipping (2, 5, 10, 11). At present, most scholars still believe that microsurgical clipping should be the preferred treatment for ruptured MCA aneurysms with hematoma. Our surgical experience was that the brain tissue was obviously swollen and the lateral fissure was difficult to separate after 3 days of subarachnoid hemorrhage. We reported six patients with ruptured MCA aneurysms with intrasylvian hematoma who were treated in our clinic. All patients had intracranial hematomas of <30 ml and GCS scores >8. The patients were treated by coil embolization and minimally invasive puncture and drainage. Good prognosis was obtained. However, microsurgical clipping remains to be the preferred treatment for patients with massive hematomas and cerebral hernia.

There were some limitations in this study. This was not a randomized study, and the number of patients and the duration of follow-up were limited. Due to the small sample and lack of randomized controlled studies, our retrospective study lacked the support of a statistical analysis, However, this paper is only published as a case report and only provides a treatment idea. For the advantages and disadvantages of this approach, a lot of comprehensive analysis of clinical cases is needed, which is our work in the future.

CONCLUSION

Coil embolization and minimally invasive puncture and drainage are viable treatments for ruptured MCA aneurysms with hematomas, especially if the patient is too old, in a complicated condition to undergo craniotomy, is unwilling to undergo craniotomy, or is at a greater risk of bleeding 3 days after surgery. In addition, for some young women or special working population, the future work might be affected by surgical scar.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author/s.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the ethics committee of Taian Central Hospital. The

patients/participants provided their written informed consent to participate in this study. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

AUTHOR CONTRIBUTIONS

All authors listed have made a substantial, direct and intellectual contribution to the work, and approved it for publication.

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ORIGINAL RESEARCH
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Safety and Efficacy of Direct Angioplasty in Acute Basilar Artery Occlusion Due to Atherosclerosis

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Background and Purpose: Endovascular treatment (EVT) is one of the promising treatment options in patients with intracranial atherosclerotic disease (ICAD)-related basilar artery occlusion (BAO). In this study, we compared the safety and efficacy of direct angioplasty (DA) with stent-retriever thrombectomy (SRT) with or without rescue treatment in ICAD-related BAO.

Methods: We retrospectively evaluated 187 patients who underwent EVT for BAO from January 2012 to July 2018. We identified patients who underwent EVT due to ICAD-related BAO. Patients who accepted SRT with or without rescue treatment were classified into the SRT group. Patients treated with DA with or without stent placement were classified into DA group. Clinical and laboratory findings and outcomes were compared between groups.

Results: A total of 108 patients were enrolled, among them 77 underwent SRT and 31 underwent DA; 61 (79.2%) SRT group patients underwent angioplasty with or without stent placement. Compared with patients in the SRT group, those in the DA group experienced a significantly shorter procedure time [60 min (60–120 min) vs. 120 min (60–120 min); $p = 0.038$] and a lower number of device passes [2 passes (1–2 passes) vs. 3 passes (2–4 passes); $p < 0.001$]. No significant differences in balloon angioplasty (35.5 vs. 22.1%; $p = 0.150$), emergent stent placement (64.5 vs. 57.1%; $p = 0.481$), successful recanalization (93.5 vs. 85.7%; $p = 0.340$), embolization in distal or new territory (3.2 vs. 9.1%, $p = 0.314$), and reocclusion (22.6 vs. 9.1%; $p = 0.109$) among DA and SRT groups were found. Additionally, no differences in symptomatic intracranial hemorrhage incidence [adjusted odds ratio (OR), 0.74; 95% CI, 0.06–9.44; $p = 0.815$], functional independence (adjusted OR, 1.44; 95% CI, 0.50–4.16; $p = 0.497$), and mortality rate (adjusted OR, 0.36; 95% CI, 0.06–2.04; $p = 0.247$) were noted among groups.

Conclusions: In certain patients with ICAD-related BAO, DA may shorten procedure time and reduce required device passes compared to SRT. In this study, DA was retrospectively found to be of similar safety and efficacy as SRT.

Keywords: basilar artery occlusion, intracranial atherosclerotic disease, mechanical thrombectomy, stent-retriever thrombectomy, direct angioplasty

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INTRODUCTION

Acute ischemic stroke secondary to basilar artery occlusion (BAO) is associated with high rates of disability and mortality (1–3). The major pathomechanisms of BAO include *in situ* thrombosis over underlying intracranial atherosclerotic disease (ICAD) and embolization from distal sources (3). The proportion of ICAD-related BAO in prior studies was reported to be about 23–41% (3–6). Although the endovascular treatment vs. standard medical treatment for vertebrobasilar artery occlusion (BEST) study did not reveal any difference in favorable outcomes among patients who underwent endovascular therapy (EVT) compared to standard medical therapy alone, those findings may have been related to the early termination of the experiment due to cross-group recognition bias and poor patient compliance (7). Another recently published cohort study reported EVT to associate with a significantly better functional outcome than standard medical therapy among patients with acute BAO (8). Consequently, EVT remains among the most effective treatment options for such patients.

However, the best EVT strategy for patients with ICAD-related BAO remains controversial. The most frequently employed therapies include stent-retriever thrombectomy (SRT) and rescue treatment. The most commonly used rescue treatment is angioplasty (with or without stent placement); other rescue treatments include switching to another modality (e.g., from using a stent retriever to performing contact aspiration), intra-arterial thrombolysis (with alteplase or urokinase), and intravenous or administration of intra-arterial glycoprotein IIb/IIIa inhibitor (GPI) (9–11). However, several studies have reported rates of rescue treatment to be as high as 68.4–100% in the setting of ICAD-related BAO (6, 11, 12). Thus, in a selected patient population, superior treatment strategies are likely. The existing study highlights acute angioplasty as a technically feasible procedure. However, whether direct angioplasty (DA) for the treatment of ICAD-related BAO is as safe and efficacious as SRT remains unclear. In this study, we analyzed data from a clinical consecutive series of patients to assess both safety and efficacy profiles of DA in the treatment of acute ICAD-related BAO.

MATERIALS AND METHODS

Patient Enrollment

We retrospectively evaluated the clinical data of patients who were diagnosed with acute stroke attributable to BAO and who consecutively underwent EVT at Beijing Tiantan Hospital from January 2012 to July 2018. Inclusion criteria were as follows: (1) age ≥18 years old; (2) baseline initial National Institutes of Health Stroke Scale score (NIHSS) ≥4; (3) onset-to-puncture time <24 h; (4) a premorbid modified Rankin Scale (mRS) score ≤1; (5) no bilateral diffuse pontine ischemia on diffusion-weighted imaging (DWI); (6) success or failure of assessable recanalization; (7) diagnosis of acute posterior circulation stroke with ICAD-related BAO; and (8) no visible thrombi. A flow chart of the patient selection process is shown in **Figure 1**. Cases in which the etiology of BAO was attributed to non-atherosclerotic conditions (e.g., cardiogenic embolism, artery-to-artery embolism, dissection, vasculitis, or moyamoya disease) were excluded from this study. The institutional review board approved this study and waived the requirement of informed consent for the inclusion of the study based on the retrospective nature of its design.

Endovascular Treatment

Endovascular treatment (EVT) was performed under local or general anesthesia in all patients. If the patient had a history remarkable for basilar artery stenosis or probable ICAD-related BAO was suggested on non-invasive angiography or catheter angiography, no visible thrombi were noted on angiography, and either SRT or DA was performed at the discretion of the treating neurointerventionalist. When underlying severe ICAD of the basilar artery was revealed on follow-up angiography after failed SRT, three different rescue treatment strategies were available, if necessary, namely, emergent angioplasty/stenting, intra-arterial thrombolysis (using alteplase or urokinase), or intra-arterial tirofiban infusion. Details of treatment techniques concerning both SRT and rescue therapy were described previously (11, 13). The DA technique, however, differed from standard endovascular methods. Initially, a microcatheter (0.018 or 0.021 in) was navigated over a microwire (0.014 in) to a position just beyond the occlusion site. Combined microcatheter and guiding catheter angiography was performed to document the length of the occluded segment. The microcatheter was exchanged over an extra-support exchange length microwire; a balloon was subsequently advanced into the occlusion site and inflated 1–3 times at 30 s each time. If successful recanalization was not achieved or if reocclusion manifested due to severe residual stenosis, rescue stenting was performed. Prior to stent deployment, a heparin bolus (3,000 IU) was administered intravenously. The type of stent (balloon- or self-expanding) was selected on the basis of both vascular characteristics and lesion morphology. Either low-dose intravenous or intra-arterial tirofiban (0.25–0.5 mg) was bolus-injected and maintained for 24 h, or an oral loading dose of aspirin and clopidogrel (300 mg each) was administered to patients prior to stent placement, according to the preference of neurointerventionist. All patients with stents were given clopidogrel (75 mg/day) and aspirin (100 mg/day) for 3 months. **Figures 2**, **3** detail how SRT and DA were performed.

Outcome Measurement

The initiation of EVT was defined as the moment the needle punctured the common femoral artery. Procedure time was defined as the interval between the time of puncture and recanalization. Among both groups, all patients underwent non-enhanced CT or MRI scans immediately and 24 h after EVT. Follow-up vascular imaging was obtained in all patients at least

Abbreviations: BAO, basilar artery occlusion; DA, direct angioplasty; DWI, diffusion-weighted imaging; EVT, endovascular treatment; ELVO, emergent large vessel occlusion; IART, intra-arterial recanalization therapy; ICAD, intracranial atherosclerotic disease; MI, myocardial ischemia; MT, mechanical thrombectomy; mTICI, modified Thrombolysis in Cerebral Ischemic; SR, stent retriever; SRT, stent-retriever thrombectomy.

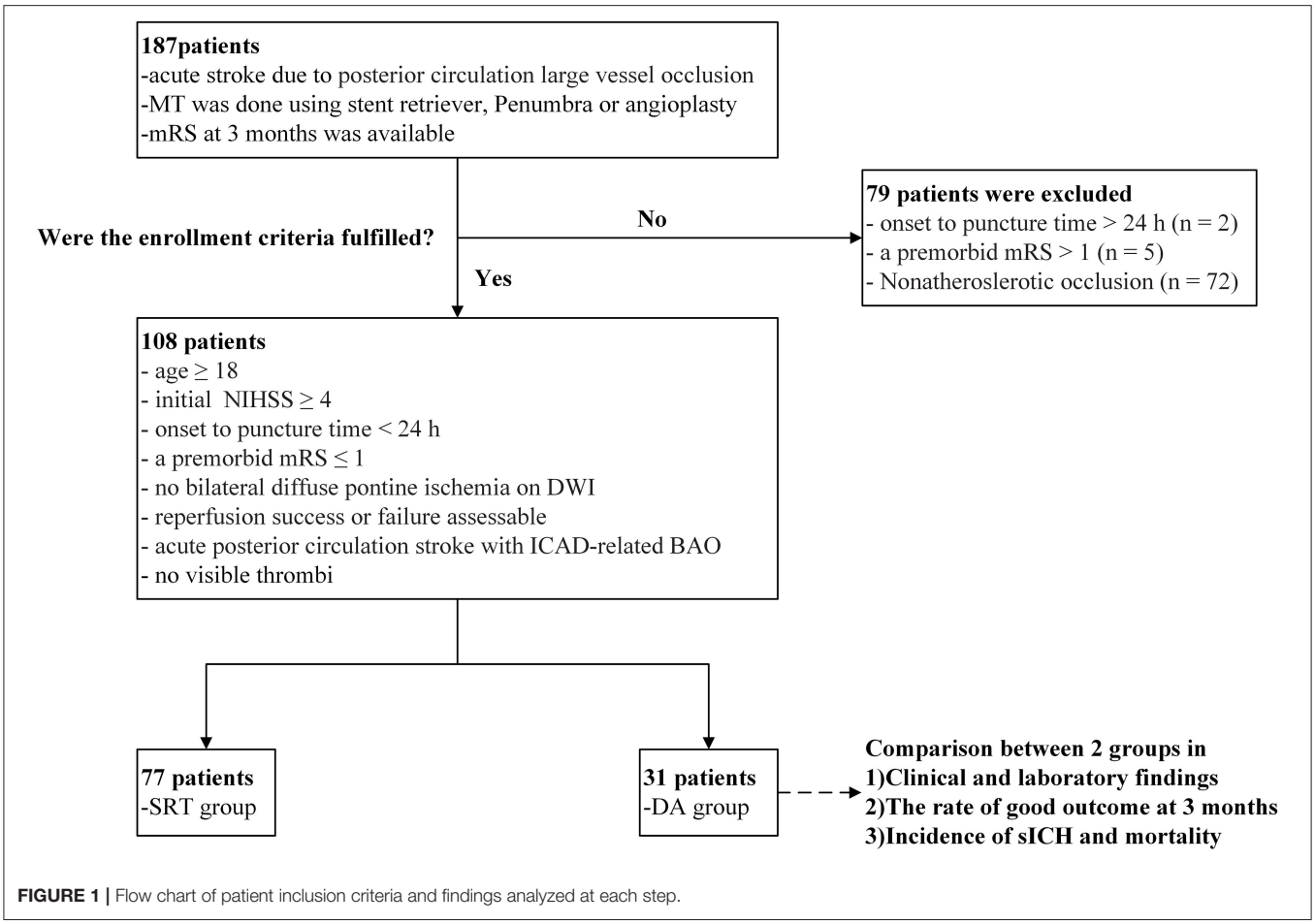

FIGURE 1 | Flow chart of patient inclusion criteria and findings analyzed at each step.

once via MRI, CT, or digital subtraction angiography 1–90 days after treatment. Symptomatic intracerebral hemorrhage (sICH) was assessed by post-treatment CT or MRI scan and classified as either hemorrhagic infarction or parenchymal hemorrhage based on European Cooperative Acute Stroke Study (ECASS III) criteria (14). Successful recanalization was defined as achieving modified thrombolysis in cerebral ischemia (mTICI) grade 2b or 3 as confirmed on angiogram at least 10 min after recanalization. All images were analyzed retrospectively by two neurologists blinded to both patient data and study protocol.

Neurological evaluation was performed by a stroke neurologist immediately after treatment and 24 h and 3 months after treatment, when there were clinical changes and prior to the discharge of the patient. Functional outcome was assessed by a stroke neurologist using the mRS score via telephone interview 3 months after treatment. Functional independence was defined as a mRS score ≤2.

Statistical Analysis

Baseline characteristics and treatment details were compared between DA and SRT groups. Successful recanalization, embolization in the new or distal territory, reocclusion, sICH, functional outcome at 3 months after treatment, and mortality were also compared between the groups. Multivariate analysis was performed with sICH, functional outcome, or mortality as dependent variables and with age, sex, baseline NIHSS, onset-to-puncture time, and tirofiban as covariates.

Medians (interquartile range: IQR) were used to summarize continuous data, and a two-sided *t-test* (for independent samples) or Mann-Whitney *U*-test was performed to detect differences between groups. Frequencies and percentages (%) were used to summarize binary data; between-group comparisons were performed using chi-squared or Fisher's exact tests, when appropriate.

All statistical analyses were performed with R (http://www.R-project.org, The R Foundation) and EmpowerStats (http://www.empowerstats.com, X&Y Solutions, Inc., Boston, MA). A $p < 0.05$ was considered significant.

RESULTS

Of the 108 patients, 77 (71.3%) patients underwent SRT therapy and 31 (28.7%) patients underwent DA therapy, respectively. In SRT group patients, stent-retriever devices used included the Solitaire AB/FR (74/77; 96.1%) and TREVO retriever (3/77, 3.9%). The Solitaire AB stent retriever was permanently detached in 16 patients, whereas Apollo and Wingspan stents were

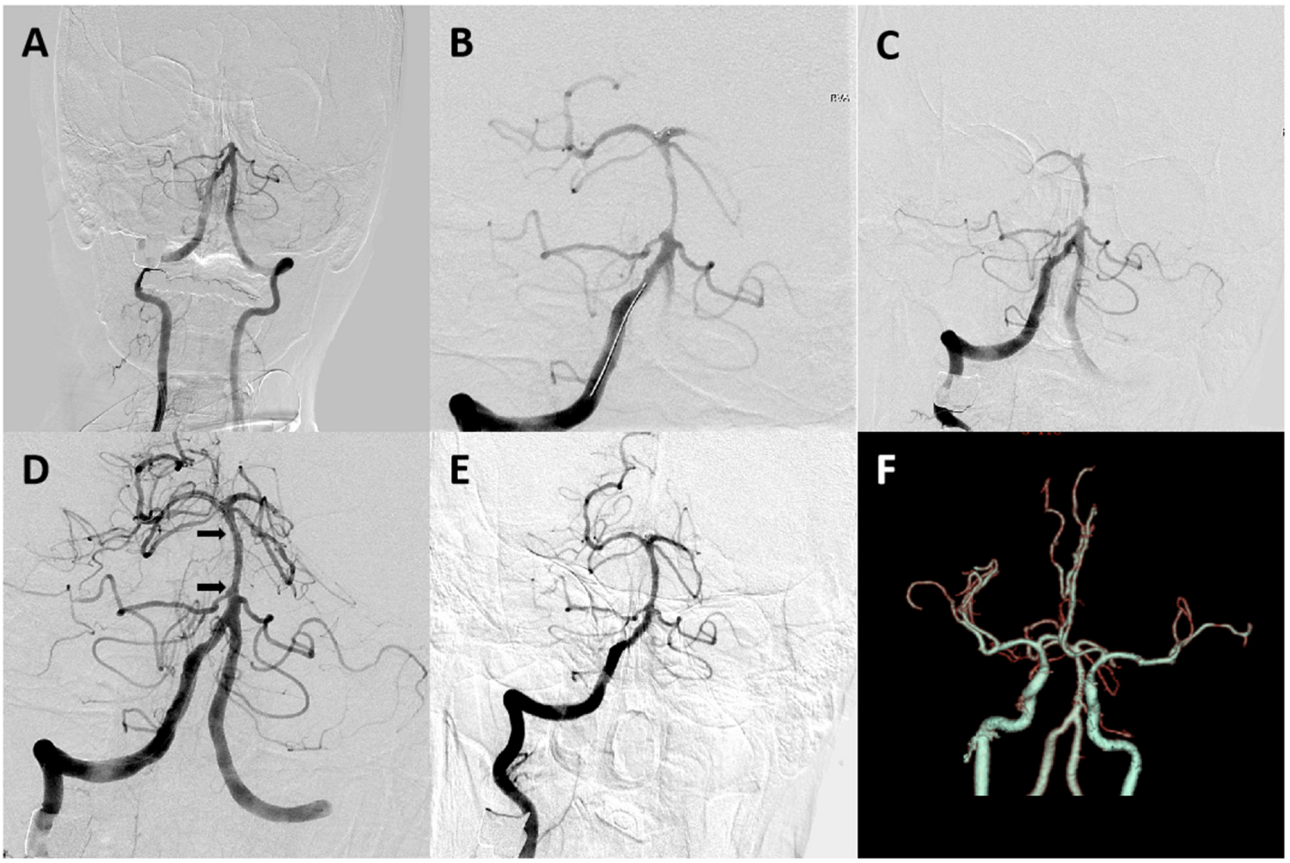

FIGURE 2 | A 62-year-old male patient with coronary artery disease for 20 years and hypertension for 3 years presented with disturbance of consciousness for 4 h. **(A)** Digital subtraction angiography revealed occlusion at the proximal basilar artery segment. **(B,C)** Angiogram obtained after one Solitaire AB pass revealed severe underlying atherosclerotic stenosis of the proximal basilar artery segment. **(D,E)** Digital subtraction angiography after stent placement revealed good perfusion with fixed, focal basilar artery stenosis. Arrows indicate proximal and distal ends of the Apollo stent. **(F)** CT angiography on 24-h follow-up revealed a patent basilar artery. The patient had a modified Rankin scale (mRS) score of 3 on a 3-month follow-up.

alternatively separately used in 24 and 16 patients, respectively. In the DA group, 11 (35.5%) patients underwent balloon angioplasty alone, whereas 20 (64.5%) patients underwent stent placement. Types of stents used in DA group patients were Wingspan (9), Apollo (7), and Enterprise (4).

As shown in **Table 1**, no differences in clinical and laboratory findings except for age, baseline NIHSS score, and mechanical thrombectomy (MT) plus tirofiban use were found. Compared with patients in the SRT group, those in the DA group experienced a significantly shorter procedure time [60 min (60–120 min) vs. 120 min (60–120 min); $p = 0.038$] and a lower number of device passes [2 passes (1–2 passes) vs. 3 passes (2–4 passes); $p < 0.001$]. No significant differences in balloon angioplasty (35.5 vs. 22.1%; $p = 0.150$), emergent stent placement (64.5 vs. 57.1%; $p = 0.481$), successful recanalization (93.5 vs. 85.7%; $p = 0.340$), embolization in distal or new territory (3.2 vs. 9.1%, $p = 0.314$), and reocclusion (22.6 vs. 9.1%; $p = 0.109$) among DA and SRT groups were found. Additionally, no differences in symptomatic intracranial hemorrhage incidence [adjusted odds ratio (OR), 0.74; 95% CI, 0.06–9.44; $p = 0.815$], functional independence (adjusted OR, 1.44; 95% CI, 0.50–4.16; $p = 0.497$), and mortality rate (adjusted OR, 0.36; 95% CI, 0.06–2.04; $p = 0.247$) were noted among groups (**Table 2**). The 90-day comparison of mRS score shift among groups is detailed in **Figure 4**.

DISCUSSION

In this study, we found that patients who underwent DA experienced significantly shorter procedure time (60 vs. 120 min; $p = 0.038$) and fewer device passes (2 vs. 3; $p < 0.001$) than those who underwent SRT. No differences in sICH and favorable outcomes between the groups were found.

The estimated incidence of ICAD varied from 8.3 to 60%, depending on racial and geographical factors (15–17). Few studies have investigated the incidence of underlying ICAD in patients presenting with emergent large vessel occlusion (ELVO), especially with the posterior circulation that is affected. Compared to other stroke etiologies such as embolic occlusions, ICAD is less well-understood by physicians, and prior randomized trials have mostly studied anterior circulatory

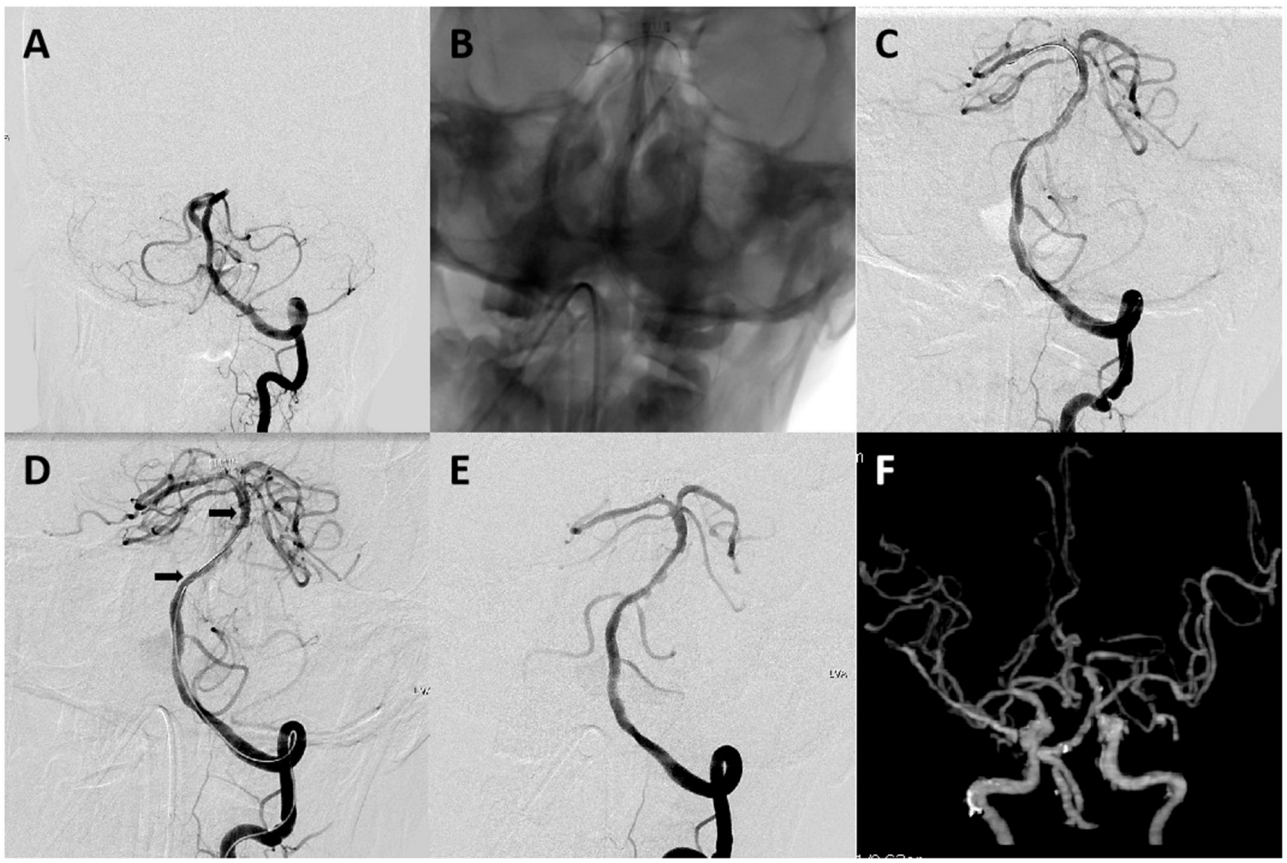

FIGURE 3 | A 64-year-old male patient with acute stroke due to acute basilar artery occlusion. **(A)** Left vertebral artery angiogram revealed occlusion at the proximal basilar artery. **(B)** A 2 mm × 15 mm balloon (gateway) was deployed and inflated in the occluded segment. **(C–E)** Left vertebral artery angiogram obtained after intracranial angioplasty and stent placement revealed complete basilar artery recanalization and good distal perfusion. Arrows indicate proximal and distal ends of the Enterprise stent (4 mm × 22 mm). **(F)** CT angiography on 24-h follow-up revealed a patent basilar artery. The patient had a mRS score of 1 on a 3-month follow-up.

occlusion in Western populations. The proportion of ICAD-related BAO was reported to be 23–41% (3–6). Recent studies reported that ICAD was responsible for ∼12–30.3% of patients with acute LVO who underwent endovascular thrombectomy in East Asia (9, 10). Severe ICAD is a major cause of treatment failure during thrombectomy in patients with acute LVO (18–20). Therefore, analyzing EVT strategies for ICAD-related BAO is highly warranted.

The treatment of patients with ICAD-related BAO with EVT typically involves two steps: initially, the performance of SRT to identify underlying culprit stenosis and, subsequently, administering rescue treatment to both remove the underlying stenosis and prevent reocclusion (20, 21). Rescue treatments (angioplasty with or without stenting) were reported to be essential for achieving successful recanalization in such patients in the setting of failed SRT (6, 9, 18, 20–22). In this study, 79.2% of SRT group patients ($n = 61$) underwent angioplasty with or without stenting as a rescue treatment. The main disadvantage of this strategy, however, is instant or early reocclusion of the target vessel due to severe stenosis (18, 23). Importantly, switching to another technique (i.e., from SRT to rescue treatments) after SRT failure leads to delays, and retrieval of stent retrievers distal to the stenosis frequently damages endothelium or the atherosclerotic plaque itself, thereby leading to an increased risk of acute thrombosis and reocclusion. This is likely because the use of a stent retriever predisposes to increased platelet activation and vessel dissection. These phenomena partly explain why the rate of GPI used among SRT patients was higher than that among DA patients (87.0 vs. 64.5%, $p = 0.014$). Complicated therapeutic strategies thus lead to longer procedure duration and poorer outcomes.

The advantages of emergent angioplasty are well-appreciated in the setting of acute myocardial ischemia. Approximately two decades ago, stenting began to replace angioplasty as the primary method of revascularization for the treatment of acute coronary syndrome (24–26). Although substantial differences in the typical etiology and vascular anatomy of stroke as compared to myocardial infarction exist, the pathogenesis of ICAD-related LVO is similar to that of myocardial infarction. Building on experience in treating and knowledge of the coronary intervention, the concept of angioplasty for acute stroke warrants serious consideration. One prospective study

TABLE 1 | Comparison of baseline data and treatment procedure outcomes among SRT and DA groups.

Baseline characteristics, treatment procedures, and outcomes	All ($n = 108$)	SRT group ($n = 77$)	DA group ($n = 31$)	*P*-Value
Age, median (IQR), years	60 (53–64)	59 (52–63)	64 (55–71)	0.013
Male sex	94 (87.0)	67 (87.0)	27 (87.1)	>0.999
NIHSS score, median (IQR)	22 (12–34)	28 (13–35)	14 (7–29)	0.002
Pc-ASPECTS, median (IQR)	7 (5–8)	7 (5–8)	7 (6–8)	0.326
Pons-Midbrain Index, median (IQR)	2 (0–3)	2 (0–4)	2 (1–3)	0.475
Onset-to-puncture time, median (IQR), min	420 (300–600)	420 (300–570)	420 (300–600)	0.418
Medical history				
Hypertension	82 (75.9)	58 (75.3)	24 (77.4)	>0.999
Diabetes mellitus	27 (25.0)	18 (23.4)	9 (29.0)	0.625
Dyslipidemia	24 (22.2)	15 (19.5)	9 (29.0)	0.312
Current smoking	43 (39.8)	33 (42.9)	10 (32.3)	0.309
Coronary heart disease	8 (7.4)	4 (5.2)	4 (12.9)	0.223
Previous ischemic stroke	24 (22.2)	16 (20.8)	8 (25.8)	0.613
Site of occlusion				
Proximal BA	74 (68.5)	55 (71.4)	19 (61.3)	
Middle BA	33 (30.6)	21 (27.3)	12 (38.7)	0.541
Distal BA	1 (0.9)	1 (1.3)	0 (0.0)	
Good collateral (ASITN/SIR = 3–4)	11 (10.2)	7 (9.1)	4 (12.9)	0.726
Standard IV t-PA preoperative	21 (19.4)	15 (19.5)	6 (19.4)	> 0.999
General anesthesia	92 (85.2)	67 (87.0)	25 (80.6)	0.388
MT procedure				
Balloon angioplasty	28 (25.9)	17 (22.1)	11 (35.5)	0.150
Emergent stent placement	64 (59.3)	44 (57.1)	20 (64.5)	0.481
IA tPA or Urokinase	21 (19.4)	12 (15.6)	9 (29.0)	0.177
IV or IA tirofiban	87 (80.6)	67 (87.0)	20 (64.5)	0.014
Treatment outcome				
Procedural time, median (IQR), min	90 (60–120)	120 (60–120)	60 (60–120)	0.038
Number of device passes, median (IQR)	2 (2–3)	3 (2–4)	2 (1–2)	< 0.001
Successful recanalization (mTICI 2b-3)	95 (88.0)	66 (85.7)	29 (93.5)	0.340
Distal or new territory embolization	8 (7.4)	7 (9.1)	1 (3.2)	0.314
Reocclusion	14 (13.0)	7 (9.1)	7 (22.6)	0.079

Numbers are shown as median (IQR, interquartile range) or percentage (%). ASITN/SIR, American Society of Interventional and Therapeutic Neuroradiology/Society of Interventional Radiology; BA, basilar artery; DA, direct angioplasty; IA, intra-arterial; NIHSS, National Institute of Health Stroke Scale; IV, intravenous; mTICI, modified thrombolysis in cerebral ischemia; pc-ASPECTS, posterior circulation Alberta Stroke Program Early CT Score; SRT, stent-retriever thrombectomy; tPA, tissue-type plasminogen activator.

TABLE 2 | Multivariate regression analysis of effects of DA on sICH, functional outcomes and mortality.

Outcome	SRT group	DA group	*P*-value	OR (95% CI)	Adjusted *P*-value	Adjusted OR (95% CI)
sICH*	4 (5.2)	1 (3.2)	0.663	0.61 (0.07–5.67)	0.815	0.74 (0.06–9.44)
3-mo mRS, 0–2*	22 (28.6)	14 (45.2)	0.101	2.06 (0.87–4.88)	0.497	1.44 (0.50–4.16)
3-mo mortality*	17 (22.1)	2 (6.5)	0.070	0.24 (0.05–1.13)	0.247	0.36 (0.06–2.04)

CI, confidence interval; DA, direct angioplasty; mRS, modified Rankin Scale; OR, odds ratio; sICH, symptomatic intracerebral hemorrhage; SRT, stent-retriever thrombectomy.
**Adjusted for age, sex, baseline NIHSS, onset-to-puncture time, and tirofiban use.*

demonstrated that DA with stenting resulted in a 100% recanalization rate, although the study did not distinguish the mechanism of LVO (27). In a prospective registry [the Acute Basilar Artery Occlusion Study (BASILAR) study], a total of 10.2% (66/643) of subjects with BAO received DA as the first-choice treatment in the EVT group (8). In this study, we propose consideration of DA as a safe and technically feasible treatment strategy for a highly select group of patients with ICAD-related BAO.

In addition, a standardized periprocedural antiplatelet regimen for angioplasty with or without stenting due to ICAD in the setting of EVT of acute BAO was needed. Unfortunately, there are little data and a lack of consensus up to now. In a Delphi study, an oral loading dose of aspirin in combination

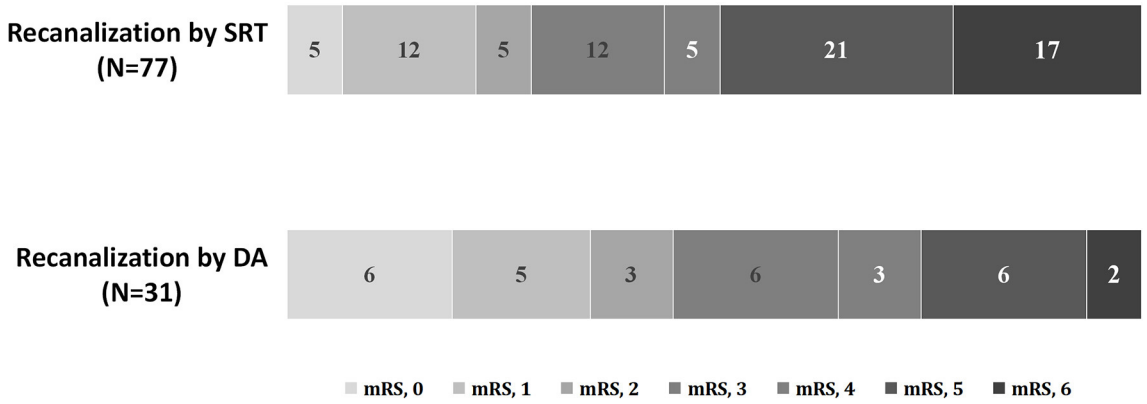

FIGURE 4 | Distribution of 90-day mRS scores of patients with ICAD-related BAO. mRS, modified Rankin Scale; BAO, basilar artery occlusion; ICAD, intracranial atherosclerotic disease.

with a P2Y12 inhibitor was suggested if a stent deployed during EVT (28). Recent studies indicated a more promising role of tirofiban as the periprocedural antiplatelet treatment of EVT (29, 30). Baek et al. reported that intravenous tirofiban was associated with a low reocclusion rate after emergent angioplasty with or without stenting in patients with ICAD-related large vessel occlusion stroke (31). In this study, the reocclusion rate in the SRT group was lower, which might be related to a higher percentage of patients receiving intravenous or intra-arterial tirofiban. Intriguingly, although the rate of reocclusion was higher in subjects treated with DA, the functional outcome was much better. Fewer pass numbers and shorter procedure time may be the underlying reason for this discrepancy.

Unless ICAD-related BAO can be diagnosed prior to MT, DA will remain as one of several available treatment options rather than a first-line strategy. Lin et al. found that opacification of the basilar tip, absence of convex edge, and long occlusion length on preprocedural CT angiography might be helpful in the diagnosis of ICAD-related BAO (32). Lee et al. reported the occluded vascular segment and the presence or absence of bilateral thalamic infarction to be helpful for predicting ICAD-related BAO (6). However, no effective method for identifying the etiology of BAO prior to MT has been proposed up to now. As such, future studies devoted to identifying ICAD-related BAO will likely provide greater treatment options in this subgroup of patients. Nevertheless, there is currently no valid reason to withhold DA from patients with a history remarkable for basilar artery stenosis and low clot burden.

LIMITATIONS

This study had several limitations, including those inherent in a retrospective and uncontrolled study design. The selection of patients for stent placement depended on the preference of neurointerventionist. In particular, opinions concerning permanent stenting for failed SRT or DA treatment differed among the six involved physicians. In addition, this study was single centered and studied a relatively small sample size. Moreover, a special caution was needed when interpreting this result because all analyses were considered exploratory, especially the rate of functional outcome for 3 months in the DA group was much higher than that in the SRT group. A randomized, prospective trial is required to adequately assess the clinical efficacy of treatment modalities. Finally, angiograms were not reviewed by an independent core laboratory team blinded to clinical information.

CONCLUSIONS

In certain patients with ICAD-related BAO, DA shortens procedure time and reduces device passes as compared to SRT. In this retrospective study, we found DA to be of similar safety and efficacy in a select group of patients as compared to SRT.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by IRB of Beijing Tiantan Hospital, Capital Medical University. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

AUTHOR CONTRIBUTIONS

DM and ZM designed, led the study and had full access to all of the data in the study, and took responsibility for the

integrity of the data and the accuracy of the data analysis. GM prepared the first draft of the report. XT did statistical analyses. All authors except GM and BJ participated in patient enrolment and collection of data. All authors critically reviewed the report and approved the final version.

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Safety and Efficacy of Coils in Conjunction With the Pipeline Flex Embolization Device for the Treatment of Cerebral Aneurysms

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Background: Flow diverters (FD) have shown promising results in the treatment of intracranial aneurysms (IAs). However, there is still controversy whether pipeline flex embolization device (PED flex)-assisted coils can facilitate the curing of aneurysms. Our aim was to assess the safety and effectiveness of PED flex adjunctive with coils (PED flex + coil) in the treatment of IAs.

Method: Patients who underwent PED flex treatment in combination with coiling between January 2018 and June 2020 were included in this study. The clinical and radiographic characteristics before and after treatments were retrospectively evaluated. The study cohort comprised of 125 patients with 140 IAs, which was subdivided into two subgroups: one group included patients treated only through PED alone, and the other group included patients treated through PED flex adjunctive with coil. Patient baseline characteristics, aneurysm characteristics, treatment-related factors, and outcomes were analyzed to determine the effectiveness of both techniques.

Results: Aneurysms in the PED flex + coil group were larger (10.0 ± 5.8 mm, $P < 0.001$) and wider (7.2 ± 4.6 mm, $P = 0.002$) compared with those in the PED flex group. There was no statistical difference in the perioperative complication rate between the two groups. The overall complete occlusion rate was 75.7% at 6.2 months, with 71.7% at 6.2 ± 1.7 months in the PED flex group and 85.4% at 6.2 ± 1.8 months in the PED flex + coil group, respectively. A higher percentage of satisfactory angiography results was found in the PED flex + coil group during follow-up (92.7 vs. 78.8%, $P = 0.047$).

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Conclusion: PED flex placement with adjunctive coil embolization represents a safe alternative option for the treatment of IAs. In these cases, coil embolization increases the occlusion rate in PED flex-treated patients without increasing the periprocedural complications.

Keywords: cerebral aneurysms, flow diverter (FD), coil, occlusion, safety and efficacy

INTRODUCTION

Flow diversion (FD) techniques, such as the pipeline embolization device (PED), have been largely accepted as important treatment options for large and complex intracranial aneurysms (IAs) (1–3). Similar to other flow diversions, PED represents a novel concept of curing aneurysms by redirecting the blood flow and reconstructing the parent vessel. Compared with conventional endovascular techniques (coiling or stenting), PED provides better neck reconstruction and contributes to complete occlusions (1, 4–6). Unfortunately, the rate of hemorrhagic complications caused by PED is reported to be up to 4%, especially among patients with large and giant aneurysms (4, 7), which may bring life-threatening disasters to the patients.

The underlying mechanisms leading to hemorrhage after PED deployment is complex and unclear yet (2, 8–10). Adjunctive coil embolization is recommended with PED to protect the aneurysm dome (2, 11). However, the safety and efficacy of this endovascular technique has not been fully defined. The pipeline flex embolization device (PED flex), a second-generation of PED, has been clinically available and widely adopted in the treatment of aneurysms recently. Thus, the aim of our study was to assess the safety and efficacy of the PED flex together with coil embolization in the treatment of IAs.

MATERIALS AND METHODS

Study Design and Patient Selection

This study was conducted by our institution, and the ethics committee of the institute approved the study protocol. A consecutive series of patients with intracranial aneurysms treated by PED flex has been maintained in our center. Medical records from January 2018 to June 2020 were retrospectively reviewed to collect the clinical and radiologic data of patients.

Patients whose treatment included PED flex were enrolled in our study. Routine angiographic follow-up was performed post-treatment. The exclusion criteria were as follows: (1) patients who were lost in the follow-up time, which made the clinical data insufficient, (2) patients who were followed up in other hospitals, and (3) patients who were treated with any other stent when the PED flex was deployed at the same time. The study cohort was subdivided into two subgroups: one group included patients treated only through PED alone, and the other group included patients treated through PED flex adjunctive with coil.

Treatment Strategy

Informed consents were provided by all patients or their relatives before endovascular treatment. All procedures were conducted under general anesthesia. Premedication usually consisted of dual antiplatelet management of aspirin (100 mg) and clopidogrel (75 mg) once a day for 5–7 days before the procedure. The antiplatelet resistance test was performed in all patients 1 day prior to the procedure. Those who underwent endovascular treatment on emergencies received a loading dose of tirofiban (10 m) prior to the endovascular procedure, which was maintained with a dosage of 6–8 ml/h intraoperatively. An intravenous heparin infusion was taken continuously in case of the potential thromboembolic events during the operation.

PED flex was selected based on the diameter of the parent vessel and the morphological characteristics of the aneurysm. In detail, the aneurysm was large in size (>10 mm), with significant morphological irregularity, or with a wide neck (>4 mm). To maximize flow diversion, we attempted to match the size of the nominal PED flex diameter relative to the diameter of the parent vessel and the landing zone. The decision of whether to use coils in combination with PED flex was considered seriously and decided by the discretion of the interventionists in specific scenarios. In detail, (1) when an aneurysm ruptured or had a high risk of precursory rupture due to the irregular morphological features—daughter aneurysms, for example; (2) when the aneurysm was large (>10 mm) or giant (>25 mm); and (3) when the patients had obvious clinical symptoms, such as serious headache or oculomotor nerve paralysis.

All procedures were performed *via* a standard transfemoral approach. A triaxial system with a guiding catheter, an intermediate catheter, and a marksman microcatheter was used to deliver the PED flex. After positioning the microcatheter distal to the aneurysmal neck, a second microcatheter paralleling to the intermediate catheter was navigated into the aneurysmal sac to subsequently deploy coils. According to previous reports, dense coil packing could cause a mass effect on the PED and result in device thrombosis (11, 12). Thus, we placed limited coils to make loose coiling embolization after the deployment of PED flex.

After the completion of endovascular treatment, all patients were kept on dual-antiplatelet medication for at least 6 months. Subsequently, the regimen was changed to aspirin monotherapy, which was continued for their whole life. Raymond classification was used to assess the angiographic results immediately after treatment and during follow-up (13). The radiological outcomes were classified as satisfactory (Raymond I and II) and poor (Raymond III).

Statistical Analysis

Statistical analysis was performed with statistical software (SPSS v19.0; IBM, Chicago, IL, USA). One-sample Kolmogorov–Smirnov test was used to test the normal distribution for

TABLE 1 | Demographic and clinical characteristics of patients.

	PED flex ($n = 99$)	PED flex+coil ($n = 41$)	*P*
Age (mean ± SD, year)	53.3 ± 9.5	53.2 ± 10.0	0.068
Female sex (*n*, %)	73 (73.7%)	32 (78.0%)	0.592
Smoking (*n*, %)	13 (13.1%)	6 (14.6%)	0.813
Drinking (*n*, %)	11 (11.1%)	4 (9.8%)	1
Basic disease (*n*, %)			
Hypertension	46 (46.5%)	20 (48.8%)	0.803
Diabetes	10 (10.1%)	3 (7.3%)	0.606
Hyperlipidemia	11 (11.1%)	6 (14.6%)	0.767
Symptom (*n*, %)			
Asymptomatic	31 (31.3%)	11 (26.8%)	0.598
Dizziness	27 (27.3%)	10 (24.4%)	0.725
Headache	24 (24.2%)	13 (31.7%)	0.362
Other	17 (17.2%)	7 (17.1%)	0.825

TABLE 2 | Aneurysm characteristics.

	PED flex ($n = 99$)	PED flex+coil ($n = 41$)	*P*
Size (mean ± SD, mm)	6.0 ± 4.3	10.0 ± 5.8	<0.001*
Width (mean ± SD, mm)	5.1 ± 3.4	7.2 ± 4.6	0.002*
Anterior circulation (*n*, %)	89 (89.9%)	37 (90.2%)	1
ICA	84	36	1
MCA	2	1	
ACA	3	0	
With side branch	7 (7.1%)	3 (7.3%)	
Rupture (*n*, %)	4 (4.0%)	4 (9.8%)	0.355

ICA, internal carotid artery; MCA, middle cerebral artery; ACA, anterior cerebral artery.
**P < 0.05.*

TABLE 3 | Treatment-related factors.

	PED flex ($n = 99$)	PED flex+coil ($n = 41$)	*P*
Periprocedural complication (*n*, %)	1 (1.0%)	2 (4.9%)	0.205
Initial angiography (*n*, %)			<0.001*
Complete occlusion	0(0%)	15 (36.6%)	
Residual neck	0(0%)	2 (4.9%)	
Residual aneurysm	99 (100%)	24 (58.5%)	
Follow-up angiography (*n*, %)			0.137
Complete occlusion	71 (71.7%)	35 (85.4%)	
Residual neck	7 (7.1%)	3 (7.3%)	
Residual aneurysm	21 (21.1%)	3 (7.3%)	
Satisfactory angiography results	78 (78.8%)	38 (92.7%)	0.047*
Follow-up time (mean ± SD, month)	6.2 ± 1.7	6.2 ± 1.8	0.998

**P < 0.05.*

continuous variables, followed by independent-samples *t*-test of approximately normally distributed data. The Mann–Whitney *U*-test was used to compare non-parametric data, while χ^2 test was used for categorical variables. The categorical variables were presented as frequencies, and the continuous variables were presented as mean ± SD or median (interquartile range). A $P < 0.05$ was considered statistically significant.

RESULTS

A total of 200 patients were treated with PED flex in our institute from January 2018 to June 2020. We excluded a total of 75 patients, eight of them due to loss of follow-up and the remaining 67 patients due to follow-up in other hospitals. Therefore, our patient cohort included 125 patients with 140 IAs that underwent PED flex placement with/without adjunctive coiling. Of these, 41 aneurysms were treated by PED flex plus coils (PED flex + coil group), while the other 99 aneurysms were treated with PED flex alone (PED flex group).

Baseline Characteristics of Patients

The patient demographic and clinical characteristics are shown in **Table 1**. There was no statistically significant difference between the PED flex group and the PED flex + coil group in age, sex, smoking, drinking, basic diseases, and clinical symptoms ($P > 0.05$, **Table 1**). The most frequent clinical presentation in PED flex + coil group patients was headache (13/41, 31.7%), whereas the majority of the PED flex group patients were asymptomatic (**Table 1**).

Aneurysm Characteristics

The mean aneurysm size was 6.0 ± 4.3 mm in the PED flex group, with a mean width of 5.1 ± 3.4 mm, and 10.0 ± 5.8 mm in the PED flex + coil group, with a mean width of 7.2 ± 4.6 mm. A larger size of aneurysms was observed in the PED flex + coil group than that in the PED group (10.0 ± 5.8 vs. 6.0 ± 4.3 mm, $P < 0.001$, **Table 2**). Aneurysms in the PED flex +coil group were likewise wider than those in the PED flex group (7.2 ± 4.6 vs. 5.1 ± 3.4 mm, $P = 0.002$, **Table 2**). In both groups, the majority of aneurysms were located in the anterior circulation, which had no statistical significance (89.9 vs. 90.2%, $P > 0.05$, **Table 2**). Additionally, the number of aneurysms with a side branch coming from the sac in the two groups was similar (7.1 vs. 7.3%, $P > 0.05$, **Table 2**). A higher proportion of ruptured aneurysms was observed in the PED flex + coil group, although there was no statistical difference between the two groups ($P = 0.355$, **Table 2**).

Treatment-Related Factors

In our cohort, PED flex deployment and coil embolization were successful in all patients. The periprocedural complications, angiographic results of initial postoperative and follow-up, and intervals of follow-up are summarized in **Table 3**.

One periprocedural complication occurred in a patient who received PED flex, while two complications were observed in subjects who received additional coiling. All complications were considered ischemic events, which were mainly caused by the poor wall apposition of the PED flex that resulted in significant

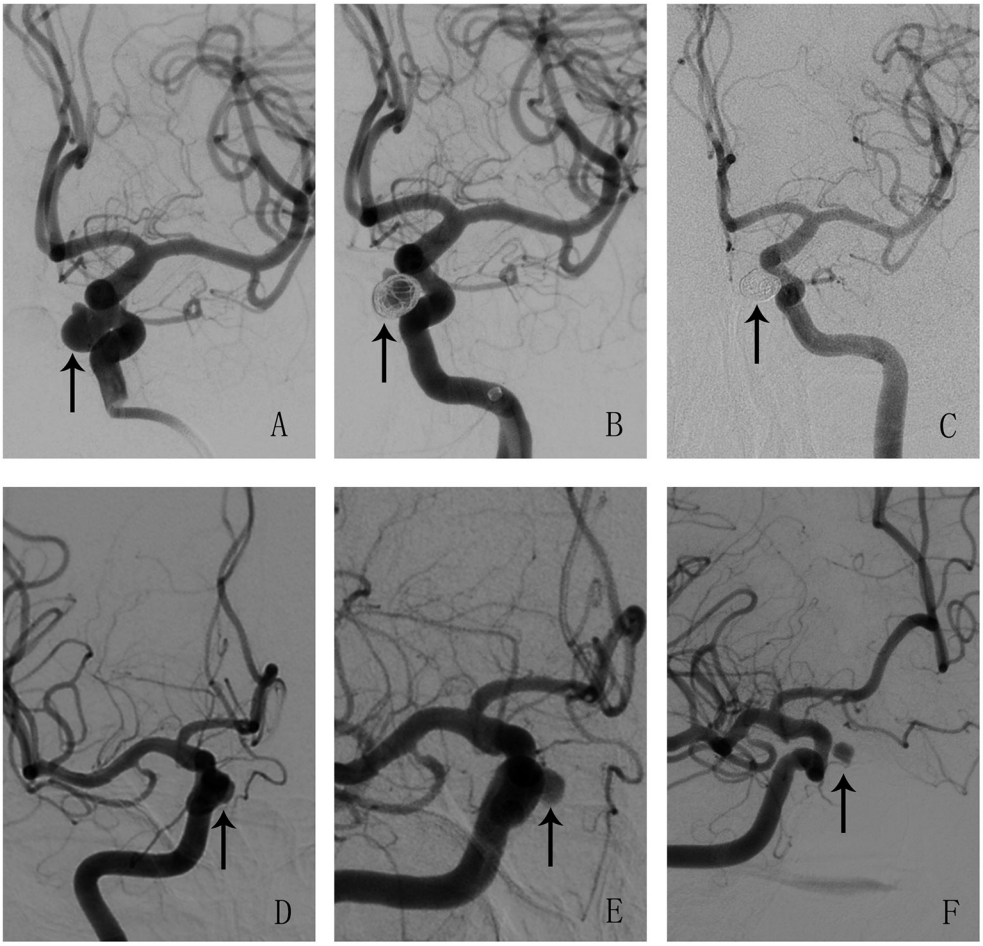

FIGURE 1 | Illustrations of angiographic results in a case treated by pipeline flex embolization device (PED flex) adjunctive with coils (**A–C**) and a case treated by PED flex alone (**D–F**). Aneurysms were pointed out with arrows. (**A–C**) An aneurysm treated by PED + coil at pre-treatment, post-treatment, and follow-up. The angiography results showed that the aneurysm was cured completely after operation at 6 months. (**D–F**) An aneurysm treated by PED flex at pre-treatment, post-treatment, and follow-up. This aneurysm was incompletely occluded and was classified as Raymond III at 6 months.

in-stent stenosis rather than the coil embolization technique itself. The percentages of perioperative complications in both groups were statistically comparable (1.0 vs. 4.9%, $P = 0.205$, **Table 3**). No patient suffered adverse events during the follow-up period.

In the PED flex group, all aneurysms presented remarkable stagnation, graded as Raymond III, as indicated from the immediate postoperative angiograms. Conversely, patients who received PED flex + coil had better immediate angiographic results, with 15 cases (36.6%) showing complete occlusion (Raymond I) and two cases (4.9%) showing residual aneurysms (Raymond II). Overall, the initial angiographic results of the two groups were statistically different ($P < 0.001$, **Table 3**). The mean follow-up interval after surgery was 6.2 ± 1.7 months for the PED flex group and 6.2 ± 1.8 months for the PED flex + coil group, respectively. The total complete occlusion rate was 75.7% during follow-up. Aneurysms treated by PED + coil could be completely occluded nearly 6 months after surgery, while the aneurysms remained Raymond III when treated by PED flex alone (**Figure 1**). A higher rate of complete occlusion was achieved in the PED flex + coil group at follow-up (85.4 vs. 71.7%, respectively, **Table 3**). However, the whole angiography result classifications on follow-up at 6.2 months were comparable ($P = 0.137$, **Table 3**). Of note is that a higher percentage of aneurysms presented with satisfactory angiography results (Raymond class I and II) in the PED flex + coil group during follow-up (92.7 vs. 78.8%, $P = 0.047$, **Table 3**).

DISCUSSION

The flow diverter is a milestone in the treatment of IAs despite unpredictable complications. To prevent undesired hemorrhagic outcomes, coils in conjunction with PED became an alternative treatment option gradually (12, 14). However, before being widely accepted and used as a

treatment modality, this technique therapy requires an understanding of its benefits and potential disadvantages. Therefore, we report our single-center experience of the concomitant use of PED flex in adjunction with coil embolization and determine its feasibility, safety, and effectiveness by comparing to PED flex embolization as standalone technique.

Our data demonstrated that aneurysms treated by PED flex-assisted coils tend to be larger and wider. For these aneurysms, using PED flex alone may need a longer time to achieve complete occlusion, posing a significant risk of rupture to the patients (15). As shown in our cohort, the concurrent use of coils is clearly beneficial and safe. We did not experience fatal complications such as hemorrhage or delayed aneurysmal rupture, with no statistical difference of periprocedural complication rate within both treatment groups. To our knowledge, there is no consensus on the indications for coils adjunctive with PED flex, and the underlying mechanism of coils sparing aneurysms from rupture in PED flex-deployed cases remains unknown. Studies based on computational flow dynamics have quantitatively illustrated the critical effect of intra-aneurysmal pressure and flow velocities on the prognosis of the aneurysm (16, 17). It has been reported that the mere application of FD may only reduce relatively low the amplitude and pressure despite significant flow velocity changes inside the aneurysms (16, 18, 19). Thus, a combination of PED flex and coils may become a suggestive way of modifying the blood velocities and pressures distinctly at the same time. Additionally, the use of coils may also elicit a biological effect. An animal study conducted by Evan et al. demonstrated that concomitant coiling could reduce the level of active-MMP9 in FD-treated aneurysms by blocking the activation of pro-MMP9 (20). MMPs, whose expression was regulated by the adjunctive use of coils, played key roles in delayed ruptures after FD deployment. Moreover, the effective use of PED flex along with coils could avoid the technical difficulty and challenge of deploying multiple PEDs, lowering the risk of potential ischemic events (4, 15, 21).

It is worth to mention that all the periprocedural complications in our cohort are non-hemorrhagic events, which may correlate with thrombosis closely. Intravascular deployment of PED stimulates platelet aggregations as soon as it is exposed to the blood. As reported, the wall apposition of PED and the management of antiplatelets are of great value for preventing thrombotic events (11, 12, 21, 22). Therefore, in addition to the intraprocedural anticoagulation, prophylactic antiplatelet therapy should be executed strictly before and after the procedure. Excitingly, coil packing following PED flex is technically easy to achieve, and there was no technique-related complication regarding coiling in our study.

Similar to previous studies, our present results demonstrated that coiling in conjunction with PED could achieve a higher occlusion rate for certain IAs (11, 23, 24). It is known that coils were initially designed to pack the aneurysm tightly, thereby preventing blood from flowing into the aneurysm and protecting the aneurysm from growing. Multiple mechanisms account for the improved occlusion results by the combination of coils and PED flex, mainly including hemodynamic changes and thrombosis. One possibility is that the coils contribute to the thrombosis inside the aneurysm, acting as a foreign body material and activating inflammatory responses (25–27). Another possibility is that the flow hemodynamics, especially velocities and wall shear stress, which are changed profoundly with the implantation of coils, is conducive to neointima formation on the aneurysm orifice (16, 27).

Overall, coils adjunctive with PED flex are complementary, rather than competing, for cerebral aneurysm treatment (11). On the one hand, coils can serve as an essential architecture to protect the PED flex from herniating into the aneurysm, thus avoiding shortening or poor wall apposition of the flow diverter. On the other hand, PED flex acts as a scaffold to prevent the coils from prolapsing into the parent vessel. Although randomized controlled trials comparing PED flex alone and PED flex adjunction with coiling are not available yet, coils in conjunction with PED flex are likely to play a dominant role in improving the occlusion rate of aneurysms.

CONCLUSION

PED flex placement with adjunctive coil embolization represents a safe alternative option for the treatment of IAs. In these cases, coil embolization increases the occlusion rate at an early stage without increasing the periprocedural complications. Further clinical and basic studies are needed to identify the impact and role of coils in PED flex-treated cases to establish treatment guidelines.

Limitation

There are some potential limitations in our current study. First, this is a retrospective single-center study with a relatively small case series; thus, multicenter studies with a larger number of patients are required for in-depth analysis. Second, our reports are mainly based on short-term follow-up time points, and the prognosis of aneurysm may evolve into other acceptable results over time. Longer temporal follow-up is needed to point out the potential complications and adverse effects. Besides this, the treatment strategy for which aneurysm was warranted adjunctive coiling was determined at the discretion of the attending surgeon. In the future, further randomized researches are supposed to be performed in order to provide stronger evidence to support these preliminary results.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding authors.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Henan Provincial

People's Hospital. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

QZ contributed to the preparation of the manuscript and data collection. KC, HZ, XM, and QS contributed to data analysis and interpretation. ZS, HA-B, and AZ contributed to the editing and revision of the manuscript. YH and LL contributed to the revision of the manuscript. LL and TL contributed to the study design. All authors contributed to the article and approved the submitted version.

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Safety and Efficacy of Rapamycin-Eluting Vertebral Stents in Patients With Symptomatic Extracranial Vertebral Artery Stenosis

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Background and Purpose: Drug-eluting stents generally have superior performance to bare metal stents in the treatment of vertebral artery stenosis (VAS). This prospective, multicenter, and single-arm clinical trial was initiated to assess in-stent restenosis (ISR) and midterm outcome after rapamycin-eluting stent placement in patients with symptomatic extracranial VAS.

Methods: The subjects underwent angiographic follow-up at 6 months and final clinical follow-up at 12 months. The primary efficacy endpoint was ISR at 6 months. Secondary endpoints included technical success, target lesion-related transient ischemic attack (TIA), stroke, or death, and all-cause TIA, stroke, or death during the 12-month follow-up period.

Results: A total of 104 stents were implanted in the 101 patients and 83 patients (82.2%) completed angiographic follow-up at 6 months. The technical success rate was 86.1% (87/101); mean in-stent stenosis rate was 25.1 ± 17.1% and ISR rate was 5.9% (95% CI: 0.8–10.9%). All the patients with ISR were completely asymptomatic and no stent fractures were observed during angiographic follow-up. At the 12-month clinical follow-up, target lesion-related TIA, stroke, or death had occurred in two (2.0%) patients and all-cause TIA, stroke, or death had occurred in six (6.1%) patients.

Conclusion: The placement of rapamycin-eluting stents in patients with symptomatic extracranial VAS yields favorable ISR results and showed a trend of favorable safety outcomes including low rates of perioperative complications and late stroke. However, further study is needed to establish the long-term clinical benefits of this stent in the treatment of VA disease.

Keywords: vertebral artery stenosis, drug-eluting stent, symptomatic stenosis, in-stent restenosis, objective performance criterion

INTRODUCTION

Posterior circulation strokes are associated with high morbidity and mortality rates and account for approximately 20% of all the ischemic strokes, with up to 20% of cases involving vertebral artery stenosis (VAS) (1). In patients who are refractory to medical treatment, endovascular treatment by balloon angioplasty or stenting is recommended (2–6). However, endovascular stenting was shown to be superior to balloon angioplasty, as it yields immediate results and has a low rate of periprocedural complications (7).

Despite the promising results achieved with endovascular stenting, high rates of in-stent restenosis (ISR) ranging from 11.1 to 66.7% have been reported (5, 8–10), which is mainly caused by neointimal hyperplasia. To overcome this problem, drug-eluting stents (DESs) were developed for the treatment of severe coronary artery stenosis. Both the paclitaxel and rapamycin are the commonly used drugs for DES, with the latter shown to be more effective for preventing coronary ISR (11, 12). Additionally, DESs have shown promising results in the treatment of cerebrovascular stenosis. However, most of these studies were case reports or case series and there are limited comparative data on the efficacy of rapamycin- and paclitaxel-eluting stents in the treatment of VAS. The former is increasingly being used because of its low neurotoxicity, but its safety has yet to be validated in a large sample.

It is worth noting that DESs used to treat VAS in previous studies were "off-label" and only indicated for coronary artery stenosis. A prospective, multicenter, and single-arm safety and efficacy evaluation of a rapamycin-eluting stent specifically indicated for VAS was recently completed. In this study, we investigated the applicability of rapamycin-eluting stents to the treatment of symptomatic extracranial VAS.

MATERIALS AND METHODS

Study Design and Population

This prospective, single-arm clinical trial based on objective performance criteria was carried out at six high-volume centers. Eligible patients were between 18 and 80 years of age and presented with symptomatic extracranial VAS resulting from presumed arteriosclerotic disease, defined as posterior circulation stroke or transient ischemic attack (TIA) in the previous 90 days despite receiving intensive antiplatelet therapy (with aspirin and clopidogrel) and management of risk factors (13, 14). Angiographic inclusion criteria were lesion length $\leq$ 21 mm and degree of stenosis $\geq$ 50% [i.e., the Warfarin-Aspirin Symptomatic Intracranial Disease (WASID) trial definition] (15–18).

Key clinical exclusion criteria were tandem stenoses and previous surgical or endovascular intervention in the target lesion area; a potential cause of stroke or TIA other than stenosis in a VA (e.g., atrial fibrillation or lacunar stroke); severe neurologic dysfunction (the Modified Rankin Scale score $\geq$3); myocardial infarction within 2 weeks of the procedure; excessive tortuosity or severe calcification of the target lesion; non-atherosclerotic lesion; other concurrent intracranial diseases such as intracranial hemorrhage, aneurysm, arteriovenous malformation, and/or intracranial tumor; severe renal dysfunction; and allergy or other contraindications to oral antiplatelet medication, rapamycin and its derivatives, cobalt-base alloy, polylactic acid, or steel.

The protocol was approved by the Institutional Review Board or Ethics Committee of each participating hospital. A written informed consent was obtained from each patient prior to enrollment. The trial was conducted in compliance with Chinese medical device regulations.

Device Description

The Firehorus Rapamycin Target-eluting Vertebral Artery Stent System (Shanghai Microport NeruoTech, Shanghai, China) is a novel balloon-expandable stent fabricated from L605 cobalt chromium alloy with a strut thickness of 86 μm (**Figure 1**). Recessed grooves on the abluminal surface contain a D,L-polylactic acid biodegradable polymer of 10 μm thickness, which provides controlled release of the antiproliferative drug rapamycin. The remaining three sides of the stent strut are devoid of drug or polymer. The rapamycin density is 0.3 μg/mm^2, with approximately 90% released by 90 days postimplantation. The stent is premounted on a custom rapid-exchange balloon delivery catheter system to avoid injury or distortion of the coating during the crimping process. The Firehorus stents were available for this trial in diameters of 2.25–4.0 mm and lengths of 13–23 mm.

Procedure

Dual antiplatelet therapy consisting of 100 mg aspirin plus 75 mg clopidogrel once daily was administered at least 3 days prior to the procedure. A loading dose of 300 mg aspirin plus 300 mg clopidogrel was given, if the procedure was scheduled to begin immediately. All the patients were evaluated for aspirin and clopidogrel resistance with the VerifyNow Platelet Function Assay (Accumetrics, San Diego, California, USA). Stent implantation was carried out according to the instructions of the manufacturer provided with each device and current hospital and neurovascular standard practices. All the procedures were routinely performed under local anesthesia without intravenous sedation. Procedures were performed via the transfemoral or transradial route, which was selected based on the most stable guiding catheter position for treatment. Heparin was administered to maintain an activated clotting time of 250–300 s. A 6F guiding catheter was placed into the subclavian artery proximal to the origin of the target VA. At this point, a 0.014-inch guidewire was advanced across the lesions. In a minority of cases, pre-dilation with a coronary balloon catheter was performed in order to facilitate the passage of the rapamycin-eluting stent, which was deployed across the stenosis. Post-dilation was not routinely performed. At the end of the procedure, an angiogram was performed to measure residual stenosis. The combined antiplatelet medication (100–300 mg aspirin and 75 mg clopidogrel daily) was continued for at least 1 year postimplantation. Intensive management of risk factors after stent implantation was continued in all the patients (13, 14). Protocol-specified angiographic follow-up was required at 6 months (±30 days) posttreatment. Clinical follow-up was scheduled at 1, 6, and 12 months postimplantation.

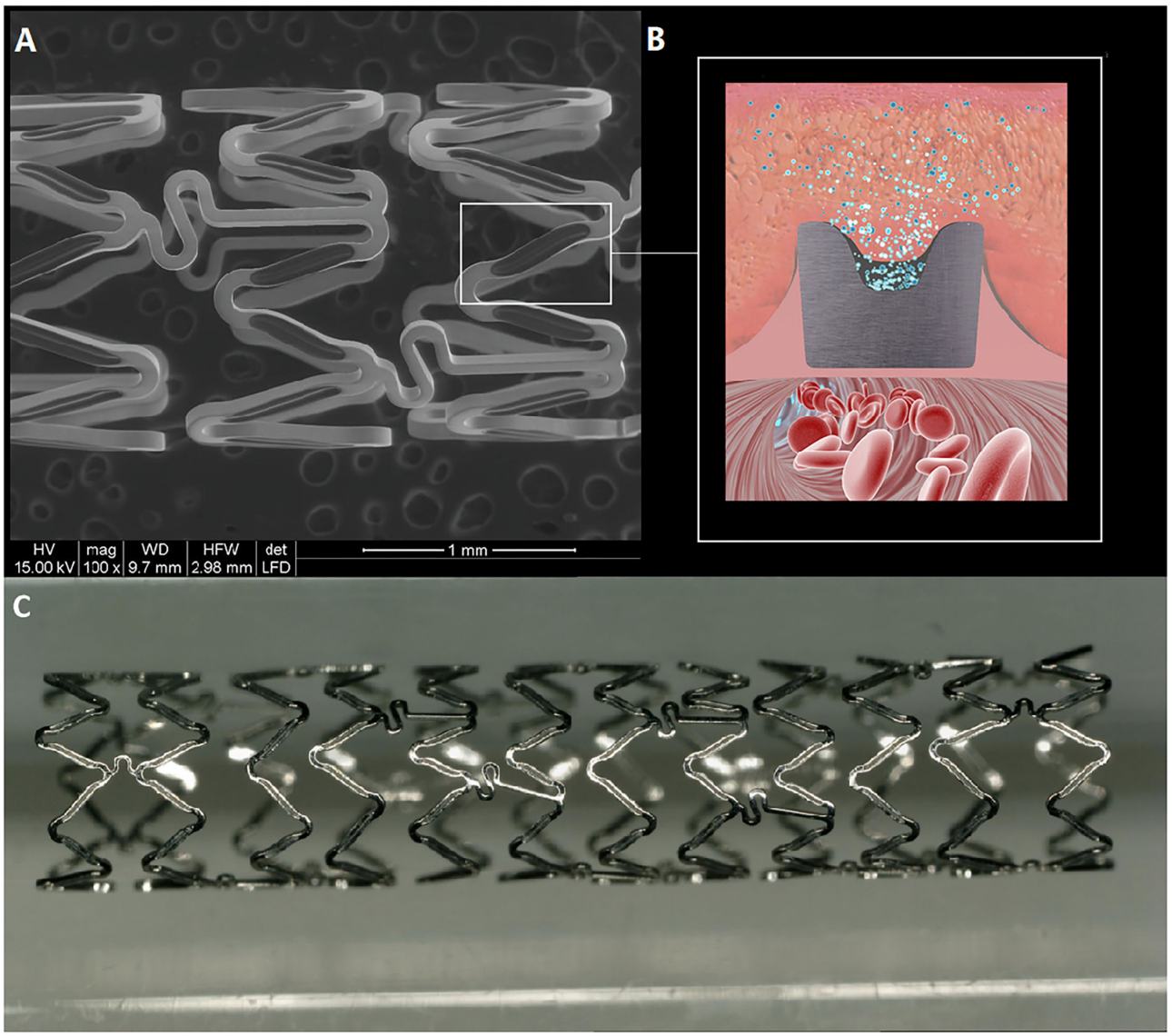

FIGURE 1 | The Firehorus stent design. **(A)** The Firehorus stent is made of L605 cobalt chromium alloy; **(B)** Abluminal surface with recessed grooves containing D, L-polylactic acid biodegradable polymer, which provides controlled rapamycin (sirolimus) release; and **(C)** The Firehorus stent.

Endpoints and Definitions

The primary endpoint was ISR at 6 months (±30 days), defined as ≥50% stenosis within the stent or just outside the stent margins (19). Technical success was defined as residual stenosis of ≤20% after final treatment with the DES. Safety endpoints included target lesion-related TIA, stroke, or death and all-cause TIA, stroke, or death during the follow-up period. Stroke was defined as a focal neurologic deficit lasting more than 24 h. Target lesion-related stroke was defined as clinical features indicative of stroke of the brainstem, cerebellum, or occipital lobe. Posterior circulation TIA was defined as a transient episode of neurologic dysfunction caused by posterior circulation ischemia without acute infarction (20). If a new stroke was suspected, a CT or MRI scan was performed for verification. All the serious adverse events and safety endpoints were adjudicated by a Clinical Endpoint Committee. All the angiographic endpoints were evaluated by an independent core laboratory.

Statistical Methods

Performance Goal and Sample Size

The performance goal in this present study was determined based on a systematic review of 27 articles reporting ISR rates (21); the mean ISR rate was 11% in patients with the DES and 30% in patients treated with a bare metal stent (BMS). It was evident that compared to BMS, DES offered a mean net benefit of 19% for ISR (30–11%). Since the Firehorus is a new DES to treat vertebral stenosis, an absolute difference of 9.5% (half of the benefit) was used to calculate a performance goal of 20.5% (11% plus the

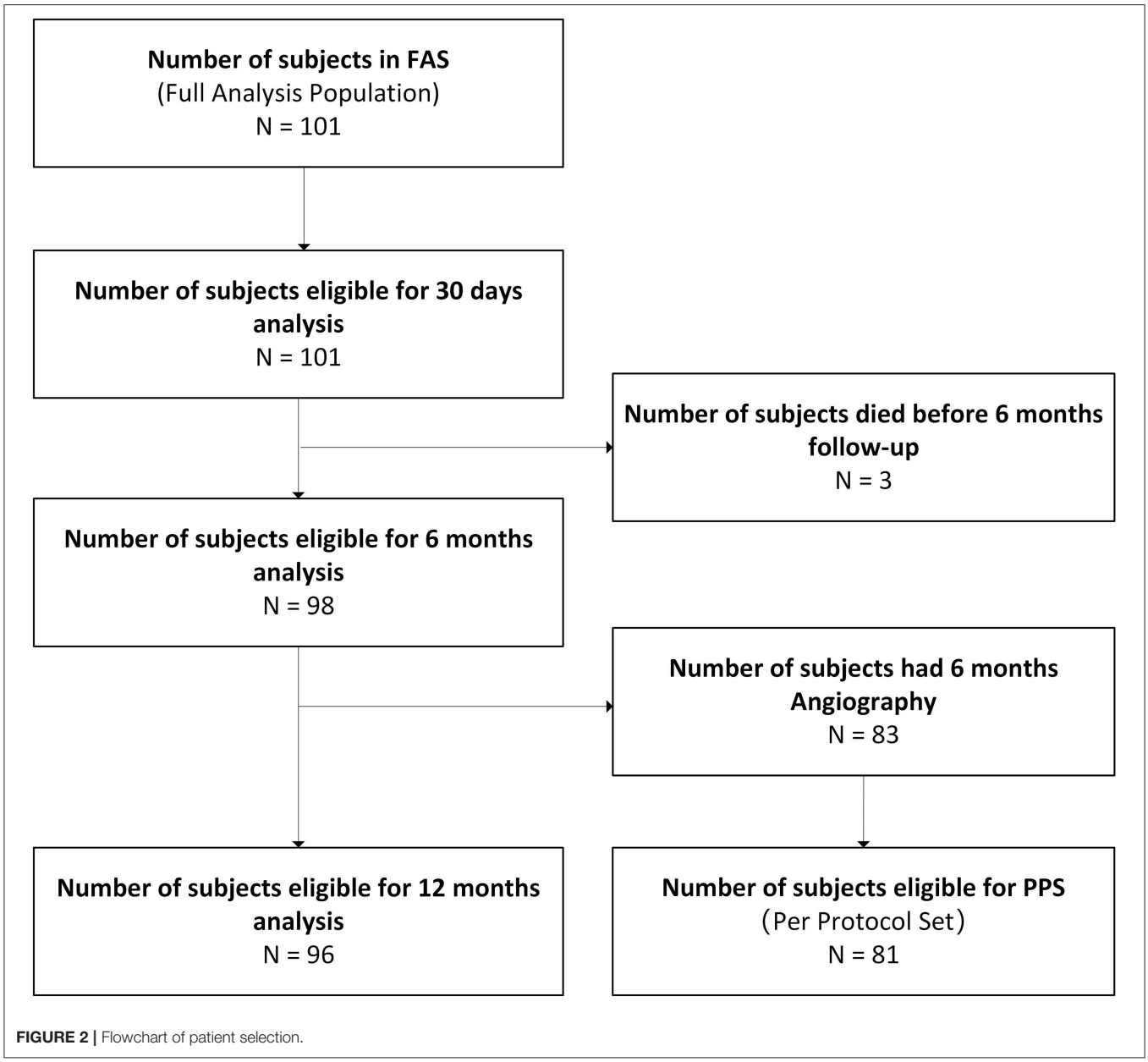

FIGURE 2 | Flowchart of patient selection.

prespecified margin of 9.5%). Allowing for a 20% loss to follow-up for the primary endpoint, a sample size of 100 patients was deemed necessary for 80% power to reject the null hypothesis, with a two-tailed α-value of 0.05.

Statistical Analysis

The primary analysis was based on the intention-to-treat (ITT) principle, defined as enrollment in the study and attempted placement of the rapamycin-eluting stent. Demographics, lesion characteristics, procedural characteristics, and outcome variables of the patient were analyzed with descriptive statistics. Continuous variables are reported as mean ± SD, median with interquartile range, and maximum and minimum values. Categorical variables are reported as counts and percentages. The Kaplan–Meier analysis was used to assess the primary endpoint and determine 95% CI. Sensitivity analysis was performed using the tipping point method to estimate the rate of ISR and 95% CI at 6 months after the procedure. All the statistical analyses were performed using SAS software version 9.4 (SAS Institute, Cary, North Carolina, USA).

RESULTS

Trial Population With Baseline and Procedural Characteristics

Between July 7, 2014, and November 26, 2015, a total of 101 patients were enrolled in the trial and 104 stents [102 DESs and 2 BMSs (Apollo, MicroPort Scientific, Shanghai, China)]

were implanted (1.03 stents per patient) (**Figure 2**). Baseline demographics, clinical conditions, angiographic characteristics, and procedural data for the patients are shown in **Table 1**. The mean age of the subjects was 62.87 ± 8.41 years and 18.8% were female; 57 (56.4%) patients had stroke, 37 (36.6%) patients had TIA, and 7 (6.9%) patients had stroke combined with TIA. Cerebrovascular risk factors were highly prevalent including hypertension in 78.2% patients, current or previous smoking in 49.5% patients, hyperlipidemia in 41.6% patients, and diabetes in 28.7% patients. Complete baseline and postprocedure angiographic data were available for the 104 treated lesions. Cerebral angiography showed that all the patients suffered from stenosis in the dominant VA, of which 24 (23.8%) patients suffered from contralateral VA hypoplasia or occlusion. The target lesion involved the V0 segment in 85.6% of patients, V1 segment in 10.6% of patients, V2 segment in 1.9% of patients, and V4 segment in 1.9% of patients. The mean reference vessel diameter was 3.49 ± 0.63 mm and mean lesion diameter was 1.16 ± 0.39 mm.

The lesions presented an average pretreatment degree of stenosis of 66.86 ± 9.47% and mean lesion length of 7.18 ± 3.35 mm. Predilation was performed in 8 lesions, whereas postdilation was performed in 16 lesions. Technical success was achieved in 86.1% of patients. There were no intraoperative complications and no fatal or non-fatal stroke, in-hospital death, acute or subacute stent thrombosis, or target lesion revascularization occurred during the perioperative period. After stent implantation, the mean percent diameter stenosis was reduced to 10.59 ± 9.89%. **Figure 3** shows the digital subtraction angiograms of two subjects treated with the DES for V0 stenosis.

TABLE 1 | Baseline characteristics and pre/post-procedure angiographic results.

Characteristic	Patients (n = 101)
Age, years	62.87 ± 8.41
Female	19 (18.8)
History of diabetes	29 (28.7)
Insulin therapy	12 (41.4)
History of hypertension	79 (78.2)
History of hyperlipidemia	42 (41.6)
Current smoking	31 (30.7)
Prior myocardial infraction	4 (4.0)
Prior transient ischaemic attack	44 (43.6)
Prior Ischemic Stroke	64 (63.4)
Target vessel (n = 104 lesions)	
V0	90 (86.5)
V1	10(9.6)
V2	2 (1.9)
V3	0 (0.0)
V4	2 (1.9)
Reference vessel diameter, mm	3.49 ± 0.63
Lesion length, mm	7.18 ± 3.35
Minimum luminal diameter, mm	1.16 ± 0.39
Percentage diameter stenosis	66.9 ± 9.5
Total stent length, mm	15.15 ± 2.75
Stent diameter, mm	3.66 ± 0.50
Pre-dilation	8 (7.7)
Post-dilation	16 (15.4)
Final in-stent minimum luminal diameter, mm	3.14 ± 0.53
Final in-stent percentage diameter stenosis	10.59 ± 9.89
Technical success (Lesion level)	90 (86.5)
Technical success (Patient level)	87 (86.1)
Adverse events in the procedure	0(0.0)

Values are mean ± SD or n (%); Technical success = residual percentage diameter stenosis ≤20%; Percentage diameter stenosis = (1–[$D_{Stenosis}$/D_{Distal}]) × 100%; Angiographic results analyzed on Core-lab data (except Target vessel, Total stent length, Stent diameter, Pre -dilation, Post-dilation).

Angiographic Outcomes at 6 Months

Three subjects (3.0%) died within 6 months and 15 patients (14.8%) declined participation in the invasive follow-up; thus, 83 subjects (82.2%) were assessed for the primary endpoint at 6 months. Two subjects with tandem stenoses (V0 and V4 segments) were excluded from the per protocol set (PPS) and two patients with V2 segment stenosis refused to undergo angiographic follow-up; thus, the PPS comprised only patients with V0 or V1 segment stenosis. In the full analysis set and the PPS, the mean in-stent stenosis rates were 25.1 ± 17.1% and 24.4 ± 16.1%, respectively, and the primary endpoint of 6-month ISR rate was 5/83 (5.9%) and 3/81 (3.7%), respectively (**Table 2**). A 51-year-old female experienced asymptomatic in-stent occlusion. Baseline angiography showed 77.3% stenosis in the ostium of the right VA. A 3.5 × 13 mm Firehorus stent was implanted without pre- or postdilation. Residual stenosis immediately after stenting was 5.8%. A branch of the right thyrocervical trunk supplied a retrocorporeal artery collateral to the right VA at the 6-month angiographic follow-up. All the ISR subjects were completely asymptomatic and no stent fractures were observed during angiographic follow-up.

The upper 95% CI of the primary endpoint calculated with the Clopper–Pearson exact method was 10.9%, well below the performance goal of 20.5%. Sensitivity analysis with the tipping point method showed that only if ≥ 50% of patients (i.e., ≥9 patients) had restenosis can reach the threshold required to accept the null hypothesis. However, in the PPS, only 3.7% of patients (3/81) had restenosis at 6 months. There were no differences in baseline characteristics between subjects who were lost to follow-up and those who were not lost to follow-up; accordingly, there was a low probability of a restenosis rate ≥ 50% among the 18 patients for whom there were no 6-month angiographic results. Thus, the DES was associated with a low ISR rate as predicted.

The cumulative distribution frequency for late in-stent lumen loss (LL) is shown in **Figure 4A**. More than 89% of subjects had LL < 1.0 mm and only one subject had LL > 2.0 mm. The cumulative frequencies of luminal diameter and ISR pre- and postprocedure and at the 6-month follow-up are shown in **Figures 4B,C**.

Clinical Outcomes at 12 Months

Clinical follow-up data at 12 months were available for 99 patients (98.0%). Target lesion-related TIA, stroke, or death

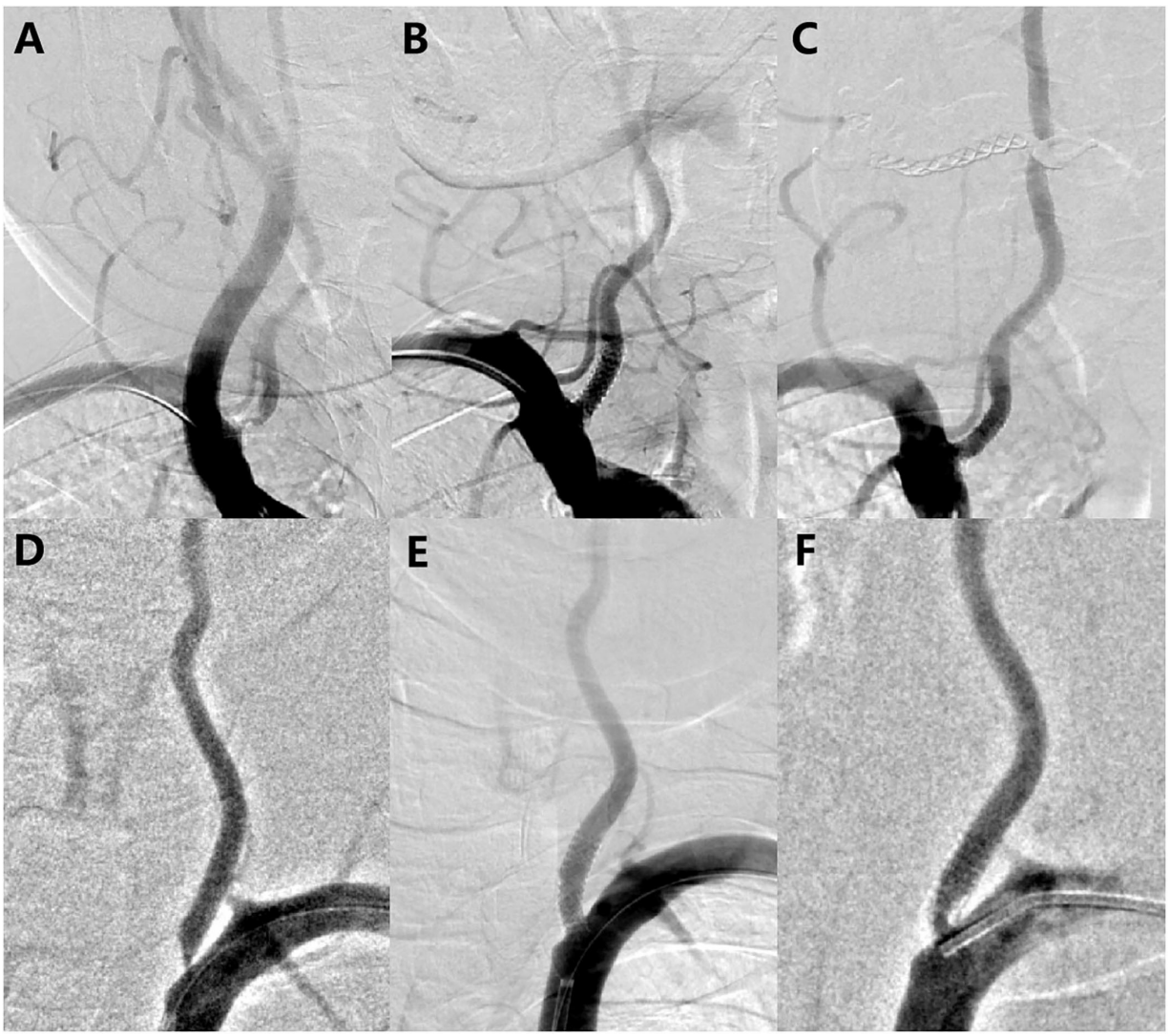

FIGURE 3 | Before and after treatment with the rapamycin-eluting stent. **(A)** Left vertebral artery high-grade stenosis before placing a long 16 × 4.0 mm stent; **(B)** Immediately after implantation, demonstrating a wide-open arterial lumen with 4.5% residual stenosis; **(C)** 6-month follow-up angiogram showing approximately 12.7% restenosis; **(D)** Left vertebral artery high-grade stenosis before placing a long 16 × 4.0 mm stent; **(E)** Immediately after implantation, demonstrating a wide-open arterial lumen with 12% residual stenosis; and **(F)** 6-month follow-up angiogram showing approximately 57% restenosis.

TABLE 2 | 6-month angiographic results.

Parameters	FAS	PPS
	101 Subjects/104 Lesions	81 Subjects/82 Lesions
Reference vessel diameter, mm	3.50 ± 0.56	3.50 ± 0.57
Minimum luminal diameter, mm	2.63 ± 0.69	2.65 ± 0.66
Percentage diameter stenosis	25.1 ± 17.1	24.4 ± 16.1
In-stent stenosis (Lesion level)	5 (5.9)	3 (3.7)
In-stent stenosis (Patient level)	5 (6.0)	3 (3.7)

Values are mean ± SD or n (%); FAS, Full Analysis Set; PPS, Per Protocol Set; In-stent stenosis = percentage diameter stenosis ≥ 50%; Percentage diameter stenosis = (1–[$D_{Stenosis}$/D_{Distal}]) × 100%; 6-month angiographic results analyzed on Core-lab data.

occurred in two (2.0%) patients including one (1.0%) patient with death and one (1.0%) patient with thalamic hemorrhage; both the events occurred within 6 months. Any TIA, stroke, or death occurred in six (6.1%) patients including three (3.0%) patients with death, one (1%) patient with transient ischemic stroke in the anterior circulation, one (1.0%) patient with anterior circulation ischemic stroke, and one (1.0%) patient with thalamic hemorrhage. Of the three patients who died in the follow-up period, one patient died of ischemic stroke recurrence in the area of the target vessel, one patient died of traumatic cerebral hemorrhage, and one patient died of intestinal tumors. Until the 12-month follow-up, there were 34 serious adverse events in 25 patients, but none was related to either the device or the procedure (**Supplementary Table S1**).

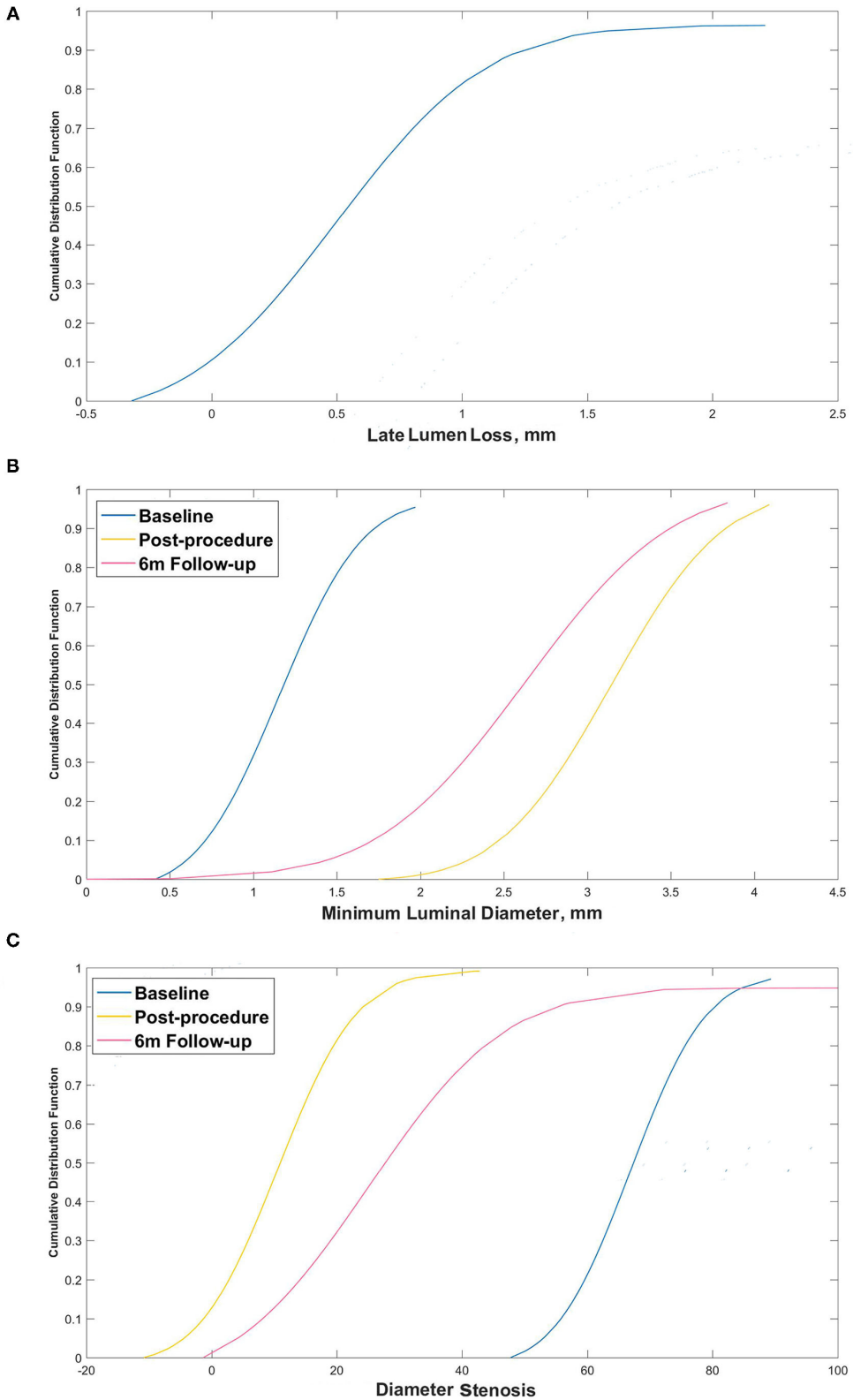

FIGURE 4 | Cumulative frequency distribution curves. **(A)** Cumulative frequency distribution curve for late lumen loss at 6 months; **(B)** Minimum luminal diameter pre- and postprocedure and at the 6-month follow-up; and **(C)** Percentage diameter stenosis pre- and postprocedure and at the 6-month follow-up.

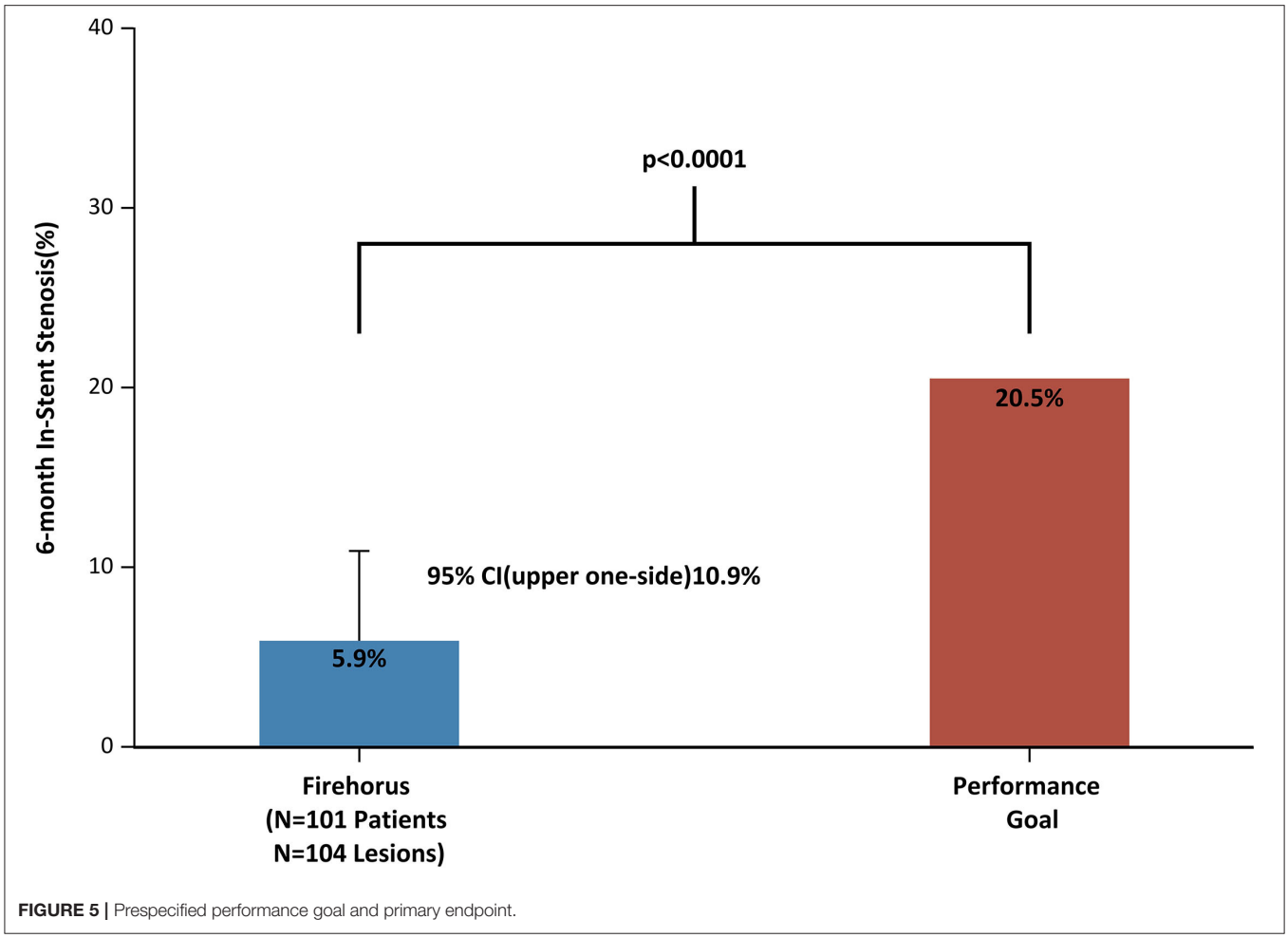

FIGURE 5 | Prespecified performance goal and primary endpoint.

DISCUSSION

In this prospective, multicenter, and single-arm clinical trial, the rapamycin-eluting stent met the prespecified performance goal for the primary endpoint (**Figure 5**), supporting the safety and efficacy of the stent for the treatment of symptomatic extracranial VAS. The angiographic endpoints evaluated by the core laboratory showed that the 6-month ISR for the PPS subjects was just 3.7%. This is comparable to the rates reported in other trials of patients treated with a DES in the VA (**Table 3**) (22–38).

The efficacy of interventional therapy for symptomatic VAS is controversial. The Carotid and Vertebral Artery Transluminal Angioplasty Study (CAVATAS) failed to show any benefit of VAS intervention (39). However, the result was underpowered due to the small number of patients enrolled in this study. The Vertebral Artery Stenting Trial (VAST) was halted after enrolling 115 patients because of regulatory problems and lack of funding (16). At present, there is no evidence to justify the contraindication of endovascular treatment in patients with medically refractory VAS. Moreover, there are no definite evidence-based guidelines with respect to the role of medical treatments such as risk factor modification and antiplatelet treatment vs. percutaneous transluminal angioplasty and stenting (PTAS) (8, 16, 39). On the other hand, there is no valid reason to withhold PTAS and there is increasing evidence from case series and cohort studies that it is safe and effective, especially at the VA origin (7, 21, 31, 40). The results of this study provide evidence for the safety and efficacy of the rapamycin-eluting stent for the treatment of VAS; ISR rate of 3.7% in the PPS at the 6-month angiographic follow-up was comparable to those reported in recent DES studies (34, 40).

The rapamycin-eluting stent had an excellent safety profile. During the entire follow-up period, target vessel stroke or death occurred in 2.0% (2/99) of subjects and any stroke or death occurred in 6.1% (6/99) of subjects, in contrast to the Stenting of Symptomatic Atherosclerotic Lesions in the Vertebral or Intracranial Arteries (SSYLVIA) study in which the composite 1-year stroke rate associated with target vessels was 13.1% (8/61) (8). Similarly, in the VAST trial, 9% (5/57) of patients in the stenting group had a stroke in the territory of the symptomatic VA during the follow-up period of 1 year.

Despite the low ISR rate and excellent safety profile of the rapamycin-eluting stent in this study, the technical success rate was lower than that reported in other trials with more restricted populations (40). This may be an inherent limitation of an open-label device evaluation where variable behavior according to operator experience cannot be ruled out. In studies with new

TABLE 3 | Summary of reports of vertebral artery angioplasty and stenting with drug-eluting stents.

Trail	Patients (n)	Drug-eluting	Location	Technical success definition	Technical success rate	Peri-procedural TIA/Stroke	Mean imaging follow-up (m)	Imaging mode	Restenosis definition	Restenosis rate
Gupta et al. (22)	31	Paclitaxel Rapamycin	EVA	Successful stent deployment	100%	0	4	DSA CTA	>50% Stenosis	7.4% (2/27)
Vajda et al. (23)	48	Paclitaxel	VAO	NR	100%	0	7.7	DSA	>50% Stenosis	12.5% (6/48)
Yu et al. (24)	10	Paclitaxel	VAO	Successful stent deployment	100%	0	12	DSA	>50% Stenosis	0% (0/10)
Ogilvy et al. (25)	15	Paclitaxel Rapamycin	VAO	Successful stent deployment	100%	0	NR	CTA	>50% Stenosis	16.7% (2/12)
Park et al. (26)	20	Paclitaxel	VAO	NR	100%	0	14.7	DSA	>50% Stenosis	21.1% (4/19)
Werner et al. (27)	28	Paclitaxel	VAO	Residual stenosis of <20%	100%	0	16	DSA	>50% Stenosis	21.4% (6/28)
Chen et al. (28)	47	Paclitaxel Rapamycin	VAO	Residual stenosis of <20%	100%	0	16.3	DSA	>50% Stenosis	5.3% (2/38)
Fields et al. (29)	14	NR	VAO	Successful stent deployment	100%	0	8	DSA	>50% Stenosis	21.4% (3/14)
Song et al. (30)	112	Paclitaxel Rapamycin	VA	Residual stenosis of <30%	98.3%	2.7%	43	DSA*	>70% Stenosis	6.3% (7/112)
Langwieser et al. (31)	16	Paclitaxel	EVA	Residual stenosis of ≤30%	100%	0	18	DUS	≥70% Stenosis	0% (0/16)
Lu et al. (32)	24	Paclitaxel Rapamycin	VAO	Residual stenosis of ≤30%	100%	0	35	DSA	>50% Stenosis	10.0% (2/20)
Raghuram et al. (33)	13	NR	EVA	Successful stent deployment	100%	0	12	DSA	>50% Stenosis	23.1% (3/13)
Che et al. (34)	147	Paclitaxel	VAO	Residual stenosis of <30%	100%	NR	34.8	CTA MRA DSA	≥50% Stenosis	8.2% (12/147)
He et al. (35)	20	Rapamycin	VA	Successful stent deployment	100%	0	6.5	DSA	>50% Stenosis or luminal loss >30%	5.0% (1/20)
Maciejewski et al. (36)	148	Paclitaxel Rapamycin Everolimus Biolius Zotarolimus	EVA	Residual stenosis of <30%	96.7%	1.4%	>6	DUS CTA DSA	≥50% Stenosis	27.9% (31/111)
Ortega-Gutierrez et al. (37)	30	Zotarolimus Everolimus	VAO	Successful stent deployment	100%	0	8.8	CTA DSA	≥70% Stenosis	7.7% (2/26)
Li et al. (38)	76	NR	VAO	Residual stenosis of <30%	100%	0	12.3	DSA CTA DUS	>50% Stenosis	18.4% (14/76)

*CTA, computed tomography angiography; DSA, digital subtraction angiography; DUS, duplex ultrasonography; EVA, extracranial vertebral artery; IVA, intracranial vertebral artery; MRA, magnetic resonance angiography; NR, not reported; VA, vertebral artery; VAO, vertebral artery origin. *Patients with recurrent symptoms underwent DSA.*

devices that have a unique mode and method of deployment, there may be a learning curve influence on early applications. Given the broad patient inclusion criteria, unmatched and limited stent sizes (2.25–4.0 mm) may have influenced the rate of technical success. Our result was also related to the more stringent criteria adopted by the independent core laboratory because the technical success rate determined by researchers was as high as 98%. Nonetheless, the difference in technical success did not appear to influence the ISR rate or translate into any differences in safety or efficacy in the ITT population and the PPS in this study.

The antiproliferative activity of rapamycin may contribute to reducing ISR rates by interfering with smooth muscle cell migration and delaying endothelialization; additionally, rapamycin may delay stent thrombosis (41, 42). The coronary DES made with first-generation durable polymer was found to be associated with higher rates of late and very late stent thrombosis, which were partly attributed to hypersensitivity reactions to the polymer (43–45). Antiplatelet therapy is thought to play an important role in reducing the risk of stent thrombosis (46). In the Randomized Study with the Sirolimus-eluting Velocity Balloon-expandable Stent (RAVEL) trial, the rates of stent thrombosis at the 5-year follow-up were similar between DES and BMS groups (47). In this study, only one subject experienced asymptomatic stent occlusion, which was likely due to in-stent thrombosis caused by prolonged use of dual antiplatelet therapy. The 12-month rates of aspirin and clopidogrel usage were 84.4 and 76.0%, respectively. Future studies on the use of DESs for the treatment of VAS may provide an additional evidence that long-term dual antiplatelet therapy is essential.

There were several limitations to this study. Firstly, the lack of randomization precluded direct comparisons with optimal medical therapy or BMSs. As a single-arm trial, it was impossible to blind investigators, adjudicators, and personnel at the angiographic core laboratory. Secondly, to characterize a new implantable medical device such as the rapamycin-eluting stent, 6 months of angiographic follow-up and 12 months of clinical follow-up may be insufficient to observe all the occurrences of ISR, delayed stent thrombosis, and other late events. Thirdly, the small sample size limited our ability to perform additional analyses of whether certain patient subsets (especially those with V2 stenosis) have the lower ISR risk after placement of the rapamycin-eluting stents. Fourthly, we did not conduct a hemodynamic evaluation or acetazolamide challenge test before DES placement (48, 49). Finally, although a low dose of drug was released by the stent and there was no indication of rapamycin-induced neurotoxicity, further study is needed to assess the potential risk thereof in a neurovascular territory.

CONCLUSION

The placement of the rapamycin-eluting stents in patients with symptomatic extracranial VAS yields favorable ISR results and showed a trend of favorable safety outcomes including low rates of perioperative complications and late stroke. However, further study is needed to establish the long-term clinical benefits of this stent in the treatment of the VA disease.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by IRB of Beijing Tiantan Hospital, Capital Medical University. The patients/participants provided their written informed consent to participate in this study. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

AUTHOR CONTRIBUTIONS

ZM and KC designed, led the study and had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. GM prepared the first draft of the report. WL did statistical analyses. All authors except WL participated in patient enrolment, collection of data. All authors critically reviewed the report and approved the final version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2021.649426/full#supplementary-material

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The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Predictors of First-Pass Effect in Endovascular Thrombectomy With Stent-Retriever Devices for Acute Large Vessel Occlusion Stroke

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Background and Purpose: Successful recanalization after the first pass of the device in endovascular thrombectomy (EVT) can significantly improve patients' prognosis. We aimed to investigate the possible factors that influence achieving the first-pass effect (FPE).

Methods: We retrospectively analyzed the patients who underwent EVT caused by anterior circulation large vessel occlusion stroke (ALVOS) in our center. The FPE was defined as a successful recanalization [modified Thrombolysis in Cerebral Infarction (mTICI) 2b/3 defined as modified FPE (mFPE); mTICI 3 as true FPE (tFPE)] after one pass of the device without rescue therapy. Univariate and multivariate regression analyses were used to explore the predictors of FPE and the relationship between FPE and prognosis.

Results: There were 278 patients (age, 69.3 ± 10.9 years, male, 51.1%) included, 30.2% of them achieved mFPE, while 21.2% achieved tFPE. We found the higher clot burden score (CBS), the truncal-type occlusion, and the favorable anatomy of both extracranial and intracranial segments of the internal carotid artery (ICA) were associated with achieving mFPE. The higher CBS and truncal-type occlusion were statistically significant predictors of tFPE. Moreover, FPE was significantly associated with improved clinical outcomes, regardless of mFPE and tFPE.

Conclusions: The CBS, tortuosity of ICA, and angiographic occlusion type were independent predictors of achieving FPE. The rate of improved clinical and safety outcomes was higher in patients with FPE, which has important clinical significance.

Keywords: endovascular thrombectomy, stroke, stent-retriever, first-pass effect, recanalization

INTRODUCTION

Endovascular thrombectomy (EVT) with stent-retriever (SR) has been recommended as a first-line treatment for patients with acute large vessel occlusion stroke (ALVOS) (1). However, in the real world, to achieve complete recanalization, multiple attempts and rescue therapy were often required, which may prolong the procedure time and cause vascular endothelial injury, leading to a high incidence of hemorrhagic transformations (2).

Previous studies suggest that patients had significantly improved outcomes with successful recanalization after the first pass of the thrombectomy device (3). Hence, a new conception has been proposed: the "true first-pass effect" (tFPE), defined as complete revascularization (modified Thrombolysis in Cerebral Infarction, mTICI 3) after one single pass of the device without rescue therapy (4). Modified first-pass effect (mFPE) was defined as mTICI 2b/3 after one pass of the device (3). The first-pass effect may therefore constitute the main goal in the treatment of patients with ALVOS in the EVT era.

Current evidence demonstrated an association between procedural difficulty and angiographic occlusion type (5). Moreover, the tortuosity of the vascular anatomy can also present technical challenges during the procedure (6, 7). However, the factors that affected the achievement of mFPE have not yet been clear. We aimed to investigate the possible factors that influence achieving mFPE in patients undergoing EVT with stent-retriever devices.

METHODS

Patients and Baseline Variables

We enrolled patients treated with emergency EVT in Yijishan Hospital, Wannan Medical College from July 2015 to June 2020. The local ethics committee approved the study protocol. Patients were included in our study if they were treated with stent-retriever devices (Solitaire, Covidien, Irvine, California, USA). Time from onset to puncture, baseline modified Rankin Scale (mRS) score, National Institute of Health Stroke Scale (NIHSS) score, and Alberta Stroke Program Early CT (ASPECT) score were not considered as exclusion criteria.

All consecutive patients were prospectively documented. This included demographics, medical history (hypertension, diabetes mellitus), NIHSS score, the Trial of ORG 10172 in Acute Stroke Treatment (TOAST) classification, laboratory measures, procedural factors (ASPECT score, leptomeningeal collaterals, and occlusion site), and outcomes. For all enrolled subjects, the imaging characteristics were evaluated by two neurologists/interventionalists who were blinded to the clinical information.

The proximal middle cerebral artery (MCA) or the anterior cerebral artery (ACA) occlusion was defined as M1 or A1 of MCA/ACA occlusion as confirmed by preoperative imaging. The distal MCA/ACA occlusion was M2/A2 or distal of M2/A2 MCA/ACA occlusion.

True First-Pass Effect

According to previous studies, the tFPE was defined as follows: (1) one single pass of the device; (2) near-complete revascularization of the large vessel occlusion and its downstream territory (mTICI 3); (3) with no use of rescue therapy (4).

Modified First-Pass Effect

The mFPE was defined as follows: (1) one single pass of the device; (2) near-complete revascularization of the large vessel occlusion and its downstream territory (mTICI 2b/3); (3) with no use of rescue therapy (3, 8).

Collateral Circulation State

Collateral circulation was assessed based on retrograde contrast opacification of vessels within the occluded territory on delayed digital subtraction angiography (DSA) images. The collateral state was classified as follows: grade 0 was assigned if there was little or no significant reconstitution in the territory of the occluded vessel or less than one-third of the occluded territory, grade 1 was assigned if the collaterals reached less than two-thirds of the occluded territory, and grade 2 was assigned if the collateralization reached more than two-thirds of the territory or the proximal main stem (9).

Clot Burden Score

The clot burden score (CBS) is an angiography-based scoring system that calculates a score from 0 to 10 to determine the extent of thrombus. Particularly, a score of 10 implies clot absence, while a score of 0 means that the vessel is completely occluded. A score of 2 is subtracted if the thrombus is found in each of the supraclinoid internal carotid artery (ICA), the proximal half of the MCA trunk, and the distal half of MCA trunk. A score of 1 is subtracted if the thrombus is found in the infraclinoid ICA, ACA, and for each affected MCA M2 branch (10).

Angiographic Occlusion Type Classification

For all enrolled patients with ALOVS, the occlusion type was classified as truncal-type or branching-site occlusion through angiography (**Figure 1**). The occlusion was defined as a branching-site occlusion when (1) contralateral ICA flow could not further advance across the relevant ICA bifurcation site, (2) Y- or T-shaped filling defect involving branching site is directly observed, or (3) another branch could not be seen even on stent-retriever deployment to one branch across occlusion site. Conversely, the occlusion type was classified as truncal-type occlusion when all major branches and relevant bifurcations are clearly observed (5, 11).

Vascular Tortuosity Classification and Measurements

The anatomy may exist alone or in combination at many different levels, including the ICA and aortic arch. We divided the ICA vessel into extracranial and intracranial segments to be separately considered. Each type of arterial tortuosity was defined based on prior studies.

The extracranial ICA vessel was considered to be straight if the angle between the common carotid artery (CCA) and the ICA centerlines was $<15°$. Patients were considered to have significant extracranial ICA tortuosity if they were presented with kinking or coiling (12). Kinking represents solitary bends in the ICA with acute ($<90°$) angulation, while coiling produces a full 360°turn in the artery (13, 14) (**Figure 2**). We classified the normal vessel or mild tortuosity as grade 1, while severe tortuosity of the vessel, including kinking and coiling, was classified as grade 2.

The previous study showed a four-level classification system of the tortuosity of the intracranial ICA segment based on the angular and height differences between the anterior and posterior

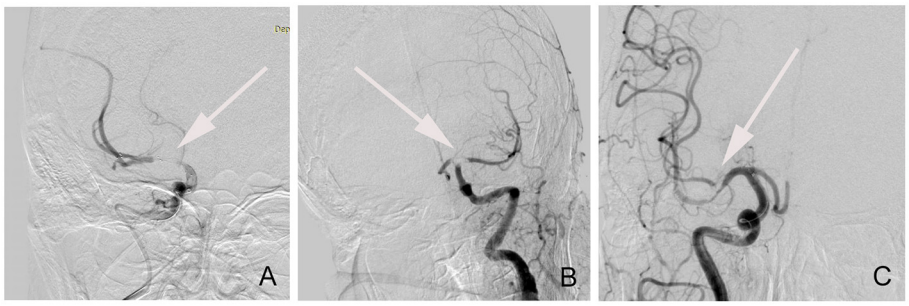

FIGURE 1 | The classification of angiographic occlusion type. **(A)** Truncal-type occlusion; **(B)** T-shaped branching-site occlusion; **(C)** Y-shaped branching-site occlusion.

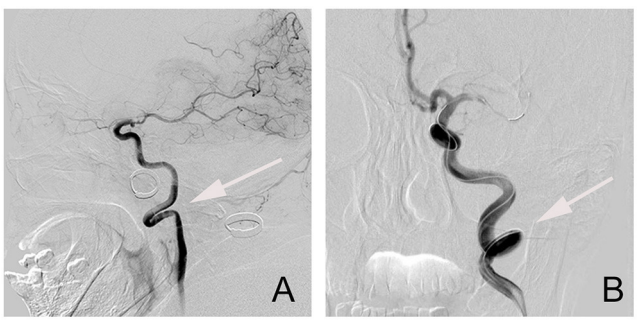

FIGURE 2 | The types of tortuosities of an extracranial segment of the internal carotid artery (ICA) vessel. **(A)** Kinking; **(B)** Coiling.

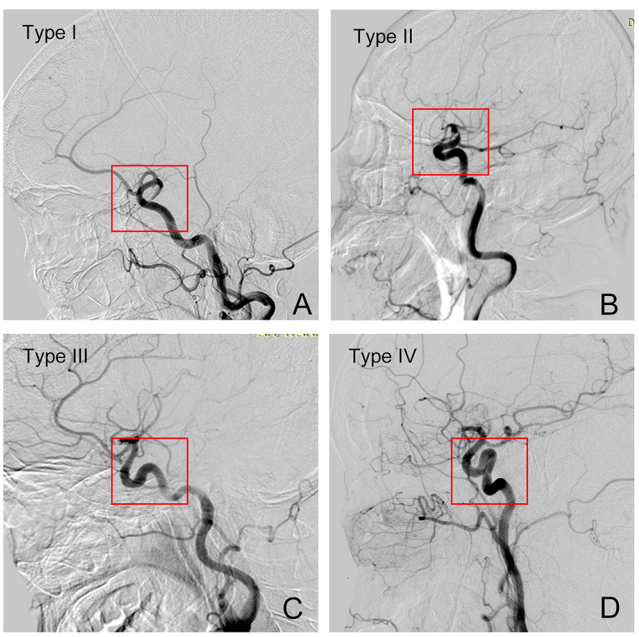

FIGURE 3 | Grades of tortuosity of intercranial segment of the ICA vessel. **(A)** Type I; **(B)** Type II; **(C)** Type III; **(D)** Type IV.

genera from the top of the posterior genus to the anterior genus. Type I was defined as the anterior and posterior genu of ICA cavernous segment configurations are opened the angle is <90°, while Type II has a more acute angle of anterior genu in comparison to type I. Type III has a superior deflection of posterior genu. Type IV is the most tortuous, with a shape characteristic of Simmons catheter (13, 15) (**Figure 3**). In the present study, we regarded all types as 3 different grade levels, in which type I was regarded as grade 1, type II/III as grade 2, and type IV as grade 3.

As to aortic arch anatomy, the I, II, and III arch types were determined by the vertical distance from the origin of the innominate artery to the top of the arch. The bovine aortic arch is defined as the common origin of the innominate artery and left CCA or a left CCA that arises directly from the innominate artery (6). We regarded arch type I/II as grade 1 and type III/ bovine aortic arch as grade 2.

Statistical Analysis

Patients were divided into the mFPE group and non-mFPE group, or good and poor outcomes groups. Continuous variables (age, baseline systolic blood pressure, baseline diastolic blood pressure, NIHSS, ASPECT score, CBS, and procedure time) are presented as the mean ± SD or as the median (IQR). Categorical variables (gender, hypertension, smoke, TOAST, tortuosity of extracranial and intracranial segments of ICA, aortic arch classification, occluded site, collateral state, and angiographic occlusion type) are presented as percentages. Continuous variables were analyzed using the Mann-Whitney U test. Categorical variables were analyzed using the χ^2 test and the Fisher exact test, as appropriate. We then implemented backward stepwise logistic regression analysis to determine the independent factors of mFPE. In addition, the association between mFPE and clinical outcome or mortality at 90 days was also analyzed. Variables with a value of $p < 0.1$ from the univariate analysis were entered into the logistic regression analysis. ORs and 95% CIs were calculated. For all analyses, a two-tailed value of $p \leq 0.05$ was considered significant. All statistical analyses were performed using the SPSS (IBM Corp, Armonk, NY. 25.0) software package.

TABLE 1 | Univariable analysis of predictors of modified first-pass effect (mFPE) and true first-pass effect (tFPE).

	All *N* = 278	mFPE			tFPE		
		mFPE (+) *N* = 84	mFPE (–) *N* = 194	*P*	tFPE (+) *N* = 59	tFPE (–) *N* = 219	*P*
Age, y, mean (SD)	69.3 (10.9)	68.9 (10.1)	69.5 (11.3)	0.674	70 (9.5)	69.1 (11.3)	0.680
Sex (male), *n* (%)	142 (51.1)	51 (60.7)	91 (46.9)	**0.034**	37 (62.7)	105 (47.9)	**0.044**
Smoke, *n* (%)	72 (26.3)	27 (32.9)	45 (23.4)	0.102	20 (34.5)	52 (24.1)	0.110
Hypertension, *n* (%)	202 (72.7)	65 (77.4)	137 (70.6)	0.245	46 (78.0)	156 (71.2)	0.303
Diabetes mellitus, *n* (%)	44 (15.8)	12 (14.3)	32 (16.5)	0.643	10 (16.9)	34 (15.5)	0.790
NIHSS, media (IQR)	15 (12, 19)	15 (12, 19)	16 (13, 19)	0.330	15 (12, 19)	16 (13, 19)	0.397
ASPECT, media (IQR)	8 (8, 10)	8 (8, 10)	8 (8, 9)	0.207	8 (8, 10)	8 (8, 10)	0.263
TOAST, *n* (%)				**0.017**			**0.009**
Atherosclerosis	74 (26.6)	32 (38.1)	42 (21.6)		23 (39.0)	51 (23.3)	
Cardioembolic	175 (62.9)	45 (53.6)	130 (67.0)		32 (54.2)	143 (65.3)	
Other or unknown	29 (10.5)	7 (8.4)	22 (11.3)		4 (6.8)	25 (11.4)	
CBS, media (IQR)	8 (6, 8)	8 (8, 8)	7 (5, 8)	**<0.001**	8 (8, 8)	7 (5, 8)	**<0.001**
Favorable collateral Status, *n* (%)	109 (39.2)	39 (46.4)	70 (36.1)	0.268	30 (50.8)	79 (36.1)	0.115
IVT, *n* (%)	29 (10.4)	7 (8.3)	22 (11.3)	0.451	2 (3.4)	27 (12.3)	**0.046**
Aortic arch, *n* (%)				0.151			0.538
I/II	229 (82.4)	65 (77.4)	164 (84.5)		47 (79.7)	182 (83.1)	
III/Bovine	49 (17.6)	19 (22.6)	30 (15.5)		12 (20.3)	37 (16.9)	
Extracranial segment of ICA, *n* (%)				**0.002**			0.161
Normal or mild tortuosity	133 (47.8)	52 (61.9)	81 (41.8)		33 (55.9)	100 (45.7)	
Severe tortuosity	145 (52.2)	32 (38.1)	113 (58.2)		26 (44.1)	119 (54.3)	
Intracranial segment of ICA, *n* (%)				**0.055**			**0.043**
Type I	176 (63.8)	61 (72.6)	115 (59.9)		43 (72.9)	133 (61.3)	
Type II/III	81 (29.3)	21 (25.0)	60 (31.3)		16 (27.1)	65 (30.0)	
Type IV	19 (6.9)	2 (2.4)	17 (8.9)		0 (0)	19 (8.8)	
Angiographic occlusion type, *n* (%)				**<0.001**			**<0.001**
Truncal-type occlusion	159 (57.6)	68 (81.0)	91 (47.4)		49 (83.1)	110 (50.7)	
Branching-site occlusion	117 (42.4)	16 (19.0)	101 (52.6)		10 (16.9)	107 (49.3)	
Intermediate catheter, *n* (%)	57 (20.5)	24 (28.6)	33 (17.0)	**0.028**	16 (27.1)	41 (18.7)	0.156
Site of occlusion, *n* (%)				**0.013**			0.118
ICA	102 (36.7)	20 (23.8)	82 (42.3)		15 (25.4)	87 (39.7)	
Proximal MCA/ACA	155 (55.7)	56 (66.7)	99 (51.0)		38 (64.4)	117 (53.4)	
Distal MCA/ACA	21 (7.6)	8 (9.5)	13 (6.7)		6 (10.2)	15 (6.8)	

mFPE, modified first-pass effect; tFPE, true first-pass effect; NIHSS, National Institutes of Health Stroke Scale; ASPECT, Alberta Stroke Program Early CT; TOAST, the Trial of ORG 10172 in Acute Stroke Treatment. IVT, intravenous thrombolysis; CBS, clot burden score; MCA, middle cerebral artery; ACA, anterior cerebral artery; ICA, internal carotid artery; mTICI, modified Thrombolysis in Cerebral Infarction. The bold values indicate the variable's P value < 0.05.

RESULTS

Baseline Characteristics

From July 2015 to June 2020, a total of 419 patients who underwent EVT met the inclusion criteria for this study. Of them, 137 were not treated with stent-retriever devices and 4 missed the procedure images and were therefore excluded from our study.

The mean age of the 278 included patients was 69.3 ± 10.9 years, 51.1% ($n = 142$) of which were men, while the median baseline ASPECT score was 8 (IQR 8–10), and the median baseline NIHSS score was 15 (IQR 12–19). Seventeen-point-six percent ($n = 49$) of the patients were identified to have a type III/Bovine configurations aortic arch and 52.2% ($n = 145$) had a severe tortuosity of extracranial ICA. The angiographic occlusion type was determined to be a truncal-type occlusion in 57.6% ($n = 159$) of patients. The other baseline characteristics are shown in **Table 1**. All eligible patients underwent a 90-day follow-up, 43.9% ($n = 122$) of patients had 90-day functional independence, and 27.0% ($n = 75$) of them died (**Table 3**).

Frequency and Predictors of FPE

Among the enrolled patients, mFPE was achieved in 30.2% (84 out of 278) patients. In the mFPE group, a significantly high proportion of male patients (60.7 vs. 46.9%, $p = 0.034$) were present. In addition, patients with mFPE had higher CBS (media, 8 vs. 7; $p < 0.001$) and more patients had mild tortuosity of both

extracranial segment (61.9 vs. 41.8%, $p = 0.002$) and intracranial segment of ICA (type I: 72.6 vs. 59.9%, $p = 0.055$). Patients with mFPE were more likely to have a truncal-type occlusion (81.0 vs. 47.4%, $p < 0.001$) and higher rate of atherosclerosis (38.1 vs. 21.6%, $p = 0.017$). In addition, the intermediate catheters were used more frequently (28.6 vs. 17.0%, $p = 0.028$) than the non-mFPE group (**Table 1**).

After adjustment for confounding factors (sex, TOAST, CBS, the tortuosity of extracranial and intracranial ICA, the occlusion type, the use of intermediate catheter, and the occluded site), we found that lower CBS (OR = 1.384; 95%CI:1.119–1.713; $p = 0.003$) can affect the rate of mFPE. Furthermore, the severe tortuosity of extracranial segment of ICA (OR = 0.506; 95% CI: 0.288–0.889; $p = 0.018$), the Type IV tortuosity of intracranial segment of ICA (Type IV vs. Type I: OR: 0.195, 95% CI: 0.041–0.918, $p = 0.039$), and branching-site occlusion type (OR = 0.354; 95%CI: 0.179–0.701; $p = 0.003$) were also associated with a reduced likelihood of mFPE (**Table 2**).

TABLE 2 | Multivariable analysis of predictors of mFPE and FPE.

	OR (95%CI)	P
mFPE		
CBS	1.384 (1.119–1.713)	0.003
Extracranial segment of ICA	0.506 (0.288–0.889)	0.018
Intracranial segment of ICA		0.112
Type II/III to Type I	0.835 (0.438–1.591)	0.583
Type IV to Type I	0.195 (0.041–0.918)	0.039
Branching-site occlusion	0.354 (0.179–0.701)	0.003
tFPE		
CBS	1.335 (1.043–1.709)	0.022
IVT	0.248 (0.054–1.129)	0.071
Branching-site occlusion	0.356 (0.153–0.828)	0.016
TOAST		0.110
Cardioembolic to atherosclerosis	0.574 (0.288–1.142)	0.114
Other or unknown to atherosclerosis	0.305 (0.087–1.067)	0.063

mFPE, modified first-pass effect; tFPE, true first-pass effect; CBS, clot burden score.

In addition, tFPE was achieved in 21.2% (59 out of 278) of patients, the details of which are shown in **Table 1**. When comparing patients' characteristics after adjustment for confounding factors in the backward stepwise logistic regression analysis, we found that higher CBS (OR = 1.328; 95%CI:1.045–1.688; $p = 0.021$) and truncal-type occlusion (OR: 0.356; 95%CI: 0.153–0.828; $p = 0.016$) were statistically significant predictors of tFPE (**Table 2**).

FPE and Functional Outcomes

Table 3 demonstrates a significantly shorter median time to revascularization in the mFPE group (media, 40 vs. 78 min, $p < 0.001$). The FPE group of patients had significantly better 90-day clinical outcomes than those in the non-FPE group (**Figure 4**).

Based on patients' 90-day functional outcomes, we further divided the population into a good outcome group (mRS $\leq$ 2) and poor outcome group (mRS > 2), and significant variables in the univariate analysis were entered into the multivariate logistic model (**Table 4**). After adjusting for variables, including mFPE, age, sex, smoking, NIHSS, ASPECT, TOAST, CBS, collateral, occluded site, mTICI, and sICH, mFPE (OR: 0.347; 95%CI: 0.159–0.760; $p = 0.008$) and tFPE (OR: 0.315; 95%CI: 0.134–0.743; $p = 0.008$), still remained a separate independent predictor of favorable clinical outcome (**Table 5**).

DISCUSSION

In our study, the predictors that reduced reaching FPE include lower CBS and branching-site occlusion type. However, the severe tortuous anatomy of both extracranial and intracranial segments of ICA could reduce reaching mFPE. Patients who achieved FPE, regardless of mFPE and tFPE, had shorter procedure time, lower NIHSS score at 24 h, and were associated with a higher likelihood of favorable outcomes.

The frequency of FPE in our study was 30.2% (mFPE) and 21.2% (tFPE). In general, the probability of achieving mFPE in previous studies was 39–47.3% (16, 17), while tFPE was 25.1–38.7% (4, 8). The difference in frequency among these studies

TABLE 3 | Comparison in efficacy and safety outcomes according to mFPE and tFPE.

	All N = 278	mFPE			tFPE		
		mFPE (+) N = 84	mFPE (–) N = 194	P	tFPE (+) N = 59	tFPE (–) N = 219	P
Procedural time, media (IQR)	65 (46, 95)	40 (34, 51)	78 (60, 105)	<0.001	40 (35, 52)	74 (56, 102)	<0.001
Number of passes, media (IQR)	2 (1, 3)	1 (1, 1)	3 (2, 3)	<0.001	1 (1, 1)	2 (2, 3)	<0.001
NIHSS at 24 h, media (IQR)	13 (10, 20)	10 (6, 18)	14 (10, 22)	<0.001	10 (6, 15)	14 (10, 22)	<0.001
sICH, *n* (%)	28 (10.2)	6 (7.1)	22 (11.6)	0.264	2 (3.4)	26 (12.1)	0.051
90d mRS $\leq$ 2, *n* (%)	122 (43.9)	54 (64.3)	68 (35.1)	<0.001	41 (69.5)	81 (36.0)	<0.001
90 d Death, *n* (%)	75 (27.0)	17 (20.2)	58 (29.9)	0.096	12 (20.3)	63 (28.8)	0.195

mFPE, modified first-pass effect; tFPE, true first-pass effect; NIHSS, National Institutes of Health Stroke Scale; sICH, Symptomatic Intracerebral Hemorrhage Risk Score; mRS, modified Rankin Scale.

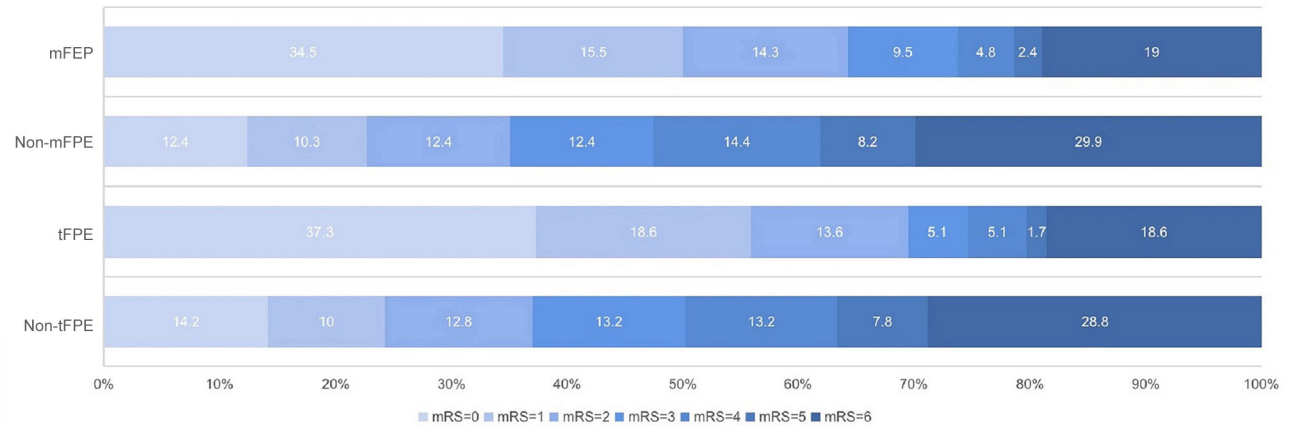

FIGURE 4 | The 90-day modified Rankin Scale (mRS) score in patients who underwent endovascular treatment with or without first-pass effect.

may be due to their combined strategies and the use of different thrombectomy devices.

In this study, we found that the tortuosity of the extracranial segment of ICA can significantly affect the acquisition of mFPE (severe tortuosity vs. normal or mild tortuosity: OR = 0.506; 95%CI: 0.288–0.889; $p = 0.018$). Moreover, in the intracranial segment of ICA, the mFPE rate of Type I is five times more than Type IV (Type IV vs. Type I: OR: 0.195, 95%CI: 0.041–0.918, $p = 0.039$). Tortuous vascular pathways may be age-related degenerative changes and associated with the burden of atherosclerotic disease (18). A previous histological examination of tortuous ICAs found that metaplastic changes occurred in the tunica media of affected vessels, wherein muscular and elastic tissue was replaced by loose connective tissue (19). The severe anatomic difficulties could not only affect the ability and speed of SR getting into the target vessel, but also hinder the removal of the thrombus. The stent may get stuck in the curved vessels and be stretched under the pulling force, deforming the stent that originally fit closely with thrombi, resulting in detachment (7). However, with the development of technology and equipment of EVT, the newer-generation large-bore contact aspiration (AC) or distal access catheter (DAC) was suggested to be used to overcome the tortuosity of the vascular path to provide a good support for distal progression and aspiration capacity (20). In addition, it is suggested that a direct carotid approach should be considered when a patient is presented with unfavorable anatomy to minimize the operation difficulty and duration (13).

Due to the acute angle of the left CCA origin in relation to the aortic arch, the anatomy of type III/bovine aortic arch adds difficulty in navigating the aortic arch for left-sided strokes (21). However, it was not statistically significant with FPE in this study. We speculate that it may be due to the aortic arch being the beginning of the vessel path. After the guidewire and catheter have passed through the aortic arch, it has little effect on whether the distal occlusion site can be recanalized for the first time.

A low CBS means that the thrombus is more widely obstructed, and we found that a thrombus with lower CBS was more difficult to remove through just one pass. Since EVT is a mechanical method of thrombus removal, the physical properties of the thrombus (e.g., length, volume) are critical to its technical success. In addition, a large clot burden often implies increments in volume and length. Hence, the friction between the thrombus and the vessel wall would be higher. Pulling the stent can lead to deformation and elongation of the vascular tissue, making the pathway longer and more difficult to manipulate (22). Previous studies have determined thrombus size on 3-dimensional CT images and found that patients with mFPE had significantly smaller thrombus volumes (23).

In our study, we observed that the truncal-type occlusion could achieve FPE much easier. We hypothesized that in the branching-site occlusions, it is difficult to remove both branches of the Y- or T- type occlusions through just one pass. In most instances, one of the branches can be removed in one operation at most, while the other branch would most likely break off in the vessel and require another attempt or more. Previous studies have correlated the angiographic occlusion type with the etiology. They found that truncal-type occlusion usually originated from atherosclerosis in large intracranial arteries, whereas branching-site occlusion is mostly due to cardiogenic embolism, lodged in the sharp turns of the bifurcation of a vessel (5, 11). One of the reasons of this is that cardiogenic thrombi seemed to have a higher proportion of fibrin compared to other stroke etiologies, making it associated with worse interventional recanalization (24). It was suggested that the atherosclerotic occlusion is more likely to cause intima injury, which would activate the platelets and again lead to occlusion. However, this situation is not very common and occurs after getting recanalization. Hence, this is not related to the rate of FPE in our study. In addition, for most patients with suspected intracranial arteriosclerosis, angioplasty or stent is the first choice in our center. Hence, these patients have been excluded.

Research showed that the rate of FPE would be increased by 3–4 times with the use of a balloon-guide catheter (8). The size of AC and the combined strategy (SR+AC) were also

TABLE 4 | Univariable analysis of 90-day outcomes in patients with endovascular thrombectomy (EVT).

	Good outcome, *N* = 122	Poor outcome, *N* = 156	*P*
Age y, mean (SD)	66.4 (10.9)	71.6 (10.5)	**<0.001**
Sex (male), *n* (%)	71 (58.2)	71 (45.5)	**0.040**
Smoking, *n* (%)	40 (33.3)	32 (20.8)	**0.019**
Baseline SBP, media (IQR)	145 (131, 160)	150 (135.5, 165)	0.111
Baseline DBP, media (IQR)	82 (72, 90)	81 (74, 92)	0.535
HBP, *n* (%)	82 (67.2)	120 (76.9)	0.071
DM, *n* (%)	15 (12.3)	29 (18.6)	0.186
NIHSS, media (IQR)	14 (12, 17)	17 (14, 20)	**<0.001**
ASPECT, media (IQR)	9 (8, 10)	8 (7, 9)	**<0.001**
TOAST, *n* (%)			**<0.001**
Atheroma	46 (37.7)	28 (17.9)	
Cardio-emboli	63 (51.6)	112 (71.8)	
Others	13 (10.6)	16 (10.3)	
OTP, media (IQR)	270 (220, 385)	270 (210, 311)	0.904
OTR, media (IQR)	330 (277, 385)	348 (290, 395)	0.149
CBS, media (IQR)	8 (7, 8)	7 (5, 8)	**<0.001**
Collateral, *n* (%)			**<0.001**
Grade 0	7 (5.7)	61 (39.1)	
Grade 1	42 (34.4)	59 (37.8)	
Grade 2	73 (59.8)	36 (23.1)	
IVT, *n* (%)	15 (12.3)	14 (9.0)	0.431
Modified First-pass effect, *n* (%)	54 (44.3)	30 (19.2)	**<0.001**
True First-pass effect, *n* (%)	41 (33.6)	18 (11.5)	**<0.001**
mTICI <2b, *n* (%)	15 (12.3)	61 (39.1)	**<0.001**
Site of occlusion, *n* (%)			**0.005**
ICA	32 (26.2)	70 (44.9)	
Proximal MCA/ACA	78 (63.9)	77 (49.4)	
Distal MCA/ACA	12 (9.8)	9 (5.8)	
sICH, *n* (%)	2 (1.6)	26 (17.1)	**<0.001**

NIHSS, National Institutes of Health Stroke Scale; ASPECT, Alberta Stroke Program Early CT; TOAST, the Trial of ORG 10172 in Acute Stroke Treatment. IVT, intravenous thrombolysis; MCA, middle cerebral artery; ACA, anterior cerebral artery; ICA, internal carotid artery; mTICI, modified Thrombolysis in Cerebral Infarction; OTP, symptom onset to groin puncture time; OTR, time from stroke onset to recanalization; baseline SBP, baseline systolic blood pressure; baseline DBP, baseline diastolic blood pressure; sICH, Symptomatic Intracerebral Hemorrhage Risk Score. The bold values indicate the variable's P value < 0.05.

TABLE 5 | Multivariable analysis of predictors of 90-day outcomes mFPE and FPE.

	OR (95%CI)	*P*
mFPE		
Age	1.038 (1.007–1.070)	0.016
NIHSS	1.133 (1.042–1.231)	0.003
ASPECT	0.639 (0.484–0.843)	0.002
CBS	0.826 (0.683–0.999)	0.049
Collateral		<0.001
Grade 1 to Grade 0	11.351 (3.860–33.378)	<0.001
Grade 2 to Grade 0	2.396 (1.211–4.741)	0.012
Modified First-pass effect	0.347 (0.159–0.760)	0.008
mTICI <2b	0.486 (0.211–1.118)	0.090
sICH	8.553 (1.535–47.655)	0.014
tFPE		
Age	1.043 (1.011–1.076)	0.008
NIHSS	1.130 (1.041–1.228)	0.004
ASPECT	0.643 (0.488–0.848)	0.002
CBS	0.806 (0.668–0.973)	0.025
Collateral		<0.001
Grade 1 to Grade 0	10.220 (3.571–29.249)	<0.001
Grade 2 to Grade 0	2.338 (1.179–4.639)	0.015
True First-pass effect	0.315 (0.134–0.743)	0.008
mTICI <2b	0.439 (0.195–0.990)	0.047
sICH	7.904 (1.509–41.391)	0.014

mFPE, modified first-pass effect; tFPE, true first-pass effect; NIHSS, National Institutes of Health Stroke Scale; ASPECT, Alberta Stroke Program Early CT; CBS, clot burden score; mTICI, modified Thrombolysis in Cerebral Infarction; sICH, Symptomatic Intracerebral Hemorrhage Risk Score.

critical factors (25–27). We believe that the achievement of FPE would improve over time with experienced operators and new equipment and strategies specifically designed to improve clot removal efficiency.

Consistent with previous studies (8, 28), we also found that FPE can significantly improve the good prognosis of patients, regardless of mFPE and tFPE. The technically complete recanalization achieved after several passes is related to longer procedural time and poorer outcomes (20, 29), hence it being the so-called "futile" reperfusion. Furthermore, after multiple passes, the elastic morphology of thrombus changes, resulting in an increase in the sliding friction coefficient and make the clot become harder to retrieve (30). The future randomized clinical trials should pay more attention on how to provide a fast, complete, and safe revascularization during EVT.

LIMITATIONS

Our study has several limitations. First, it was an observational study based on retrospective analysis. Hence, missing and unknown data might cause a selection bias. Second, this study included patients who were treated with SR, therefore, the interpretation of our results should be limited to the use of an SR. This is because the association between the thrombus characteristics and recanalization might differ among the mechanical devices used. Finally, this was a single-center, small sample-sized study. Therefore, a multicenter prospective study might be required in the future.

CONCLUSION

In this study, the FPE rate was associated with CBS, the tortuosity of ICA, and the angiographic occlusion type. The rate of improved clinical and safety outcomes was higher in the FPE group compared to the non-FPE group. Therefore, achieving complete reperfusion at the first pass seems to be pivotal in the future of EVT treatment.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Scientific Research and New Technology IRB of Wannan Medical College Yijishan Hospital. The patients/participants provided their written informed consent to participate in this study. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

AUTHOR CONTRIBUTIONS

CC, TZ, and XH designed the study. XX, JX, and KY contributed to data acquisition. YX, LY, and QY performed image analysis. CC and TZ wrote the primary manuscript. XH and ZZ contributed to critical revision and final approval of the manuscript. All authors contributed to the article and approved the submitted version.

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