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New insights into the treatment of aneurysms with flow diverters: Novel indications and therapeutic advances, 2nd Edition

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New insights into the treatment of aneurysms with flow diverters: Novel indications and therapeutic advances, 2nd Edition

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Editorial: New insights into the treatment of aneurysms with flow diverters: novel indications and therapeutic advances

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intracranial aneurysm, flow diverter, safety, indication, treatment advance

Editorial on the Research Topic
New insights into the treatment of aneurysms with flow diverters: novel indications and therapeutic advances

Flow diverters (FD) have originally been used primarily for large or giant unruptured aneurysms in the internal carotid artery. In recent years, the efficacy of such devices has led to their application in different circumstances, which include small or medium aneurysms, posterior circulation aneurysms, distal artery aneurysms, ruptured aneurysms, and traumatic aneurysms. However, while the use of FD in internal carotid unruptured aneurysms has been well-established, the usage in other scenarios remains a topic of debate. More information is needed for such applications. In addition, with the wide usage of FD in various aneurysms, new devices, novel therapeutic strategies, and approaches emerged, which simplify the usage of FD, and may have helped in reducing the complications. This Research Topic has collected a series of studies concerning such topics, i.e., FD out-of-the-box usage and therapeutic advances, to provide new insights into the treatment of aneurysms with FD.

The topic included 10 papers concerning different usages of FDs. Two of them were about the usage of FDs in the treatment of Blood Blister Aneurysms. Liu P. et al. introduced the results of 12 BBA patients in their single-center study, and Yan et al. studied the clinical and angiographic results of 13 recurrent BBAs. In both studies, all patients had favorable outcomes and satisfactory complete occlusion at the last follow-up. Two articles studied the application of FDs in small or medium aneurysms. Both Xie et al.'s and Li et al.'s articles showed that the treatment of small unruptured intracranial aneurysms with FD can be performed safely with satisfactory outcomes. Another six articles concentrated on posterior circulation aneurysms. Zhang et al. compared the safety of FD vs. conventional stent-assisted coiling in the treatment of vertebrobasilar dissecting aneurysms with intramural hematoma, basilar trunk and vertebrobasilar junction aneurysms, and intradural large vertebrobasilar artery aneurysms, respectively. Interestingly, all of them indicated a potential superiority of FD over conventional stents due to fewer complications and their effect in reducing intramural hematoma size. In the remaining three articles, Wang et al. introduced their experience of FD implantation in 16 patients with basilar artery aneurysms, which also indicated that FD is feasible and relatively safe in selected patients. Among 16 included patients, three experienced procedural complications (18.8%), including two ischemic

strokes and one hydrocephalus, with resultant mortality in one case (6.3%). Median follow-up was 7.7 months and was available for 15 aneurysms. Complete/near-complete occlusion was seen in 13 (86.7%) aneurysms. A favorable result was also observed in Lu et al.'s study with 17 unruptured vertebral artery dissecting aneurysms. Xu et al. compared the results of FDs in anterior and posterior circulations and concluded that anterior circulation fusiform aneurysms have a lower occlusion rate than posterior circulation fusiform aneurysms.

In addition, another seven articles concerning new devices and treatment strategies were included. Liu X. et al. conducted a meta-analysis to evaluate the feasibility and safety of flow diversion in the treatment of intracranial aneurysms via the trans-radial approach and concluded that the trans-radial approach has a higher success rate and lower access-related complication rate. *Nan Li* introduced a new method, i.e., staged flow diverter implantation, to prevent delayed aneurysm rupture after FD treatment for large or giant aneurysms. In 30 patients with morphologies prone to rupture, no delayed aneurysm rupture occurred. Specifically, although Leo Bay and Neuroform atlas stent are not conventional FDs as we mentioned, the authors mentioned their flow diversion effects, and hence two articles by Duan et al. and Dong et al. were also included.

From the included studies in this Research Topic, it seems FDs are safe and effective in various off-label aneurysms, such as BBA, posterior circulation aneurysms, and small or medium aneurysms. These studies provide new insight into the treatment of aneurysms with FD as we anticipated. However, it also must be noted that patient bias existed in these studies, and overall, the complication rate was not eligible in posterior circulation aneurysms. FD should be chosen only for selected patients. In the future, more studies are needed to explore strategies, such as individual antiplatelet regimens, to decrease the potential complications.

Author contributions

YZ and JL competed the draft. J-HB revised the manuscript extensively. All authors contributed to the article and approved the submitted version.

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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Reconstructive Endovascular Treatment of Basilar Trunk and Vertebrobasilar Junction Aneurysms: A Review of 77 Consecutive Cases

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Background: Basilar trunk and vertebrobasilar junction (BTVBJ) aneurysms have a poor prognosis and are challenging to treat.

Objective: This study aimed to evaluate the efficacy of reconstructive endovascular treatment for BTVBJ aneurysms and explore a treatment selection paradigm.

Methods: Clinical and angiographic data from 77 patients with 80 BTVBJ aneurysms who underwent endovascular treatment with flow diverters (FDs) or conventional stent-assisted coiling between January 2016 and December 2020 were retrospectively analyzed. Aneurysm characteristics and treatment outcomes were compared between treatment groups.

Results: Among the 77 study patients, 34 (44.2%) were treated with FDs and 43 (55.8%) with conventional stent-assisted coiling. Overall, 72.7% of patients achieved favorable clinical outcome at follow-up. The rate of procedure-related complications was 23.4%. The aneurysm occlusion rate at last follow-up did not differ between the FD and conventional stent groups (79.2% vs. 77.1%, $p = 0.854$). Although the occlusion rate immediately after the procedure was lower in the FD group (29.4%), incidence of progressive occlusion was significantly higher (62.5 vs. 5.7%; $p < 0.001$). The proportion of patients with large and giant aneurysms (≥10 mm) was significantly higher in the FD group (70.6 vs. 34.8%; $p = 0.002$). In patients with large or giant aneurysms, favorable clinical outcome at last follow-up was achieved in 75% of patients in the FD group but only 43.8% of patients in the conventional stent group ($p = 0.046$). Moreover, the complication rate was lower in the FD group, but the difference was not significant (20.8 vs. 37.5%; $p = 0.247$). The same analyses were performed for patients with small aneurysms (<10 mm) but no significant differences between the two groups were observed.

Conclusion: Endovascular treatment of small BTVBJ aneurysms using either FDs or conventional stents was feasible and effective. In patients with large or giant aneurysms, treatment using FDs achieved higher rates of occlusion and favorable clinical outcome at last follow-up than conventional stent-assisted coiling.

Keywords: intracranial aneurysm, basilar trunk, vertebrobasilar junction, endovascular treatment, prognosis

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INTRODUCTION

Aneurysms of the basilar trunk and vertebrobasilar junction (BTVBJ) are rare, comprising only 2.7% of all intracranial aneurysms (1). According to the International Study of Unruptured Intracranial Aneurysms, posterior circulation aneurysms, particularly those located on the basilar artery, have a higher risk of rupture (2). Considering their high rupture risk and the potentially fatal consequences of rupture, treatment of these aneurysms is necessary. Surgery of posterior circulation aneurysms is difficult and risky because of their anatomical location; therefore, endovascular therapy has become the mainstay of treatment (3–6). Treatment using conventional stents and flow diverters (FDs) has been shown to be safe and effective (7–9). The use of FDs to treat posterior circulation aneurysms has become more common in recent years (10). This study aimed to evaluate the efficacy of reconstructive endovascular treatment (EVT) for BTVBJ aneurysms and explore a treatment selection paradigm.

MATERIALS AND METHODS

Patient Selection and Data Collection

We retrospectively reviewed the data of patients with intracranial aneurysms who were treated in our center from January 2016 to December 2020. Patients who met the following criteria were included for analysis: (1) BTVBJ aneurysm was diagnosed using digital subtraction angiography (DSA); (2) the aneurysm was not dolichoectatic, traumatic or iatrogenic; (3) the aneurysm was treated using stent-assisted coiling or flow diversion; and (4) clinical follow-up data were available. The study flowchart is shown in **Figure 1**. BTVBJ aneurysm was defined as an aneurysm located anywhere from and including the vertebrobasilar junction to the superior cerebellar artery. Data including age, sex, smoking and alcohol use history, history of hypertension and diabetes mellitus, clinical profile, aneurysm characteristics, and procedural details and complications were obtained from the medical records. Imaging studies were examined to determine aneurysm number, size, shape, and parent artery. Approval by the institutional review board and ethics committee of Beijing Tiantan Hospital was obtained.

Antiplatelet and Anticoagulation Therapies

Patients with an unruptured aneurysm received clopidogrel 75 mg and aspirin 100 mg each day for at least 5 days before the procedure. Those with a ruptured aneurysm received clopidogrel 300 mg and aspirin 300 mg 2 h before the procedure. Systemic intravenous heparin was administered throughout the endovascular procedure to maintain an activated clotting time between 250 and 300 s. Patients were treated with conventional stenting or flow diversion as appropriate. After the procedure, patients who underwent FD placement received clopidogrel for 6 months and aspirin indefinitely; those treated with conventional stenting received clopidogrel for 3 months and aspirin for 6 months.

Endovascular Procedure

Procedures were performed by multiple neurointerventionalists. Treatment decisions were discussed among the neurointerventionalists and made by consensus at the daily peer-reviewed endovascular conference in our center. General anesthesia was used in all patients. After using the Seldinger technique to puncture the femoral arteries bilaterally, the sheath was placed. The guiding catheter was placed in the vertebral

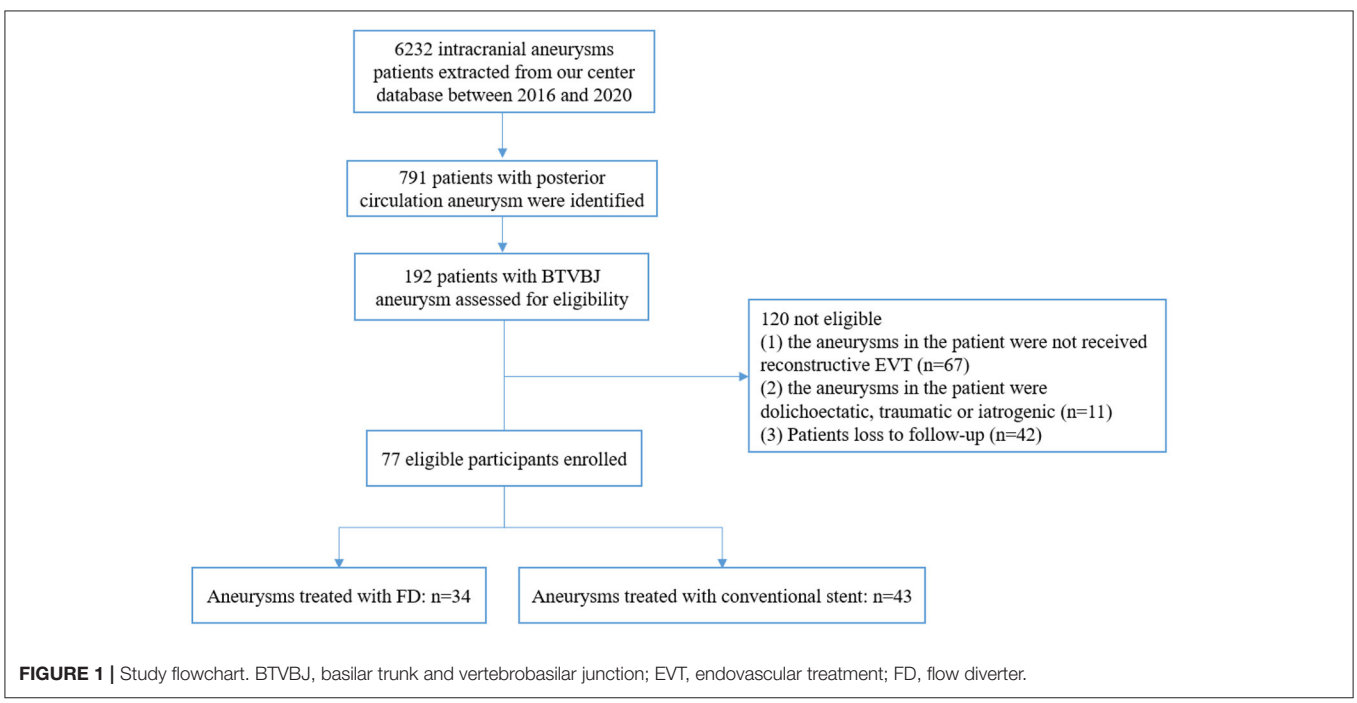

FIGURE 1 | Study flowchart. BTVBJ, basilar trunk and vertebrobasilar junction; EVT, endovascular treatment; FD, flow diverter.

artery at the C1–C2 level for three-dimensional rotational DSA to select the best working projection and measure the parameters of the parent artery. Stent selection was at the discretion of the operator and was partly based on the results of DSA. In most cases, only implantation of a single stent or FD was required. Multiple devices were used in patients with long lesions or large aneurysms. The conventional stents used in this study included the Enterprise (Cerenovus, Raynham, MA, USA), LVIS (MicroVention, Tustin, CA, USA), Neuroform (Stryker Neurovascular, Fremont, CA, USA), and Solitaire (Covidien, Irvine, CA, USA) stents. The FD used was the Pipeline Embolization Device (Medtronic, Minneapolis, MN, USA). For aneurysms treated with flow diversion, the stent-jailing technique was used to coil the aneurysm or eccentric lumen if the diameter of the aneurysm or eccentric lumen exceeded 10 mm.

Follow-Up and Clinical Outcomes

Follow-up data were obtained from the medical records and via telephone. Two experienced neurologists performed clinical evaluations and follow-up assessments. The modified Rankin Scale (mRS) was used to evaluate patients at hospital admission, discharge, and last follow-up. Favorable clinical outcome was defined as mRS score 0–2. Postoperative imaging follow-up was performed using DSA, computed tomography angiography (CTA), and magnetic resonance angiography (MRA). Generally, DSA was performed at the 6-month and 1-year follow-ups; thereafter, CTA or MRA were performed yearly. Immediate and follow-up angiographic results were classified using the O'Kelly–Marotta (OKM) grading scale (A, total filling; B, subtotal filling; C, entry remnant; D, no filling). Favorable angiographic outcome was defined as OKM grades C and D. Recurrence was defined as any increase in the size of the aneurysmal remnant during follow-up.

Statistical Analysis

Statistical analyses were performed using SPSS software version 25 (IBM Corp., Armonk, NY, USA). Continuous variables are presented as means with standard deviation. Categorical variables are reported as proportions. The Shapiro–Wilk test was used to assess normality of variables. Patients and aneurysms were grouped according to type of treatment (conventional or FD stent). Group comparisons were performed using the independent samples *t*-test, χ^2 test, or Fisher exact test as appropriate. $P < 0.05$ was considered significant.

RESULTS

Patient and Aneurysm Characteristics

A total of 77 patients with 80 BTVBJ aneurysms underwent EVT: 67 (87%) were treated electively and 10 (13%) in the setting of subarachnoid hemorrhage. Forty-three aneurysms in 40 (57.3%) patients were treated using conventional stents and 34 aneurysms in 34 (42.7%) patients were treated using FDs. Overall, mean patient age was 54.57 ± 13.8 years (range, 10–76). Twenty-five were female (32.5%) and 52 were male (67.5%). Clinical presentation was as follows: incidental finding, 15 (19.5%); acute subarachnoid hemorrhage, 10 (13%); mass effect on the brain stem, 31 (40.3%); ischemic stroke, 7 (9.1%); and headache, 14 (18.2%). Mean aneurysm size was 11.8 ± 8.7 mm (range, 1.2–38.3). Mean clinical follow-up was 27.9 ± 14.9 months. Mean imaging follow-up was 12.3 ± 8.3 months.

TABLE 1 | Patient and aneurysm characteristics.

	FD group	Conventional stents group	Total	Significance (*P*-Value)
Patients	34	43	77	
Mean Age (yrs)	50.88 ± 18.6	57.5 ± 7.4	54.57 ± 13.8	0.064
Female, *n* (%)	15 (44.1%)	10 (23.3%)	25 (32.5%)	0.052
Co-morbidities, *n* (%)				
Hypertension	19 (55.9%)	31 (72.1%)	50 (64.9%)	0.139
Diabetes	4 (11.8%)	12 (27.9%)	16 (20.8%)	0.083
Cerebral infarction	7 (20.6%)	16 (37.2%)	23 (29.9%)	0.114
Cardiac disease	3 (8.8%)	7 (16.3%)	10 (13.0%)	0.334
Smoking	11 (32.4%)	22 (51.2%)	33 (42.9%)	0.098
Drinking	8 (23.5%)	19 (44.2%)	27 (35.1%)	0.059
Symptomatic, *n* (%)	31 (91.2%)	31 (72.1%)	62 (80.5%)	**0.036**
Presentation, *n* (%)				
Stroke	1 (2.9%)	6 (14.0%)	7 (9.1%)	
SAH	3 (8.8%)	7 (16.3%)	10 (13.0%)	
Mass effect	18 (52.9%)	13 (30.2%)	31 (40.3%)	
Headache	9 (26.5%)	5 (11.6%)	14 (18.2%)	
Incidental	3 (8.8%)	12 (27.9%)	15 (19.5%)	
Aneurysm	34	46	80	
Mean aneurysm diameter	16.42 ± 10.5	8.34 ± 4.9	11.79 ± 8.7	**0.000**
Aneurysm size				
Small (<10 mm)	10 (29.4%)	30 (65.2%)	40 (50.0%)	**0.002**
Large (10–25 mm)	15 (44.1%)	15 (32.6%)	30 (37.5%)	0.293
Giant (>25 mm)	9 (26.5%)	1 (2.2%)	10 (12.5%)	**0.001**
Location, *n* (%)				0.064
BA trunk	21 (61.8%)	37 (80.4%)	58 (72.5%)	
VB junction	13 (38.2%)	9 (19.6%)	22 (27.5%)	
Morphology, *n* (%)				**0.001**
Saccular	9 (26.5%)	30 (65.2%)	39 (48.8%)	
Fusiform	25 (73.5%)	16 (34.8%)	41 (51.2%)	
Treatment modality				**0.000**
Stents alone	21 (61.8%)	0 (0%)	21 (26.3%)	
Stents with coils	13 (38.2%)	46 (100%)	59 (73.8%)	
Operation time (min)	134.51	133.35	133.86	0.731

FD, flow diverter; SAH, subarachnoid hemorrhage; BA, basilar artery; VB, vertebrobasilar. Boldface type indicates statistical significance.

Age, sex, smoking, alcohol use, hypertension, diabetes, cardiac disease, and aneurysm location did not significantly differ between the groups. Aneurysm morphology significantly differed between groups ($p = 0.001$): in the FD group, 9 aneurysms (26.5%) were saccular and 25 (73.5%) were fusiform; in the conventional stent group, the corresponding numbers were 30 (65.2%) and 16 (34.8%), respectively. Mean aneurysm diameter (16.4 vs. 8.3 mm; $p < 0.001$) and proportion of aneurysms ≥10 mm in diameter (70.6 vs. 34.8%; $p = 0.002$) were significantly higher in the FD group. A significantly higher proportion of patients in the FD group were symptomatic (91.2 vs. 72.1%;

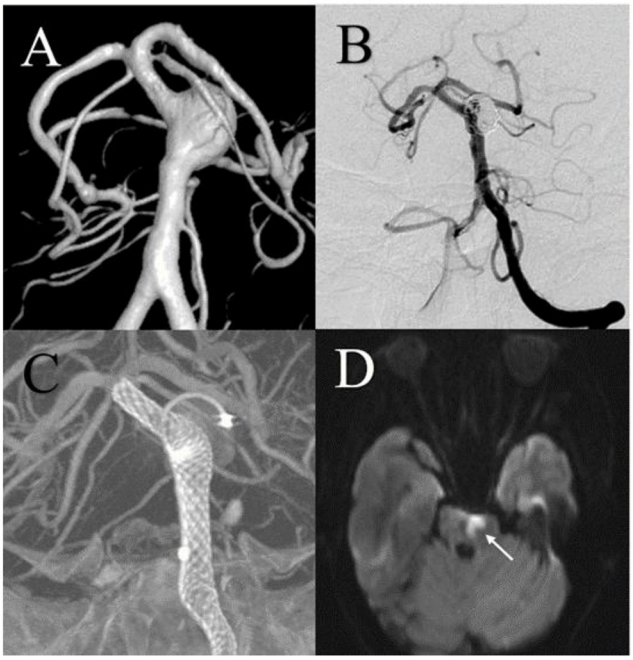

FIGURE 2 | A 68-year-old male with a large basilar trunk aneurysm was treated using a flow diversion stent and experienced an acute ischemic complication. **(A)** Digital subtraction angiography showed the large aneurysm. **(B,C)** Postembolization angiography showed almost complete embolization of the aneurysm. The Pipeline Embolization Device (Medtronic, Minneapolis, MN, USA) exhibited good vessel wall apposition. **(D)** Two days after the procedure, acute ischemic stroke was shown on diffusion-weighted imaging.

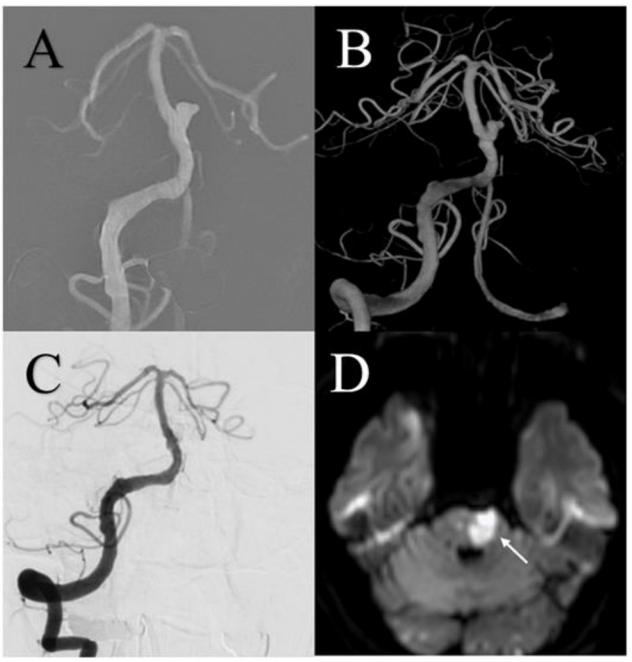

FIGURE 3 | A 61-year-old male with a small basilar trunk aneurysm was treated using an LVIS stent (MicroVention, Tustin, California, USA) and experienced an acute ischemic complication. **(A,B)** Preoperative anteroposterior and three-dimensional reconstruction digital subtraction angiography showed a small aneurysm. **(C)** Angiography immediately after the procedure showed complete aneurysm embolization. **(D)** One week after the procedure, acute ischemic stroke was shown on diffusion-weighted imaging.

$p = 0.036$). Patient and aneurysm characteristics are shown in **Table 1**.

Postprocedural Angiographic and Clinical Results

EVT was successful in all BTVBJ aneurysms. All parent arteries and relevant branches showed good patency on postoperative angiography. Twenty-one aneurysms (62.5%) in the FD group were treated with stenting alone, compared with no aneurysm in the conventional stent group ($p < 0.001$). The rate of favorable angiographic outcome (OKM grades C and D) immediately after the procedure was significantly lower in the FD group (29.4%vs. 84.8%; $p < 0.001$).

Procedure-related complications occurred in 8 patients (23.5%) in the FD group and 10 patients (23.3%) in the conventional stent group ($p = 0.978$). Ischemic events were the most common complication and occurred in 4 patients (11.8%) in the FD group and 9 patients (20.9%) in the conventional stent group ($p = 0.286$; **Figures 2**, **3**). Delayed aneurysmal rupture occurred in 1 patient (2.9%) in the FD group and 2 (4.7%) patients in the conventional stent group ($p = 0.700$). Three patients (8.8%) in the FD group experienced worsening mass effect symptoms after the procedure; all three harbored a giant aneurysm (>25 mm).

Before treatment, mRS score did not significantly differ between groups ($p = 0.942$). The incidence of poor clinical outcome at the time of hospital discharge was 14.7% in the FD group and 16.3% in the conventional stent group. The difference was not significant ($p = 0.850$). Postprocedural angiographic and clinical results are shown in **Table 2**. **Table 3** presents detailed information of the patients who experienced a poor clinical outcome at the time of hospital discharge.

Follow-Up Angiographic and Clinical Outcome

Angiographic follow-up was available for 24 patients (70.6%) in the FD group and 35 patients (81.4%) in the conventional stent group. Mean angiographic follow-up was 13.1 ± 10 months in the FD group and 11.5 ± 6 months in the conventional stent group. Favorable angiographic outcome (OKM grades C and D) was achieved at last follow-up in 19 patients (79.2%) in the FD group and 27 patients (77.1%) in the conventional stent group ($p = 0.854$).

Clinical follow-up data were available for all patients. Mean clinical follow-up was 28.5 months (range, 5–67) in the FD group and 27.4 months (range, 5–57) in the conventional stent group. Favorable clinical outcome (mRS score 0–2) was achieved at last follow-up in 25 patients (73.5%) in the FD group and 31 patients (72.1%) in the conventional stent group ($p = 0.888$).

TABLE 2 | Immediate and follow-up angiographic and clinical outcomes.

	FD group	Conventional stents group	Total	Significance (*P*-Value)
Immediate angiographic	34	46	80	
Favorable results, *n* (%)	10 (29.4%)	39 (84.8%)	49 (61.3%)	**0.000**
C	4 (11.8%)	16 (34.8%)	20 (25%)	
D	6 (17.6%)	23 (50.0%)	29 (36.3%)	
Unfavorable results, *n* (%)	24 (70.6%)	7 (15.2%)	31 (38.8%)	
A	14 (41.2%)	3 (6.5%)	17 (21.3%)	
B	10 (29.4%)	4 (8.7%)	14 (17.5%)	
Last angiographic	24	35	59	
Favorable results, *n* (%)	19 (79.2%)	27 (77.1%)	46 (78%)	0.854
C	2 (8.3%)	9 (25.7%)	11 (18.6%)	
D	17 (70.8)	18 (51.4%)	35 (59.3%)	
Unfavorable results, *n* (%)	5 (20.8%)	8 (22.9%)	13 (22%)	
A	2 (8.3%)	1 (2.9%)	3 (5%)	
B	3 (12.5%)	7 (20%)	10 (16.9%)	
Change of occlusion, *n* (%)				
Progressive occlusion	15 (62.5%)	2 (5.7%)	17 (28.8%)	**0.000**
Stable occlusion	8 (33.3%)	26 (74.3%)	34 (57.6%)	**0.002**
Recanalization	1 (4.2%)	7 (20%)	8 (13.6%)	0.081
Angiographic follow-up time (Mean, months)	13.1	11.5	12.3	0.58
mRS score at admission, n(%)				0.942
0∼2	31 (91.2%)	39 (90.7%)	70 (90.0%)	
3∼6	3 (8.8%)	4 (9.3%)	7 (9.1%)	
mRS score at discharge, *n* (%)				0.850
0∼2	29 (85.3%)	36 (83.7%)	65 (84.4%)	
3∼6	5 (14.7%)	7 (16.3%)	12 (15.6%)	
mRS score at follow-up, *n* (%)	32	40	72	0.888
0∼2	25 (73.5%)	31 (72.1%)	56 (72.7%)	
3∼6	9 (26.5%)	12 (27.9%)	21 (27.3%)	
Clinical follow-up time (Mean, months)	28.5	27.4	27.9	0.759
Mortality rate, *n* (%)	6 (17.6%)	3 (7.0%)	9 (11.7%)	0.148
Complication, *n* (%)	8 (23.5%)	10 (23.3%)	18 (23.4%)	0.978
BA trunk	5 (23.8%)	8 (21.6%)	13 (22.4%)	0.848
VB junction	3 (23.1%)	2 (22.2%)	5 (22.7%)	1
Second operation, *n* (%)	1 (2.9%)	2 (4.7%)	3 (3.9%)	0.700

FD, flow diverter; mRS, modified Rankin scale.
Boldface type indicates statistical significance.

Overall mortality was 11.7% (9/77); mortality rates in the FD and conventional stent groups were 17.6% (6/34) and 7.0% (3/43), respectively.

In the patients with angiographic follow-up, the recurrence rates were 4.2% (1/24) in the FD group and 20% (7/35) in the conventional stent group ($p = 0.124$). The re-treatment rate was 2.9% (1/34) in the FD group (because of stent migration) and 4.7% (2/43) in the conventional stent group (both because of recanalization) but the difference was not significant (**Figure 4**). Detailed follow-up outcome data are summarized in **Table 2**.

Treatment Results According to Aneurysm Size

BTVBJ aneurysms were divided into two subgroups according to size using a 10 mm cutoff. Incidence of favorable angiographic outcome at last follow-up was significantly higher in patients with aneurysms <10 mm in size (87.9 vs. 65.74%; $p = 0.038$), as was incidence of favorable clinical outcome (83.8 vs. 62.5%; $p = 0.036$). Among patients with aneurysms ≥10 mm, favorable clinical outcome was achieved in 75% (18/24) of patients in the FD group and 43.8% (7/16) of patients in the conventional stent group ($p = 0.046$); the incidence of procedure-related complications was lower in the FD group but the difference was not significant (20.8 vs. 37.5%; $p = 0.247$). Among patients with aneurysms <10 mm, the incidence of favorable clinical outcome was higher (70 vs. 88.9%; $p = 0.313$) and the incidence of procedure-related complications was lower (30 vs. 13.3%; $p = 0.471$) in the conventional stent group; however, the differences were not significant. Treatment results according to aneurysm size are summarized in **Table 4**.

DISCUSSION

The risk of enlargement and rupture is higher in aneurysms located in the posterior circulation, particularly those of the vertebrobasilar junction or basilar trunk (5, 11, 12). Considering the potentially fatal consequences, early intervention is necessary. Surgical treatment' for BTVBJ aneurysms is challenging and associated with high morbidity and mortality because they are deep, difficult to reach, and surrounded by key cerebrovascular structures. Kalani et al. (13) reported only a 27.3% favorable clinical outcome rate in conjunction with 45.4% mortality in patients with large and giant BTVBJ aneurysms who underwent extracranial-intracranial bypass and vessel occlusion. In view of the high rates of disability and mortality associated with surgical treatment of BTVBJ aneurysms, safer and more effective treatments are required, especially for large and giant ones. Traditional EVT modalities have already demonstrated acceptable safety and efficacy profiles; however, outcomes after EVT of large and giant BTVBJ aneurysms remains unsatisfactory (3, 13–16). FDs have become an important tool for treating aneurysms previously considered untreatable (17). However, since perforating arteries are often located near and within BTVBJ aneurysms, many interventionalists still prefer to use traditional techniques rather than FDs. Therefore, evaluating the

TABLE 3 | Clinical details in 10 patients who experienced a poor clinical outcome at time of hospital discharge.

Case No.	Age (Y)/ Sex	Symptoms	Group	Location	Size (mm)	Coils	Complications	Immediate OKM	Last Last OKM	mRS at admission	mRS at discharge	mRS at last
1	62/M	Dizziness	2	BT	6.22	Yes	Cerebral infarction/hemiplegia	B	D	1	4	4
2	64/M	TIA	2	BT	10.9	Yes	Cerebral infarction/ coma	B	B	1	4	4
3[#]	58/M	SAH/HH 2	2	BT	10.2 (BT)/8.84 (BT)	Yes	Cerebral infarction/hemiplegia	D/D	D/D	2	5	3
4	65/M	SAH/HH 4	2	BT	12.9	Yes	Hemorrhage/ coma	D	NA	5	4	6
5	58/F	SAH/HH 4	2	VBJ	7.01	Yes	Hemorrhage/ coma	C	B	5	4	2
6	61/M	Dizziness/ diplopia	2	BT	7.52	Yes	Cerebral infarction/hemiplegia	C	NA	2	5	2
7	68/F	Dizziness	1	BT	9.03	Yes	Perforator ischemia/hemiplegia	B	D	1	3	3
8	37/F	Headache	1	BT	31.5	Yes	Stent retraction	A	D	1	3	1
9	12/M	Headache/ diplopia	1	BT	24.7	No	Contrast neurotoxicity/ coma	B	NA	1	6	6
10	49/F	Headache/ dysphagia	1	VBJ	38.3	Yes	Mass effect/ coma	B	NA	2	3	6

[#] *This patient harbored two aneurysms.*

Patients 1–6 were treated using conventional stents and patients 7–10 using FD stents.

Y, years; F, female; M, male; BT, basilar trunk; VBJ, vertebrobasilar junction; HH, Hunt-Hess grade; SAH, subarachnoid hemorrhage; TIA, transient ischemic attack; mRS, modified Rankin scale; OKM, O'Kelly–Marotta grading scale.

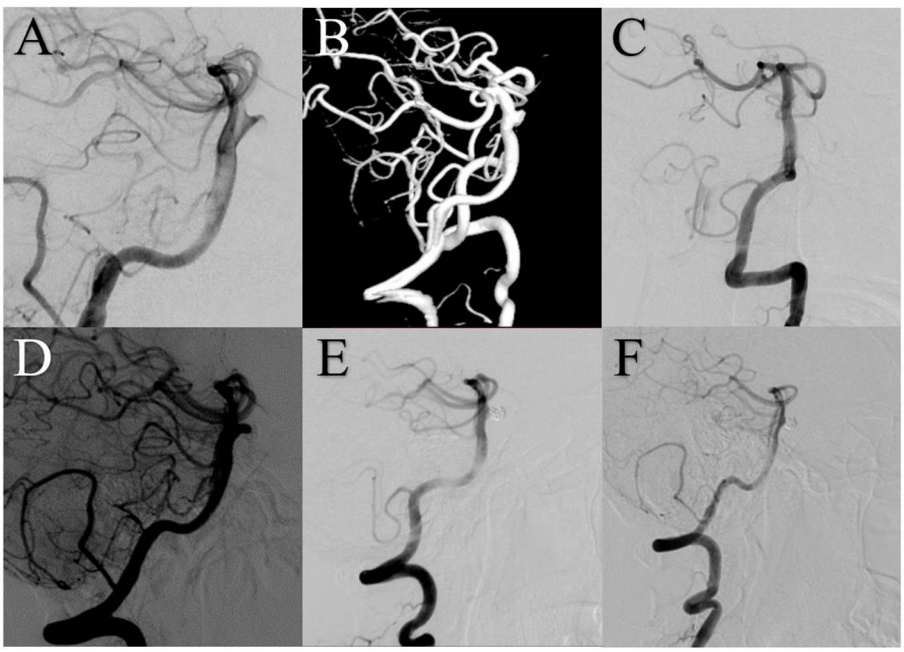

FIGURE 4 | A 44-year-old female with a small basilar trunk aneurysm was treated using an Enterprise stent (Cerenovus, Raynham, Massachusetts, USA). **(A,B)** Digital subtraction angiography (DSA) showed the small aneurysm. **(C)** DSA immediately after treatment showed complete aneurysm embolization. **(D)** Follow-up DSA at 6 months revealed aneurysm recurrence at the level of the neck. **(E)** DSA after coil embolization of the neck remnant showed complete embolization. **(F)** Six months later, DSA showed stable complete occlusion.

efficacy of EVT for BTVBJ aneurysms and comparing outcomes between FDs and conventional stenting is warranted.

In a meta-analysis of flow diversion treatment of posterior circulation non-saccular aneurysms, Kiyofuji et al. (18) reported that neurologic outcome differs according to aneurysm location. Vertebral aneurysms were associated with a higher rate of good neurologic outcome than BTVBJ aneurysms. Several studies have reported unsatisfactory outcomes after EVT of BTVBJ aneurysms. Wang et al. (19) reported an 82.1% favorable outcome rate in conjunction with 17.9% mortality. Another study reported a 78.6% satisfactory outcome rate (3). A more recent retrospective study showed a 15% mortality with a favorable clinical outcome rate of only 67.5%; however, the less favorable clinical outcome rate in this study may be due to the

TABLE 4 | Treatment results according to aneurysm size.

	FD group	Conventional stents group	Total	Significance (*P*-Value)
Aneurysm size≥10 mm				
Patients, *n* (%)	24 (70.6%)	16 (37.2%)	40 (51.9%)	
Mortality rate, *n* (%)	5 (20.8%)	2 (12.5%)	7 (17.5%)	0.497
Follow-up of angiographic[#]	17	9	26	
Favorable results, *n* (%)	12 (70.6%)	5 (55.6%)	17 (65.4%)	0.667
Unfavorable results, *n* (%)	5 (29.4%)	4 (44.4%)	9 (34.6%)	
Complication, *n* (%)	5 (20.8%)	6 (37.5%)	11 (27.5%)	0.247
Follow-up of clinical outcome	24	16	40	
mRS score, *n* (%)				**0.046**
0∼2	18 (75.0%)	7 (43.8%)	25 (62.5%)	
3∼6	6 (25.0%)	9 (56.3%)	15 (37.5%)	
Aneurysm size<10 mm				
Patients, *n* (%)	10 (29.4%)	27 (62.8%)	37 (48.1%)	
Mortality rate, *n* (%)	1 (10%)	1 (3.7%)	2 (5.4%)	1
Follow-up of angiographic[#]	7	26	33	
Favorable results, *n* (%)	7 (100%)	22 (84.6%)	29 (87.9%)	0.555
Unfavorable results, *n* (%)	0 (0%)	4 (15.4%)	4 (12.1%)	
Complication, *n* (%)	3 (30%)	4 (14.8%)	7 (18.9%)	0.471
Follow-up of clinical outcome	10	27	37	
mRS score, *n* (%)				0.313
0∼2	7 (70%)	24 (88.9%)	31 (83.8%)	
3∼6	3 (30%)	3 (11.1%)	6 (16.2%)	

[#]*Angiographic outcome was divided into favorable (O'Kelly–Marotta grading scale C and D) and unfavorable (O'Kelly–Marotta grading scale A and B).*
FD, flow diverter; mRS, modified Rankin scale.
Boldface type indicates statistical significance.

fact that 67.5% of patients presented with aneurysmal rupture (16). Two different studies that comprised 10 patients with vertebrobasilar junction aneurysms showed more encouraging results: a favorable clinical outcome was achieved in all patients in both (8, 20). In contrast, Meckel et al. (21) reported a good outcome in only 60% of patients with large or giant vertebrobasilar junction aneurysms. Although the results of EVT for BTVBJ aneurysms have not always been satisfactory, they may be acceptable compared with the results of other treatments. Furthermore, the studies above only described or reported the safety and efficacy of a single method and did not compare different EVTs.

In our study, 56 BTVBJ aneurysm patients overall (72.7%) achieved a favorable clinical outcome after EVT at last follow-up. Forty patients (50%) harbored large or giant aneurysms. Favorable clinical outcome rate did not significantly differ between patients treated using FDs or conventional stents (73.5 vs. 72.1%, $p = 0.888$). This agrees with prior studies that found no difference in clinical or angiographic outcomes among several EVTs (10, 16). However, 20% of aneurysms treated using a conventional stent later recanalized while those treated using a FD stent showed stable progressive occlusion. In the FD group, the initial occlusion rate (OKM grade C and D) was 28.1%, which increased to 79.2% at last follow-up. The initial and follow-up occlusion rates in the conventional stent group were 88.4 and 77.1%, respectively. Angiographic outcome at last follow-up did not significantly differ between the groups; however, incidence of progressive occlusion was significantly higher in the FD group (62.5 vs. 5.7%; $p < 0.001$). Although the procedure-related complication rate in our study was high, it did not significantly differ between the FD (23.5%) and conventional stent groups (23.3%) and is in line with rates reported in other studies (19, 21). The main risk in either group is an ischemic complication. Although FD treatment would appear to be a high-risk approach to BTVBJ aneurysms because of the presence of numerous brainstem perforators, our study found no significant difference in procedure-related complications between the FD and conventional stent groups.

The FD group in our study harbored a higher number of large and giant (70.6%) or fusiform (73.5%) aneurysms, which can cause brain stem mass effect and are associated with a higher risk of brain ischemia and infarction. This explains the significantly higher proportion of symptomatic patients in the FD group (91.2 vs. 72.1%, $p = 0.036$). Although sex did not significantly differ between the groups, the proportion of women was higher in the FD group. This is consistent with previous studies that reported a higher rates of aneurysm growth in women (11).

In our study, the proportions of fusiform and giant aneurysms were higher in the FD group than the conventional stent group. Considering that the natural history of non-saccular giant BTVBJ aneurysms is poor (14, 22, 23), worse results would be expected in the FD group. However, in our subgroup analysis of patients with aneurysms ≥10 mm, the incidence of favorable clinical outcome at last follow-up was significantly higher in the FD group (75 vs. 43.8%; $p = 0.046$) with a lower procedural complication rate (20.8 vs. 37.5%; $p = 0.247$). Most patients in our study had symptoms on admission and 10 (13%) presented with subarachnoid hemorrhage, which may explain the high incidence of complications. Nonetheless, the occlusion rate (OKM grades C and D) did not differ significantly between the groups, despite a higher occlusion rate in the FD group at last follow-up (70.6 vs. 55.6%; $p = 0.667$). For patients with aneurysms <10 mm, the favorable clinical outcome rate did not significantly differ between the conventional stent group (88.9%) and FD group (70%), nor did the procedure-related complication rate (14.8 and 30%, respectively) or occlusion rate (84.6 and 100%, respectively). The same analyses were performed for fusiform aneurysms but no significant differences were observed, possibly because of small sample size. Our results lead us to conclude that FD stents are superior to conventional stents for the treatment of large and giant BTVBJ aneurysms. However, for smaller aneurysms, both FD stents and conventional stents are feasible and effective.

STUDY LIMITATIONS

This study has several limitations. First, it was retrospective in nature and performed in a single center; therefore, both selection and treatment bias may have been introduced. Second, long-term angiographic follow-up results were not available in all patients and we did not have detailed data for patients who died. Third, mean imaging follow-up was 12.3 months, which is too short to

determine the rate of final complete embolization; the difference in occlusion rate between the FD and conventional stent groups may have been significant if patient follow-up was longer. Finally, our cohort was small, as BTVBJ aneurysms are rare. Future large-scale studies are warranted to confirm our findings.

CONCLUSION

EVT of small BTVBJ aneurysms (<10 mm) using either FDs or conventional stents was feasible and effective. FDs achieved a higher occlusion rate and more favorable clinical outcome at last follow-up in patients with large or giant aneurysms (≥10 mm). Future large-scale studies with long-term follow-up are warranted to determine the best EVT for BTVBJ aneurysms.

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 Institutional Review Board of Beijing Tiantan Hospital. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

QP collected the clinical data, performed the statistical analysis, and wrote the manuscript. YZho, WL, CW, and LD helped collect the clinical data. SM and YZha helped revise the manuscript, designed the research, and handled funding and supervision. All authors read and approved the final manuscript.

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Small Unruptured Intracranial Aneurysms Can Be Effectively Treated With Flow-Diverting Devices

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Purpose: To investigate the effect and safety of flow diverters in the management of small (<10 mm in diameter) unruptured intracranial aneurysms.

Materials and Methods: One hundred and ten patients with 145 small intracranial aneurysms treated with flow diverters were retrospectively enrolled. The clinical, endovascular, and follow-up data were analyzed.

Results: One hundred twenty-one flow diverters were deployed for the treatment of 145 small intracranial aneurysms in 110 patients, and the stenting success rate was 99.1%. In 133 (91.7%) aneurysms, only flow-diverting devices were deployed, and in the rest 12 (8.3%) of aneurysms, coils were used to loosely pack the aneurysm after deployment of a flow-diverting device. Five patients (4.5%) experienced ischemic complications, but no hemorrhagic complications were occurred. All patients had clinical follow-up 6–18 (median 12) after the procedure, with the modified Rankin scale score (mRS) 0 in 101 patients, 1 in four patients, 2 in three patients, 4 in one patient, and 5 in one patient. Digital subtraction angiography was performed at follow-up in 90 (81.8%) patients with 118 (81.4%) aneurysms 6–18 months (median 12) after the procedure, with the Raymond grade I in 90 (76.2%) aneurysms and Raymond grade III in 28 (23.7%). Eighteen patients with 22 partially occluded aneurysms at the first angiographic follow-up experienced the second digital subtraction angiography 12–36 months (median 26) after the procedure, and 21 (95.5%) aneurysms were completely occluded. Two patients had asymptomatic in-stent stenosis.

Conclusion: Treatment of small unruptured intracranial aneurysms with flow diverters can be performed safely and effectively with satisfactory outcomes.

Keywords: flow diverter, intracranial aneurysms, unruptured, small, complications

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INTRODUCTION

Ever since the approval of flow diversion by the Food and Drug Administration for the treatment of intracranial aneurysms, flow-diverting devices have been increasingly used in the treatment of intracranial aneurysms, especially large and giant aneurysms, which are associated with worse outcomes than small ones (1–8). The indications of treatment for the flow-diverting devices are aneurysms with a maximal diameter of over 10 mm that include large and giant aneurysms and a wide neck with a width of over 4 mm (1, 9) and for aneurysms < 10 mm with a narrow

neck, traditional stent-assisted coiling embolization is comparatively better. Nonetheless, the management of small intracranial aneurysms remains controversial, with difficulties frequently reported in the literature in both endovascular embolization and surgical clipping, as well as a high crossover rate (up to 18%) from endovascular embolization to surgical clipping (10–12). Favorable clinical and angiographic outcomes of endovascular embolization of small ruptured aneurysms have been reported recently in a study with a long-term follow-up of 5 years (13), which may indicate that experience accumulation may lead to good outcomes. With the accumulation of clinical experience in using the flow-diverting devices for intracranial aneurysms, the indication of flow diversion has been greatly expanded from large and giant unruptured aneurysms to ruptured, blister, and dissecting aneurysms as off-label use (14). This is because flow-diverting devices are different from conventional regular arterial stents in that they have a higher metal coverage surface to divert blood flow away from the aneurysm, promote flow stasis and thrombosis within the aneurysm cavity, and remodel the parent artery for aneurysm regression (14, 15). These advantages can be used to treat complex, large, and giant intracranial aneurysms, which are hard for traditional endovascular or surgical approaches, resulting in a low complication rate and a low recurrence rate (14, 16–21). For small aneurysms < 10 mm in diameter (22, 23), the flow-diverting devices also have some specific advantages, such as simple operation and low intraprocedural aneurysm rupture rates, and thus can be used in the treatment of small aneurysms. It was hypothesized that flow-diverting devices could be safely and effectively used in the treatment of small intracranial aneurysms. This study was consequently performed to investigate the effect and safety of flow-diverting devices in the treatment of small intracranial aneurysms.

MATERIALS AND METHODS

Subjects

This retrospective study was approved by the ethics committee of our hospital, and all patients or their family members had given the signed informed consent to participate. From March 2014 to April 2019, patients with small unruptured intracranial aneurysms treated with flow-diverting devices in our hospital were enrolled. The inclusion criteria were consecutive patients with small ($<$10 mm) unruptured intracranial aneurysms, which were treated with flow-diverting devices (Pipeline Embolization Device, Medtronic, Irvine, CA, USA, and Tubridge, MicroPort Medical Company, Shanghai, China) that include saccular, dissecting, or fusiform aneurysms. The exclusion criteria were patients with larger ($>$10 mm) aneurysms, ruptured aneurysms, and aneurysms, which had been treated previously using surgical clipping or endovascular embolization.

Endovascular Procedure and Medication

Three to 5 days before the endovascular procedure, dual antiplatelet therapy was administered for all patients with clopidogrel (75 mg/d) and aspirin (100 mg/d) (24). The endovascular procedure was conducted under general anesthesia and heparinization. Percutaneous access was obtained using femoral artery puncture, and a microcatheter was navigated through the guiding catheter to the aneurysm. An appropriate flow-diverting device was selected and sent to the right location for deployment. In aneurysms with an aneurysm neck > 7 mm, an irregular dome, or a daughter sac, coils were used to embolize the aneurysm. For patients with the device being opened poorly, long operation time in the procedure, and suspected thrombosis at the aneurysm neck, Tirofiban was administered intravenously after stent deployment (25), with the beginning injection dose of 5 μg/kg injected within 3 min followed by instillation in the dose of 0.05 $\mu g/kg^{-1}/min^{-1}$, which was 1/2 of the conventional dose. After the endovascular procedure, Tirofiban was continually administered for 24–36 h, and aspirin (100 mg/d) and clopidogrel (75 mg/d) were continued in all patients for 3 months followed by long-term use of aspirin (100 mg/d) alone.

Clinical and angiographic follow-up was scheduled in all patients, and the treatment effect of the flow-diverting device was evaluated 6 months after the procedure using the Raymond grading system (26), with the Raymond grade I as complete obliteration of aneurysm, grade II as a residual neck, and grade III as any opacification of the aneurysm sac or residual aneurysm. The clinical prognosis was assessed with the modified Rankin scale (mRS) scores.

Statistical Analysis

Statistical analysis was performed with the SPSS software version 19.0 (IBM, Chicago, IL, USA). Continuous data in normal distribution were presented as mean ± standard deviation (SD). Enumeration data were presented as frequency and percentages.

RESULTS

One hundred and ten patients with 145 aneurysms who met the inclusion criteria were enrolled that include 77 (70%) male and 33 (30%) female patients with an age range of 35–78 years (mean 53.7 ± 18.3; **Table 1**). Clinical symptoms included headache or dizziness in 56 (50.9%) patients and ischemic cerebral diseases in 19 (17.3%) patients. The rest 35 (31.8%) patients were incidentally found. Aneurysm location involved the internal carotid artery (ICA) C4–C7 segments in 131 (90.3%) aneurysms, ICA C2 segment in two (1.4%), V4 segment of the vertebral artery in nine (6.2%), middle cerebral artery M1 segment in one (0.7%), and M2 segment in two (1.4%). Among 110 patients, 77 (70%) patients had one aneurysm each, 22 (20%) had two aneurysms each, and eight (5.5%) had three aneurysms each.

In the endovascular procedure, 121 flow-diverting devices were deployed to treat 145 aneurysms (**Figure 1**) that include 20 (16.53%) Tubridge and 101 (83.47%) Pipeline devices. In 133 (91.7%) aneurysms, only flow-diverting devices were implanted, and in the rest of 12 (8.3%) aneurysms, coils were inserted into the aneurysm sac for loose packing after placement of the flow-diverting device. In one patient with a 4-mm aneurysm at the tortuous paraclinoid segment of ICA, the distal end of the Tubridge device (4.5 × 30 mm) was herniated into the aneurysm cavity when the micro-guidewire was withdrawn, and repeated attempts did not succeed in correct deployment of the

TABLE 1 | Demography, clinical data, and endovascular treatment.

Variables		Data
Patients	F/M	33/77
	Age (y)	35–78 (53.7 ± 18.3)
Symptoms (*n*, %)	Headache or dizziness	56 (50.9%)
	Ischemic symptoms	19 (17.3%)
	Incidentally found	35 (31.8%)
Aneurysm location (*n*, %)	ICA C4-C7	131 (90.3%)
	ICA C2	2 (1.4%)
	Vertebral V4 segment	9 (6.2%)
	MCA M1 segment	1 (0.7%)
	MCA M2 segment	2 (1.4%)
No. of aneurysms (*n*, %)	Patients with one aneurysm each	77 (70%)
	Patients with 2 aneurysms each	22 (20%)
	Patients with 3 aneurysms each	8 (5.5%)
Stenting procedures	No. of flow diverters deployed	121
	Diverters only	133 (91.7%)
	Diverters and coiling combined	12 (8.3%)
	Success rate of procedure	99.1% (109/110)
Periprocedural complications	Ischemic	5 (4.5%)
	Hemorrhagic	0
Clinical follow-up	Duration (m)	6–18 (median 12)
	mRS 0 (*n*, %)	101 (91.8%)
	mRS 1 (*n*, %)	4 (3.6%)
	mRS 2 (*n*, %)	3 (2.7%)
	mRS 4 (*n*, %)	1 (0.9%)
	mRS 5 (*n*, %)	1 (0.9%)
Angiographic follow-up at 6–18 months	No. of patients (*n*, %)	90 (81.8%)
	No. of aneurysms (*n*, %)	118 (81.4%)
	Raymond grade I	90 (76.2%)
	Raymond grade III	28 (23.7%)
Angiographic follow-up at 12–36 months (median 26)	No. of patients (*n*, %)	18 (16.4%)
	No. of aneurysms (*n*, %)	22 (15.2%)
	Raymond grade I	21 (95.5%)
	Asymptomatic instent stenosis (*n*)	2 (9.1%)

ICA, internal carotid artery; MCA, middle cerebral artery; mRS, modified Rankin scale score.

Tubridge stent, resulting in failure of stenting. All the other patients had successful stent deployment, with a success rate of stenting of 99.1% (109/110). In 17 devices, good opening and wall adherence were obtained with balloon expansion or micro-guidewire "massage" after stent deployment.

Five peri-procedural ischemic complications occurred, i.e., one patient who was treated with a Pipeline device combined with coiling and four treated with the deployment of a Pipeline device only, resulting in a complication rate of 4.5%. No hemorrhagic complications took place in this cohort. In the case with the distal stent end herniating in the aneurysm cavity, the parent artery was occluded, and the anterior cerebral artery had good compensation, resulting in an mRS of 2 at a 3-month follow-up. In one case with poor stent adherence to the arterial wall, cerebral infarction had occurred in the area supplied by the choroidal artery and anterior cerebral artery covered by the stent, resulting in an mRS score of 4 at follow-up evaluation. In one case with in-stent thrombosis leading to occlusion of the middle cerebral artery, the mRS was 5 at follow-up. In one case with an atherosclerotic plaque at the parent artery near the aneurysm neck leading to slight stenosis of the parent artery, in-stent thrombosis occurred 4 h after the procedure, and acute endovascular thrombectomy was performed, resulting in recanalization and good recovery of the patient. Complete occlusion of the aneurysm and an mRS of 0 were present at the 3-month follow-up. In one case with cerebral ischemic symptoms (hemiplegia), intravenous pumping of Tirofiban resulted in good recovery.

All patients had clinical follow-up 6–18 (median 12) after the procedure, with the mRS 0 in 101 (91.8%) patients, 1 in four (3.6%) patients, 2 in three (2.7%) patients, 4 in one (0.9%) patient, and 5 in one (0.9%) patient. Digital subtraction angiography was performed at follow-up in 90 (81.8%) patients with 118 (81.4%) aneurysms 6–18 months (median 12) after the procedure, with the Raymond grade I in 90 (76.2%) aneurysms and Raymond grade III in 28 (23.7%). Eighteen patients with 22 partially occluded aneurysms at the first angiographic follow-up experienced the second digital subtraction angiography 12–36 months (median 26) after the procedure, and 21 (95.5% or 21/22) aneurysms were completely occluded (Raymond grade I, **Figure 1**). Two patients had asymptomatic in-stent stenosis.

DISCUSSION

In this study, the safety and effect of flow diverters in treating small unruptured intracranial aneurysms were investigated, and it was found that treatment of small unruptured intracranial aneurysms with flow diverters could be performed safely and effectively with satisfactory outcomes.

Small intracranial aneurysms refer to a aneurysms with the maximal diameter < 10 mm regardless of the aneurysm nature, such as saccular, dissecting, or fusiform, accounting for a large proportion of cerebral aneurysms (22, 23, 27). These small aneurysms may be irregular, with daughter sacs, in the posterior circulation, and should be treated actively to prevent possible rupture even though they are not the conventional indications for use of flow diverters. Traditionally, stent-assisted coiling has achieved good clinical and imaging outcomes in the treatment of small (<10 mm) unruptured intracranial aneurysms (22). However, endovascular treatment of intracranial aneurysms that include small unruptured ones still faces great challenges, such as incomplete occlusion, recurrence of wide-necked aneurysms, difficult access or unstable placement of embolization catheters due to anatomical characteristics of aneurysms or poor remodeling, intraprocedural rupture during the process of dense embolization, and difficulties and complex management of multiple tandem aneurysms. Thus, it is natural

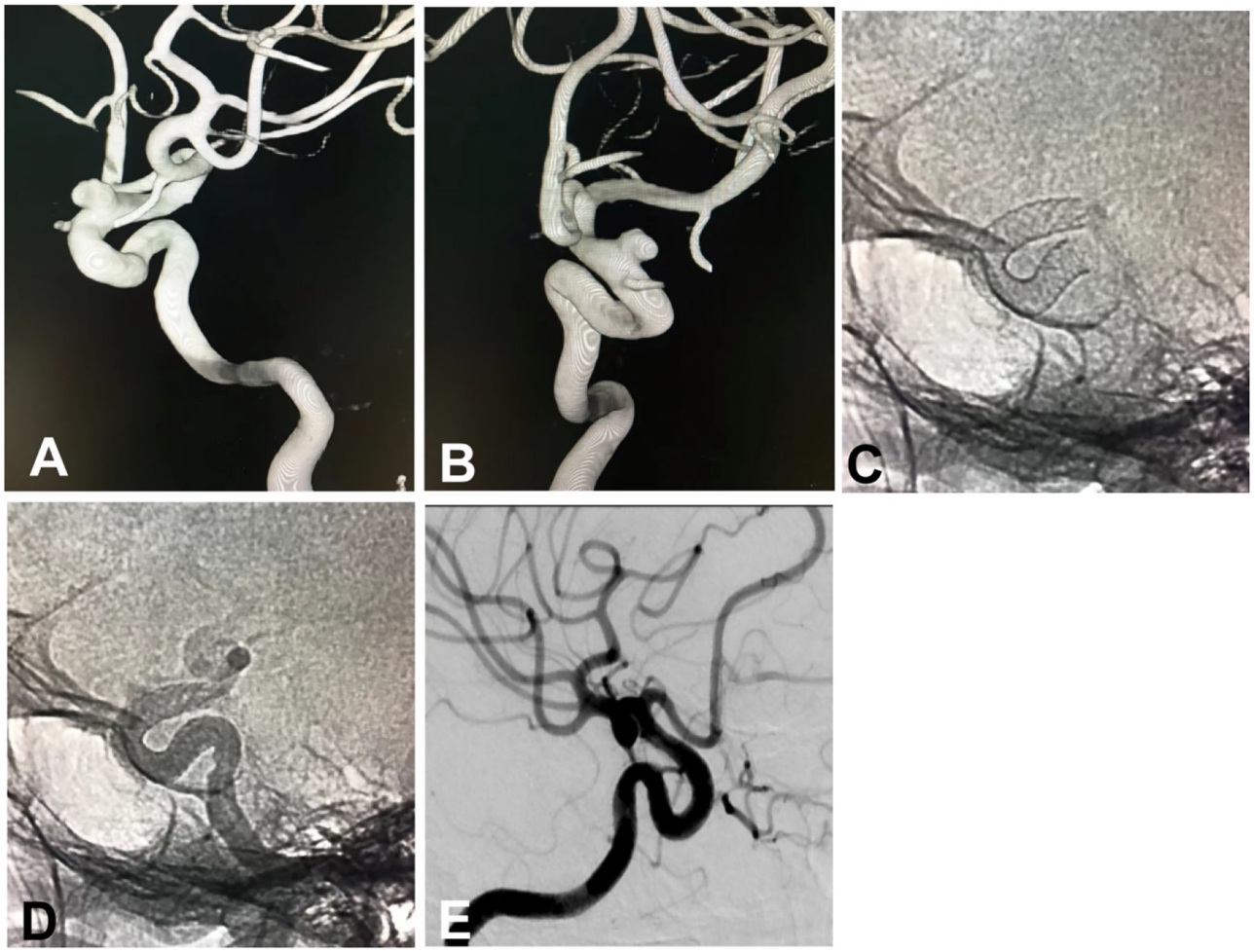

FIGURE 1 | A small intracranial aneurysm in a 53-year-old woman with dizziness was treated with the deployment of a Pipeline embolization device. **(A,B)** The small aneurysm was located at the sixth (ophthalmic) segment of the left internal carotid artery, measuring 5.1 × 3.0 mm in the sac with a 4-mm neck. **(A)** Lateral position, **(B)** Oblique position. **(C)** Immediately after deployment of a Pipeline device of 4.25 × 20 mm, the stent was shown to have a good opening on angiography. **(D)** Angiography immediately following the deployment of the stent, the parent artery was shown to be patent with good wall adherence of the stent. **(E)** Follow-up angiography 8 months later revealed patent parent artery and complete occlusion of the aneurysm.

to use flow diverters for the treatment of these kinds of aneurysms (28). The advantages of using flow diverters for these aneurysms included simplified operation with no need to use an embolization catheter into the aneurysm sac for coiling, decreased recurrence or retreatment rate in wide-necked and complex aneurysms with increased long-term effects, and loose packing in some aneurysms with no or decreased risk of aneurysm rupture. However, in conventional stent-assisted coiling, the embolization outcome may be affected by stent types, size of the first coil, proper shaping of the microcatheter, packing of the last coil, and dense packing.

Because of the advantages of flow-diverting devices, the embolization operation with flow-diverting devices is not so difficult, and the rate of peri-procedural complications is decreased. No patients experienced hemorrhagic complications, and the ischemic complication rate was only 4.5% in our study. The ischemic complication rate had been reported to be 2.7 (19) and 8.7% (28) in the use of flow-diverting devices for the treatment of intracranial aneurysms and 4.6–11.2% in traditional stent-assisted coiling of intracranial aneurysms (22, 29), similar to ours. In a meta-analysis of 41 studies that involved 2,614 patients with aneurysms <10 mm treated with flow diverters, the complication rate was reported to be 7.8% (95% CI 4.8–11.4%) (30), and another meta-analysis that investigated the safety and efficiency of flow diverters in treating small aneurysms (<10 mm) also reported procedural-related neurological mortality of 0.87% and morbidity of 5.22%. These complication rates in these meta-analyses were similar to the above complication rates of intracranial aneurysms treated with either flow diverters or stent-assisted coiling. Many reasons may contribute to the occurrence of ischemic complications, such as inexperience, poor adherence or insufficient opening of the stent, insufficiency

of antiplatelet therapy, and adjunctive coiling. In our study, the five ischemic complications may probably be associated with the early inexperience in using the flow diverters and possible stenosis of the parent artery. To decrease the ischemic complications, the following aspects should be paid attention to. Because poor wall adherence is an independent risk factor for ischemic complications (31), the flow-diverting device should be deployed to have good wall adherence. With experience accumulation in the process of learning, the flow-diverting device can be deployed with good wall adherence, and the technical complication rate related to wall adherence can be significantly decreased. Moreover, adequate antiplatelet therapy should be administered in the peri-procedural period to prevent possible ischemic complications. In our study, a small dose of Tirofiban was used 24–48 h after deployment of the device in patients with good thromboelastogram, which can significantly decrease ischemic complications without increasing the risk of rupture of intracranial aneurysms based on our experience (25, 32). In patients with parent artery stenosis >50%, balloon expansion should be performed in advance to relieve the stenosis before deployment of the flow-diverting device so as to obtain good wall adherence after deployment. The use of a microcatheter for "massaging" the flow diverter or a balloon to expand the flow diverter can effectively increase the rate of good wall adherence.

In our study, the aneurysm complete occlusion rate (Raymond grade I) was 76.2% at the first angiographic follow-up 6–18 months after the procedure, but 95.5% at the second angiographic follow-up 12–36 months (median 26) after the procedure, similar to those reported by other researchers in the treatment of intracranial aneurysms using traditional stent-assisted coiling (33) or flow diverters (34). Complete occlusion of the aneurysms may depend on several factors. Firstly, the long-term outcome of aneurysm occlusion primarily relies on neointima to completely cover the aneurysmal neck, which may require a period of 20–24 wk based on animal experiments (35). A short period of time between 6 and 18 months may not be sufficient for the neointima to cover the aneurysm neck for complete occlusion. Moreover, aneurysm occlusion outcome may also be affected by the stent adherence, metal coverage, and parent artery tortuosity. Aneurysm complete occlusion rate after treatment with flow diverters has an apparent time dependence, with the complete occlusion rate of 73.6% at 6-month follow-up but 95.2% at 5 years after endovascular treatment (34), similar to the outcomes in our study. An adjusted complete occlusion rate of 74.9% (95% CI of 69.6–79.8%) of aneurysms <10 mm has been reported at 12 months after treatment with flow diverters in a meta-analysis (30). A complete occlusion rate of 84.23% (95% CI 80.34–87.76%) has also been reported in a systematic review and meta-analysis investigating the safety and efficiency of flow diverters in the treatment of small aneurysms < 10 mm (27). The use of one or multiple flow diverters may also affect aneurysm complete occlusion rate, with multiple diverters being frequently deployed for large and giant aneurysms and one diverter for small aneurysms. It may thus be more appropriate to define the primary end point of the use of flow diverters in the treatment of aneurysms as the cure rate from 12 to 18 months after treatment.

Metal coverage and mesh size of the stent at the aneurysm neck may be factors significantly affecting the complete occlusion rate of intracranial aneurysms (36), and additional coiling in conjunction with the Pipeline embolization device may effectively increase the complete occlusion rate of intracranial aneurysms, especially for large and giant ones (37). Nonetheless, adjunctive coiling after deployment of a flow diverter may increase the risk of ischemic stroke (38, 39). In our practice, additional coiling was usually performed only in irregular aneurysms > 10 mm with daughter sacs. For small unruptured intracranial aneurysms, it is not necessary to use coils in conjunction with flow diverters for complete aneurysm occlusion so as to avoid increased operation difficulty and risk of complications.

This study had some limitations, such as the retrospective and one-center study nature, no control, no randomization, and Chinese patients enrolled only. Future studies with randomization, control, and multiple centers will have to be performed to resolve these issues for better outcomes.

In conclusion, the use of flow diverters in the treatment of small unruptured intracranial aneurysms may result in good outcomes and fewer peri-procedural complications and may become the preferential choice for small unruptured aneurysms.

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 Ethics Committee of Henan Provincial People's Hospital. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

LL and T-XL: study design. LL, B-LG, Q-JS, G-LZ, Z-LW, and L-FZ: data collection. LL, B-LG, and T-XL: data analysis. Z-LW and L-FZ: study supervision. LL: writing of the original version. B-LG: revision of the original version. All authors agree to be accountable for all aspects of the work and approve the final version of the article.

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Anterior Circulation Fusiform Aneurysms Have a Lower Occlusion Rate After Pipeline Embolization Device Treatment Than Posterior Circulation Fusiform Aneurysms: A Multicenter Cohort Study

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Objective: Intracranial fusiform aneurysms are uncommon and can occur in vessels of the anterior circulation (AC) or posterior circulation (PC). While flow diversion is one treatment option, research into Pipeline Embolization Device (PED) treatment is lacking. This study explored the efficacy and safety of PED treatment for intracranial fusiform aneurysms, and compared therapeutic effects between AC and PC aneurysms.

Methods: In the post-market multi-center cohort study of embolization of intracranial aneurysms with PED in China (PLUS) registry study, we retrospectively analyzed 71 fusiform aneurysms in 67 patients among 1,171 patients treated with a PED from November 2014 to October 2019. The general characteristics, perioperative status, aneurysm occlusion rate at the last follow-up angiography, and changes in modified Rankin Scale scores were analyzed. Aneurysms were divided into AC and PC groups, and univariate and multivariate analyses were conducted.

Results: The study included 26 AC (25 patients) and 45 PC (42 patients) aneurysms. A total of 75 PEDs were used, an average of 1.1 PEDs were used, and the median follow-up was 6.7 months. Fifty aneurysms (71.4%) were occluded and twenty (28.5%) were incompletely occluded. There were significantly more occluded aneurysms in the PC group than in the AC group (12 vs. 38; $P = 0.001$). Risk factors for incomplete occlusion were AC aneurysms ($P = 0.001$) and a perforating artery originating from the aneurysm ($P = 0.006$). The mean modified Rankin Scale score was significantly lower at the last follow up than preoperatively (0.58 vs. 0.21; $P = 0.0001$).

Conclusion: Non-overlapping PED is a safe and effective treatment for both AC and PC fusiform aneurysms. The occlusion rate of AC fusiform aneurysms is lower than that of PC.

Keywords: fusiform aneurysm, pipeline embolization device, anterior circulation, posterior circulation, flow diverter devices

INTRODUCTION

Fusiform intracranial aneurysms are rare, and their unique morphology and pathological development continue to present a challenge for neurosurgical treatment (1–4). While the Pipeline Embolization Device (PED; Medtronic, Minneapolis, MN, USA) provides a treatment option for fusiform aneurysms, few studies have investigated this (5–10), especially in posterior circulation (PC) and anterior circulation (AC) fusiform aneurysms beyond the circle of Willis, for which PED use is off-label (11). Previous studies on fusiform aneurysms have mostly been single-center studies; the present study included data from multiple centers. To summarize, this post-market multi-center cohort study of embolization of intracranial aneurysms with PED in China (PLUS) registry study investigated the clinical prognosis and occlusion rate of intracranial fusiform aneurysms treated with a PED, and the efficacy of PEDs in the treatment of AC and PC intracranial fusiform aneurysms.

MATERIALS AND METHODS

Data Collection and Follow-Up

In this consecutive, real-world cohort registry study, we retrospectively collected data on aneurysms treated with PEDs from a database of 14 participating Chinese institutions, between November 2014 and October 2019. The local institutional review boards and ethics committees approved the study and the use of patients' data. All operations were performed with patients' written informed consent.

Fusiform aneurysms were defined as aneurysmal dilatations of >50% of the vessel wall circumference without a discrete aneurysm neck (2, 10). Aneurysms were categorized as fusiform based on 3D rotational digital subtraction angiography (DSA) findings, and all cases were reviewed for inclusion by the senior author. Purely saccular aneurysms, blister aneurysms, sidewall aneurysms (aneurysms located in the lateral wall artery without involvement of the entire artery), and dissecting aneurysms (retention of contrast in the aneurysm during angiography) were excluded. The AC group and PC group were defined according to the aneurysm location.

The collected data included patients' demographic characteristics, aneurysm characteristics (side, location, clinical manifestations, preoperative modified Rankin Scale (mRS) score, diameter of parent artery, maximum diameter of aneurysm, recurrent aneurysm), and treatment status (size of PED, number of PEDs, PED + coils, operation related complications, post-operative O'Kelly–Marotta (OKM) grading scale (12)). Data from branch arteries originating from fusiform aneurysms, such as the posterior communicating artery, ophthalmic artery, anterior inferior cerebellar artery, and posterior inferior cerebellar artery, were also collected. Given that fusiform aneurysms do not have a distinct aneurysm neck, the contrast is obviously retained in the entire aneurysm after PED implantation; thus, we used the retention time of the contrast as the main basis for OKM classification. Data on the follow-up status (months of follow-up, aneurysm occlusion at the last radiogram follow-up, and mRS score at the last follow-up) were also collected. Aneurysms were divided into four categories according to maximum diameter, namely, ≤ 7 mm, 7–15 mm, 15–23 mm, and > 23mm.

Follow-up DSA was performed 6 months after operation and repeated again between 12 and 36 months. Aneurysm occlusion was classified using the OKM grading scale.

Perioperative Management

All patients received an antiplatelet regimen that included aspirin 100 mg/day or 300 mg/day and clopidogrel 75 mg/day for 5 days prior to the operation. Patients who were identified as clopidogrel non-responders received aspirin 100 mg/day and ticagrelor 90 mg twice daily. All patients demonstrated optimal platelet activity suppression before PED placement. Board-certified neuro-endovascular surgeons performed all procedures. Intravenous heparin was administered intra-procedurally to achieve an activated clotting time of >250 s. Heparin was discontinued after completing the procedure. A continuous dual antiplatelet therapy regimen was applied after PED placement, including aspirin 100 mg/day, clopidogrel 75 mg/day, or ticagrelor 90 mg/day for 6 months. After 6 months, the decision to stop clopidogrel or ticagrelor was made according to angiography results. Aspirin 100 mg/day was recommended to be taken for life.

Statistical Analysis

Categorical variables are reported as proportions, and continuous variables are reported as the median and quartile or range. The Chi-square test, Mann–Whitney U, and Wilcoxon rank sum test were used to compare variables between the two groups. Univariate analysis was performed for age, sex, hypertension, smoking status, aneurysm characteristics, treatment status, and follow-up status in relation to incomplete occlusion of the aneurysm. The predictive factors ($P < 0.10$) identified in the univariate analysis, as well as treatment method, postoperative OKM grading scale, and last radiographic follow-up time, were included in the multivariate analysis. P-values < 0.05 were considered statistically significant. Statistical analysis was performed using SPSS 25 (IBM Corp., Armonk, NY, USA).

RESULTS

Patient and Aneurysm Characteristics

A total of 71 fusiform aneurysms in 67 patients were retrospectively identified. Twenty-five patients (37.3%) were

TABLE 1 | Location of the treated aneurysms.

AC ($n = 26$), n (%)		PC ($n = 45$) n (%)	
ICA cavernous	9 (34.6%)	V4	37 (82.2%)
ICA ophthalmic	7 (26.9%)	Vertebral-basilar	5 (11.1%)
ICA Pcom	6 (23.1%)	BA	2 (4.4%)
MCA	4 (15.4%)	PCA	1 (2.2%)

AC, anterior circulation; PC, posterior circulation; ICA, internal carotid artery; MCA, middle cerebral artery; PCA, posterior cerebral artery; Pcom, posterior communicating; BA, basilar artery.

female and 42 patients (62.7%) were male (median age 51 years, range 8–75 years). There were 32 aneurysms on the left side (45.1%) and 39 on the right side (54.9%). Twenty-six aneurysms (36.6%) were located in the AC and 45 aneurysms (63.4%) in the PC (**Table 1**). Two aneurysms (3%) were recurrent and had undergone prior endovascular treatment. A total of 18 patients were asymptomatic (26.9%), 35 patients (52.2%) had headache and dizziness, 10 patients (14.9%) had neurological symptoms, including dysarthria in two, oculomotor nerve palsy in one, visual field defect in two, weak limb power in two, and limb numbness in three, and 4 patients (6%) had subarachnoid hemorrhage. Thirty-seven cases (55.2%) had a history of smoking. The median diameter (interquartile range) of the parent artery was 3.5 mm (2.9–4.17 mm). A total of 71 aneurysms were divided into the $\leq$ 7 mm group (18 aneurysms), 7–15 mm group (37 aneurysms), 15–23 mm group (10 aneurysms), and $>$ 23 mm group (6 aneurysms). In the 67 patients, a total of 75 PEDs were used; 7 patients had two PED implants, one of the other 60 patients had PED implanted in his bilateral internal carotid arteries. An average of 1.1 PEDs were used. Application PED size median was 4.0 mm (3.5–4.25 mm). Among the aneurysms, 52 aneurysms (73.2%) were treated with PED only, and 19 aneurysms (26.8%) were treated with PED + coils (**Tables 2**, **3**).

Clinical and Imaging Results

Angiography at the final follow up (median, 6.7 months; range, 3–36.2) demonstrated OKM-D type occlusion (no filling) in 50 aneurysms (71.4%), as complete obliteration; incomplete aneurysm occlusion occurred in 20 aneurysms; of these, 15 were OKM-B2 (subtotal filling), and 5 were OKM-B3. In the AC aneurysms, 12 (48%) were OKM-D, 9 (36%) were OKM-B2, and 4 (16%) were OKM-B3. In the PC aneurysms, 38 (84.4%) were OKM-D, 6 (13.3%) were OKM-B2, and 1 (2.2%) was OKM-B3 (**Table 3**). Among the 50 complete obliteration aneurysms, nine aneurysms with branch arteries originated from the aneurysms, accounting for 50% of this type of aneurysms compared with the other 41 (78.8%) aneurysms ($P = 0.02$).

TABLE 2 | Baseline characteristics of 67 patients with 71 fusiform aneurysms.

Characteristics	Total	AC	PC	*P*-value
No. of patients	$n = 67$	25	42	
No. of aneurysms	$n = 71$	26 (36.6%)	45 (63.4%)	
Median age in years (range)	51 (8–75)	53 (14–75)	51 (8–69)	0.817
Sex				0.015
Male	42 (62.7%)	11 (44%)	31 (73.8%)	
Female	25 (37.3%)	14 (56%)	11 (26.2%)	
Smoking	37 (55.2%)	10 (40%)	27 (64.3%)	0.053
Side				0.178
Left	32 (45.1%)	9 (34.6%)	23 (51.1%)	
Right	39 (54.9%)	17 (65.4%)	22 (48.9%)	
Presenting symptoms				
Asymptomatic	18 (26.9%)	10 (40.0%)	8 (19.0%)	0.061
Headache/dizziness	35 (52.2%)	11 (44.0%)	24 (57.1%)	0.298
Neurological deficit	10 (14.9%)	2 (8.0%)	8 (19.0%)	0.223
SAH				0.591
Yes $<$ 2weeks	4 (6.0%)	2 (7.7%)	2 (4.8%)	
No	63 (94.0%)	23 (92.0%)	40 (95.2%)	
Pretreatment mRS score				0.709
0–2	65 (97.0%)	24 (96.0%)	41 (97.6%)	
3–5	2 (3.0%)	1 (4.0%)	1 (2.4%)	
Parent artery (median; IQR) (mm)	3.5 (2.9–4.1)	3.7 (3.1–4.2)	3.2 (2.8–3.9)	0.04
Maximal diameter				0.553
$\leq$ 7 mm	18 (25.4%)	7 (26.9%)	11 (24.4%)	
7–15 mm	37 (52.1%)	11 (42.3%)	26 (57.8%)	
15–23 mm	10 (14.1%)	5 (19.2%)	5 (11.1%)	
$>$ 23 mm	6 (8.5%)	3 (11.5%)	3 (6.7%)	
Artery from aneurysms	19 (26.8%)	8 (30.8%)	11 (24.4%)	0.562
Previous treatment				
Endovascular	2 (3.0%)	1 (3.8%)	1 (2.4%)	0.725

AC, anterior circulation; PC, posterior circulation; IQR, Interquartile range.

TABLE 3 | Outcome measures of 67 patients with 71 fusiform aneurysms.

Characteristics	Total	AC	PC	*P*-value
No. of PEDs	75	28	47	0.792
Double PED	7 (10.3%)	3 (12.0%)	4 (9.3%)	0.792
Average number of PED (range)	1.10 (1–2)	1.12 (1–2)	1.09 (1–2)	0.726
Treatment				0.562
PED only	52 (73.2%)	18 (69.2%)	34 (75.6%)	
PED + coil	19 (26.8%)	8 (30.8%)	11 (24.4%)	
Size of PED mm (median; IQR)	4.0 (3.5–4.25)	4.0 (3.5–4.5)	4.0 (3.5–4.25)	0.451
Length of PED mm (median; IQR)	30 (25–35)	30 (25–35)	30 (25–35)	0.906
Complications				
Thromboembolic	0	0	0	
Hemorrhagic	3 (4.4%)	2 (8.0%)	1 (2.3%)	0.275
Ischemia	3 (4.4%)	1 (4.0%)	2 (4.7%)	0.900
Postoperative angiography				1.000
OKM A-B-C 3	39 (54.9%)	14 (53.8%)	25 (55.6%)	
OKM A-B-C 2	17 (23.9%)	7 (26.9%)	10 (22.2%)	
OKM A-C 1	15 (21.1%)	5 (19.2%)	10 (22.2%)	
LRF (m) median (range)	6.7 (3–36.2)	6.4 (3.6–26.8)	7.2 (3–36.2)	0.628
Follow-up occlusion rate				0.001
OKM-D	50 (71.4%)	12 (48%)	38 (84.4%)	
OKM-B2	15 (21.4%)	9 (36%)	6 (13.3%)	
OKM-B3	5 (7.1%)	4 (16%)	1 (2.2%)	
mRS at last follow-up				0.065
0–2	65 (97.0%)	23 (92.0%)	42 (100%)	
3–5	1 (1.4%)	1 (4.0%)	0	
6-death Mortality w/in ≤ 30 days	1 (1.4%)	1 (4.0%)		

AC, anterior circulation; PC, posterior circulation; PED, pipeline embolization device; IQR, Interquartile range; OKM, O'Kelly–Marotta grading scale; LRF, last radiographic follow-up; m, months; IMF, Imaging modality at follow-up; DSA, digital subtraction angiography; CTA, computed tomography angiography; mRS, modified Rankin Scale.

Multivariate Analysis

The multivariate analysis revealed that aneurysms located in the AC (odds ratio 8.979, 95% confidence interval 2.337–34.504; $P = 0.001$) and perforating artery originating from the aneurysm (odds ratio 8.655, 95% confidence interval 1.830–40.923; $P = 0.006$) were risk factors for incomplete occlusion (**Figures 1**, **2**; **Table 4**).

Clinical Outcomes

The mRS score was improved at the last follow-up compared with the preoperative score in 24 (35.8%) patients, was unchanged in 42 (62.7%) patients, and 1 patient died due to cerebral hemorrhage postoperatively (**Figure 3**). The mean preoperative mRS score (standard deviation) was 0.58 (0.89), and the mean mRS score at the last follow-up was 0.21 (0.89). This difference was significant ($P = 0.0001$; **Tables 5**, **6**).

The postoperative morbidity rate of patients was 8.8%, and the mortality rate was 1.4%. Postoperative complications included intracranial hemorrhage in 3 (4.4%) patients (2 located in the AC and 1 in the PC), ischemia in 3 (4.4%) patients (1 in the AC and 2 in the PC), 1 patient died due to cerebral hemorrhage postoperatively (**Figure 3**); 2 of the remaining 5 patients had improved mRS scores at the last follow-up compared with the preoperative score, and 3 patients had unchanged mRS scores (**Table 3**).

DISCUSSION

Fusiform aneurysms account for 3–13% of all intracranial aneurysms; AC fusiform aneurysms are rare and usually located in the internal carotid artery and middle cerebral artery, and PC fusiform aneurysms are usually located in the vertebral artery and basilar artery (1). About 70% of patients with PC aneurysms are male, and these aneurysms most commonly present as PC ischemic stroke (3). In this study, AC aneurysms accounted for 38% of all treated aneurysms, and most patients were asymptomatic. We found that 62% of fusiform aneurysms were located in the PC, 73% of cases were of male patients, and 61% of patients had headache, dizziness, and ischemia. This retrospective study assessed the safety and efficacy of PED treatment for intracranial fusiform aneurysms, and is the first to compare PED treatment between AC and PC fusiform aneurysms.

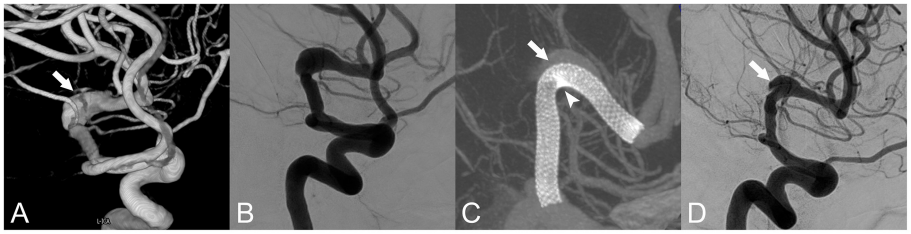

FIGURE 1 | Fusiform aneurysm of the left middle cerebral artery. **(A)** Three-dimensional reconstruction of the fusiform aneurysm (white arrow). **(B)** Anteroposterior projection by digital subtraction angiography (DSA). **(C)** Vaso CT indicated that the metal coverage of the small curve (arrow head) was higher than that of the large curve (white arrow). **(D)** A 9-month follow-up angiography showed that the aneurysm remained residual (white arrow), and the intima had formed between the stent and the aneurysm.

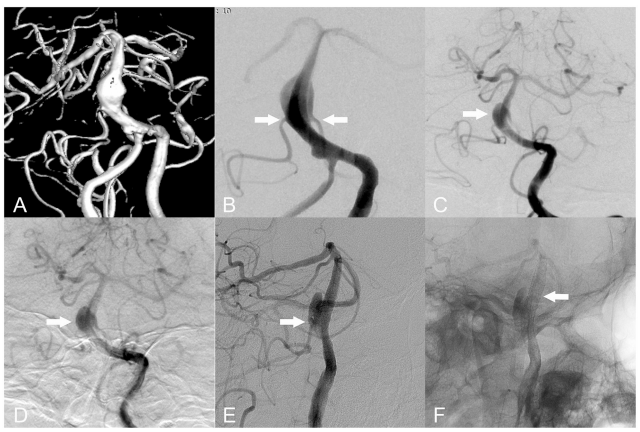

FIGURE 2 | Basilar fusiform aneurysms. **(A,B)** Bilateral anterior inferior cerebellar arteries (AICAs) originate from the aneurysmal body (white arrow). **(C,D)** A 9-month follow-up angiography revealed residual aneurysm. **(E)** Blood flow through aneurysmal bodies supplied blood to the AICA (white arrow). **(F)** A 9-month follow-up angiography revealed no intra stent stenosis (white arrow).

Occlusion of Intracranial Fusiform Aneurysms

The morphology of fusiform aneurysms is a predictor of incomplete occlusion after flow diverter treatment (13). Previous reports of intracranial fusiform aneurysms treated with flow diverter devices (FDD) have been based on small series studies, with an overall occlusion rate of 59–100% (7–10). In one meta-analysis of AC fusiform aneurysms located distal to the circle of Willis and PC fusiform aneurysms, Cagnaggo et al. reported an occlusion rate of 83% (11). Monteith et al. reported 24 intracranial fusiform aneurysms treated with PEDs, 22 of which were followed up with DSA for an average of 6.3 months, with an occlusion rate of 59% (7). Griffin et al. reported 25 cases followed up with DSA for an average of 17.4 months with an occlusion rate of 76% (10). Fischer et al. reported that PED was used to treat 67 fusiform and dissecting aneurysms, and the complete occlusion rate was 67% at the last follow-up of 27.4 months (6). The increase in follow-up time did not increase the aneurysm occlusion rate in those studies. The present multivariate analysis results are consistent with those previous findings, whereby the overall aneurysm occlusion rate was 71.4% at an average follow-up of 6.7 months. In our study, 18 aneurysms with perforating artery originating from the aneurysm, the occlusion rate was 50 vs. 78.8% of the other fusiform aneurysms at an average follow-up of 6.7 months. The difference was statistically significant. In previous studies of saccular aneurysms, the perforating artery originating from the aneurysm was an independent risk factor for incomplete aneurysm occlusion (14–16); for these aneurysms, after PED implantation, the perforating artery still has a sufficient pressure gradient to maintain forward blood flow. This means that sufficient blood flow will be retained in the aneurysm to prevent thrombosis, resulting in an aneurysm that is difficult to occlude. This conclusion applies equally to fusiform aneurysms treated with the PED, and was supported by the present multivariate analysis of intracranial fusiform aneurysms with incomplete occlusion.

The average number of PEDs used to treat AC and PC fusiform aneurysms in this study was 1.12 and 1.09, respectively, which is lower than that reported in previous studies (5, 7–10). The PED landing zone for fusiform aneurysms is just proximal and distal to the lesion. This means that it is theoretically possible to push and pull the PED mesh to increase the metal coverage of the lesion area and increase the flow guidance effect to promote aneurysm healing. Furthermore, given that the PED at the lesion is in a suspended state, especially for lesions with a large curvature, the push and pull technique is less able to achieve the above purpose (6). Multiple PED treatment is a feasible method. Each overlapping PED can increase the metal coverage by 5% and reduce the blood flow velocity in the aneurysm by 30% (6, 10). However, this also increases the complexity and duration of the operation. It can also lead to occlusion of perforating vessels and stenosis of the parent artery (6, 10). Compared with multiple PED treatment, we recommend PED with adjunctive coil treatment. Considering that there is no effective support for PEDs used to treat fusiform aneurysm lesions, adjunctive coils can act as scaffold to reduce foreshortening of the flow diverter and to promote the formation of thrombosis in the aneurysm, leading to occlusion of the aneurysm (9, 10, 17). A PED with coils is recommended for fusiform aneurysms without involvement of the branch vessels in the AC. Compared with AC fusiform aneurysms, PC aneurysms have more perforating vessels, and

TABLE 4 | Predictors of incomplete occlusion of fusiform aneurysms treated with PEDs.

Parameter	Univariate analysis*		Multivariate analysis	
	OR (95% CI)	*P*-value	OR (95% CI)	*P*-value
AC vs. PC	5.881 (1.909–18.114)	0.002	8.979 (2.337–34.504)	0.001
PED-only vs. PED + coils	2.667 (0.682–10.428)	0.159	4.133 (0.760–22.471)	0.101
Artery from aneurysms	3.727 (1.194–11.639)	0.024	8.655 (1.830–40.923)	0.006
OKM1,2 vs. OKM 3	2.250 (0.781–6.485)	0.133	2.782 (0.695–11.133)	0.148
LRF (m)< 6.7	0.755 (0.267–2.139)	0.597	0.465 (0.122–1.769)	0.261

AC, anterior circulation; PC, posterior circulation; PED, pipeline embolization device; OKM, O'Kelly–Marotta grading scale; LRF, last radiographic follow-up; m, month.
**Also entered in the univariate analysis but not significant: sex, smoking, presenting symptoms, maximum aneurysm diameter, aneurysm neck, number of PEDs.*

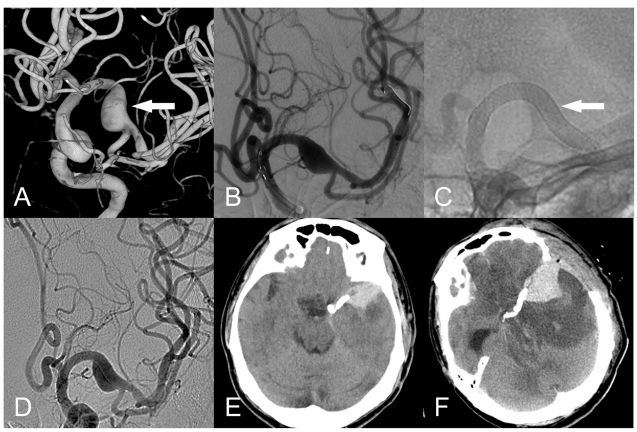

FIGURE 3 | Fusiform aneurysm of the left middle cerebral artery. **(A)** Three-dimensional reconstruction (white arrow). **(B)** The PED was implanted intraoperatively uneventfully (white arrow). **(C,D)** The PED was well adherent, and the contrast was obtained after the release of the PED. **(E)** Nine hours postoperatively, the patient developed severe headache. CT suggested cerebral hemorrhage with subarachnoid hemorrhage, and decompressive bone flap was performed urgently. **(F)** 1 day after decompressive surgery by deparaffinization flap, CT suggested significant brain edema around the intracerebral hemorrhage.

TABLE 5 | Clinical status of included patients.

mRS	Improved	Unchanged	Worse	*P*-value
Total ($n = 67$), *n* (%)	24 (35.8)	42 (62.7)	1 (1.5)	0.0001
AC ($n = 25$), *n* (%)	7 (28.0)	17 (68.0)	1 (4.0)	0.229
PC ($n = 42$), *n* (%)	17 (40.5)	25 (59.5)	0 (0)	

AC, anterior circulation; PC, posterior circulation.

the use of adjunctive coils for some selected patients has been recommended (18). However, in our study, the PED + coils cases accounted for 30.8% in the AC group and 24.4% in the PC group; the occlusion rate was thus lower in the AC group. Multivariate regression revealed that the use of a PED with adjunctive coils was not associated with aneurysm occlusion. This may be related to loosely packing coils. The degree of loose packing therefore needs to be explored in future work.

Different Occlusion Rate Between AC and PC Fusiform Aneurysms

Previous studies of small sample size PC fusiform aneurysms have reported occlusion rates in the range of 29–100% (5, 8, 9). In a study by Griessenauer et al. of 131 PC aneurysms with a median follow-up time of 9 months, the occlusion rate of 53 fusiform aneurysms was 59.7% (19). In a recent study by Griessenauer et al. in 149 PC aneurysms, including 42 fusiform aneurysms, with a median follow-up time of 12 months, the occlusion rate was 91.3% (20). Bhogal and colleagues reported 56 PC non-saccular aneurysms, including 24 fusiform aneurysms, with 75% aneurysm occlusion at the last follow-up of 25.2 months (21). There were 45 PC fusiform aneurysms in our study. The median follow-up time was 6.7 months, and the occlusion rate was 84.4%. The occlusion rate of the AC group was 48%. Szikora et al.'s (22) autopsy pathology concluded that AC and PC fusiform aneurysms belong to the same pathological type; according to this conclusion, there should be no significant difference in the occlusion rate of PED treatment. However, we found a significant between-group difference in the occlusion rate. Our multivariate analysis revealed that an aneurysm located in AC was an independent risk factor for incomplete aneurysm occlusion.

In the present study, most AC lesions were located in the cavernous sinus and ocular segments, and most PC lesions in the straight part of the V4 segment. It is easier to use the push-pull technique during PED treatment to form a higher metal coverage at the aneurysm lesion and promote the occlusion of the aneurysm, especially in the straight part of the V4 segment. To adapt to the large curvature of the AC fusiform aneurysm, the metal coverage of the PED in the aneurysm is significantly different between the inner curve and the outer curve (**Figure 1**), and the blood flow guiding effect is worse than that of a straight blood vessel (23, 24). This could explain the low occlusion rate of AC fusiform aneurysms. Hemodynamically, peak systolic flow velocity values were 30–50% higher in the AC than in the PC (25). Given that flow velocity is correlated with wall shear stress variation (which is tightly linked to aneurysm enlargement, intra-aneurysmal thrombosis, and endothelialization of the parent artery), this difference would become apparent after implantation of the PED, resulting in a differential rate of fusiform aneurysms occlusion between the AC and PC; this has not been specifically studied, but is worth exploring (26–29).

TABLE 6 | Flow diversion (PEDs) for treatment of fusiform aneurysms.

Author	Location	No. of fusiform aneurysms	Mean PED (range)	Follow up (months)	Occlusion rates *n*%	Morbidity *n*%	Mortality *n*%	Mean mRS score pretreatment	Mean mRS score at last follow-up
Siddiqui et al. (5)	PC	7	6.4 (3–9)	NA	29	14	57	2.6	3.3
Munich et al. (8)	PC	12	3.4 (1–6)	11	90	25	8.3	1.0	1.9
Monteith et al. (7)	B	24	1.8 (1–6)	6.3	59	16.7	4.2	0.7	1.2
Natarajan et al. (9)	PC	12	1.7 (1–4)	12–43	100	8.3	0	NA	NA
Griffin et al. (10)	B	30	1.6 (1–6)	17.4	76	6.7	3.4	NA	NA
Present study	B	71	1.1 (1–2)	6.7	71.4	8.8	1.4	0.58	0.21

Location, anterior or posterior circulation; PC, posterior circulation; B, both circulations; NA, not applicable.

Complications of Intracranial Fusiform Aneurysms

Previous retrospective studies have reported neurological morbidity and mortality rates of intracranial fusiform aneurysms treated with FDD of 17 and 8%, respectively, (6, 11). Monteith et al. reported a complications rate and mortality rate of 16.7 and 4.2%, respectively, in 24 intracranial fusiform aneurysms treated with PEDs (7). Griffin et al. reported 30 cases of intracranial fusiform aneurysms with a complication rate and mortality rate of 6.7 and 3.4%, respectively, (10). The overall neurological morbidity rate and mortality rate in this study were 8.8 and 1.4%, respectively. Although the mortality rate was lower, the neurological morbidity rate was higher than that reported by Griffin et al. (10). The neurological morbidity rate was not significantly different between the AC and PC aneurysms, at 12 and 7%, respectively.

Complications of AC Fusiform Aneurysms

The AC neurological morbidity and mortality rates in this group were 12 and 4%, respectively, which were lower than the complication rate of 14% in AC non-saccular aneurysms in the meta-analysis of Cagnaggo et al. (11). Postoperative thrombosis and hemorrhage of fusiform aneurysms are critical factors leading to death. Szikora et al. (22) analyzed the pathology of fusiform aneurysms in patients that died after FDD treatment. They found that the endothelialization of FDD inside the aneurysm may take 12 months or more, which can lead to the two following situations: (1) If the antiplatelet effect is insufficient, thrombotic complications are more likely to develop; (2) Due to the lack of infiltration of vascular smooth muscle cells, FDD cannot undergo endothelialization, and stagnant blood in the aneurysm sac may activate matrix metalloproteinases to break down the aneurysm wall and cause aneurysm rupture (30, 31). This mechanism could have occurred in this group of postoperative cerebral hemorrhages, which caused death in the present study (**Figure 3**).

Complications of PC Fusiform Aneurysms

In this study, the neurological morbidity rate in the PC group was 7%, and no patients died. In previous studies, the neurological morbidity rate of PC fusiform aneurysms was 8.3–25%, and the mortality rate was 0–57% (5, 8, 9). These previous results were from studies with small sample sizes. Recently, Bhogal and colleagues reported 56 cases of PC non-saccular aneurysms with a neurological complication rate and mortality rate of 15.5 and 15.5%, respectively, (21). Among these, 24 had fusiform aneurysms, with a postoperative mortality rate of 3.6%. Lopes and colleagues reported that among the 95 PC aneurysms treated with PED, 28 fusiform aneurysms had a neurological complication rate of 19.2% and a mortality rate of 11.5%, and Cox regression analysis revealed that more than 3 PEDs was a related risk factor (32). In several previous studies, the average number of PEDs used was more than 3 (5, 9, 21, 22, 32); the average number of PEDs used in this study was 1.09 in the PC, and the complication and mortality rates were the lowest in this group. The overlapping application of multiple PEDs increases the risk of perforating vessel occlusion caused by thrombosis. Therefore, the minimum number of PEDs required to cover the lesion should be used when treating post-circulating fusiform aneurysms.

Clinical Outcomes

In our series, the last follow-up mRS score had decreased compared with preoperative scores in 24 patients (35.8%), no change was seen in 42 patients, and 1 patient died. There was a significant difference between the mRS score at the last follow-up and the preoperative mRS score, which indicates that PED therapy was effective in improving patient outcomes. This was also demonstrated in patients who had postoperative complications. Postoperative complications included intracranial hemorrhage in 3 (4.4%) patients, ischemia in 3 (4.4%) patients, and death in 1 patient due to cerebral hemorrhage postoperatively; 2 of the remaining 5 patients had decreased mRS scores at the last follow-up compared with the preoperative score, and 3 patients had unchanged mRS scores of 0. There was no

significant difference in the change of mRS scores between the AC and PC groups. Previous studies in which patients' last follow-up mRS scores all increased have indicated a poor treatment outcome of PED, which could be due to the high average number of PEDs applied and the small sample sizes (5, 7–10).

LIMITATIONS

This study has some limitations that should be noted. First, this was a retrospective, multi-center study, which means that the heterogeneity of the operator's operating preferences cannot be well quantified and counted. Second, the average follow-up time was short, and a longer follow-up time is needed to evaluate long-term efficacy. Third, a prospective, systematic study is needed to evaluate the safety and efficacy of FDD in the treatment of intracranial fusiform aneurysms.

CONCLUSIONS

This study revealed that non-overlapping PED is safe and effective for the treatment of intracranial fusiform aneurysms. The long-term mRS score significantly improved after treatment. The occlusion rate of AC fusiform aneurysms was lower than that of PC fusiform aneurysms. The occlusion rate of fusiform aneurysms involving perforating vessels was low.

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.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Institutional Review Board (IRB) of Beijing Tiantan Hospital Affiliated to Capital Medical University (Ethical review No: KY288 2018-098-02). Written informed consent from the patients/participants legal guardian/next of kin was not required to participate in this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

Conception and design: CX and PW. Acquisition of data: CX, PW, and BL. Analysis and interpretation of data: CX, LZ, and BL. Drafting the article: CX. Approving the final version of the manuscript on behalf of all authors: HS. Statistical analysis: CX and SX. Study supervision: HS and XY. All authors critically revised the article and reviewed the submitted version of manuscript.

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Flow Diversion vs. Stent-Assisted Coiling in the Treatment of Intradural Large Vertebrobasilar Artery Aneurysms

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Objective: To compare the safety, angiographic, and long-term clinical outcomes of intradural large vertebrobasilar artery (VBA) aneurysms following flow diversion (FD) or conventional stent-assisted coiling (SAC).

Methods: We performed a retrospective study of 66 consecutive patients with intradural large VBA aneurysms between 2014 and 2021 who underwent FD or SAC. Patients' characteristics, postprocedural complications, and clinical and angiographic outcome details were reviewed.

Results: A total of 66 intradural large VBA aneurysms were included, including 42 (63.6%), which were treated with SAC (SAC group) and 24 (36.4%), which were treated with FD (FD group). Clinical follow-up was obtained at the median of 24.0 [interquartile range (IQR) 12.0–45.0] months, with 34 (81.0%) patients achieved the modified Rankin Scale (mRS) ≤ 2 in the SAC group and 21 (87.5%) patients in the FD group. Thirteen (19.7%) patients experienced neurological complications, of which 9 (13.6%) patients first occurred during the periprocedural phase and 4 (6.1%) patients first occurred during follow-up. The overall complication rate and periprocedural complication rate were both higher in the SAC group, but did not reach statistical significance (23.8 vs. 12.5%, $P = 0.430$; 16.7 vs. 8.3%, $P = 0.564$). The mortality rates were similar between the groups (11.9 vs. 12.5%). Angiographic follow-up was available for 46 patients at the median of 7 (IQR 6–14) months, with a numerically higher complete occlusion rate in the SAC group (82.1 vs. 55.6%, $P = 0.051$) and similar adequate aneurysm occlusion rates between the groups (85.7 vs. 83.3%, $P = 1.000$). In the multivariate analysis, ischemic onset ($P = 0.019$), unilateral vertebral artery sacrifice ($P = 0.008$), and older age ($\geq$60 years) ($P = 0.031$) were significantly associated with complications.

Conclusion: There was a trend toward lower complication rate and lower complete occlusion rate for intradural large VBA aneurysms following FD as compared to SAC. FD and SAC have comparable mortality rates and favorable outcomes. Ischemic onset, unilateral vertebral artery sacrifice, and older age could increase the risk of complications.

Keywords: vertebrobasilar artery, large aneurysms, flow diverter, stent-assisted coiling, complications

INTRODUCTION

Intradural large (≥10 mm) vertebrobasilar artery (VBA) aneurysms are a very challenging subtype for physicians among the overall cerebral aneurysms, with a greater tendency to rupture, poorer natural history, and poorer outcomes compared with small aneurysms and anterior circulation aneurysms (1–3). Currently, there is no standard of care for the treatment of VBA aneurysms. The anatomy location and pathological feature of VBA aneurysms limit open surgical options, including clipping, wrapping, vessel occlusion, and bypass, which are often associated with high morbidity and mortality rates (4, 5). Stent-assisted coiling (SAC) has been increasingly used for treating such aneurysms, which can avoid the extensive surgical invasion and cranial nerve deficits associated with open surgery (6–8). However, due to the fusiform/dissecting morphology and relationship with perforating vessels, SAC of VBA aneurysms was still associated with a high rate of complication in published studies (6, 8, 9). In recent years, flow diversion (FD) has provided an optional method in treating cerebral aneurysms, but there are also potential risks in treating posterior circulation aneurysms (10, 11). Intradural large VBA aneurysms are rare and the different outcomes regarding the occlusion rate and the benefits/risks of FD vs. SAC have not been well evaluated. Therefore, we compared the postprocedural complications and long-term outcomes associated with FD and SAC for the treatment of intradural large VBA aneurysms.

MATERIALS AND METHODS

Study Design and Patients

This study was a single-center retrospective study to compare the safety, angiographic, and long-term clinical outcomes of intradural large VBA aneurysms following FD or conventional SAC. The major criterion for inclusion in this study was aneurysms arising from the arterial segment extending from the origin of the intradural vertebral artery (VA) up to the origin of the superior cerebellar artery and measuring ≥10 mm in diameter. Aneurysms involving the extradural segment of VA, aneurysms arising from the branch vessel of VBA, basilar tip, and posterior cerebral artery aneurysms were excluded. Patients complicated by other treated anterior circulation aneurysms were also excluded.

Between January 2014 and October 2021, a total of 66 patients with intradural large VBA aneurysms, who underwent FD or SAC treatment, were consecutively enrolled in this study. The institutional review board of the First Affiliated Hospital of Harbin Medical University approved this retrospective study and a written informed consent was obtained from all the patients before the procedure.

Endovascular Procedure

For patients with unruptured aneurysms, clopidogrel (75 mg/day) and aspirin (100 mg/day) were orally administrated at least 3–5 days before the endovascular procedure. After at least 3 days of administration of oral dual antiplatelet agent, thromboelastography (TEG) was used to study the platelet function in all the patients. The desired range of platelet inhibition was defined as arachidonic acid inhibition >50% and ADP inhibition >30%. If the TEG result did not archive the desired range, the clopidogrel (75 mg/day) would be changed to ticagrelor (90 mg/twice daily). For patients with ruptured aneurysms, aneurysms were treated within 24 h after admission, and tirofiban or a loading dose of 300mg clopidogrel and 300mg aspirin were administrated.

The treatment modalities (FD or SAC) were decided by the neurointerventionists (with >10 years of experience in neurointerventional surgery), depending on patient preferences and various anatomic factors, including aneurysm morphology and incorporation of major perforating branches of VBA and VA dominance. All the procedures were performed under general anesthesia and systemic heparinization. Three-dimensional (3D) rotational angiography was performed after the guiding catheter placement. The 3D reconstruction was then performed to determine the optimal work projection, measure the diameter of aneurysm and parent artery, and determine the stent size. Patients who underwent the FD treatment in this study were treated with Pipeline embolization device (Covidien, Irvine, California, USA). A Marksman microcatheter (Covidien, Irvine, California, USA) was used to deploy the FD. Postprocedural multiangle unsubtracted angiogram and VasoCT were performed to evaluate the FD expansion. Balloon angioplasty or in-stent massage with microcatheter and micro guidewire was performed in case of improper FD expansion. For patients who underwent the SAC treatment, aneurysms were coiled with stent assisted by the Low-profile Visualized Intraluminal Support (LVIS) (MicroVention-Terumo, California, USA), Enterprise (Codman Neurovascular, Massachusetts, USA), or Solitaire (ev3, Irvine, California, USA). Coils were packed until satisfactory aneurysm occlusion was achieved and/or additional packing was not possible. Clopidogrel (75 mg/day) and aspirin (100 mg/day) were continued for at least 3 months (6 months for patients treated with FD) after the procedure and aspirin (100 mg/day) was maintained indefinitely.

Collected Data

Medical charts and imaging data were reviewed to identified patient age, sex, hypotension, diabetes mellitus, smoking, alcohol abuse, the Hunt–Hess grades for ruptured aneurysms, aneurysm size, aneurysm morphology, aneurysm location, incorporation of a branch artery, stent types, coil usage, postprocedural morbidity and mortality, follow-up imaging results, follow-up complications, clinical outcomes, and need for retreatment. Postprocedural complications (including thromboembolic events, hemorrhagic events, or new cranial nerve deficits) were diagnosed clinically as new neurologic deficits or changes in the level of consciousness or on CT/MR performed on patients of sudden neurologic deficits.

Clinical outcomes were collected at discharge and at follow-up (3, 6 months, and annual follow-up postprocedurally), which were evaluated by the modified Rankin Scale (mRS) score. The mRS score ≤ 2 was defined as a favorable outcome. Angiographic follow-up was scheduled at 6 months and 1–2 years postprocedurally. The Raymond–Roy grading

scale was used to evaluate the angiographic outcomes (12). Grade 1 of the Raymond–Roy grading scale was defined as complete aneurysm occlusion and Grade 1/2 of the Raymond–Roy grading scale was defined as an adequate aneurysm occlusion.

Statistical Analysis

Normally distributed continuous variables were presented as mean ± SD, while nonnormally distributed continuous variables were presented as median and interquartile range (IQR). Data were presented as numbers followed by percentages for qualitative variables. Analysis of variables between the two groups was carried out by using the Mann–Whitney *U* test or independent sample *t*-test for continuous variables and the chi-squared test or the Fisher's exact test for qualitative variables. The univariate and multivariate Cox regression analysis was performed to further identify the risk factors for postprocedural complications. Variables significant on the univariate analysis ($P < 0.05$) were subjected to the multivariate analysis. A *P*-value < 0.05 (two-sided) was considered to indicate statistical significance. Statistical analysis was performed using the SPSS version 22.0 software (IBM SPSS Incorporation, Chicago, Illinois, USA).

RESULTS

Patient Characteristics

A total of 66 patients harboring 66 intradural large VBA aneurysms, who underwent FD or SAC treatment, were included in this study. The cohort comprised 24 (37.0%) females and 42 (63.0%) males, with a mean age of 55.4 ± 9.0 (range: 32–79) years. For 12 patients with ruptured aneurysms, 4 (33.3%) patients were the Hunt–Hess grade 1, 5 (41.7%) patients were the Hunt–Hess grade 2, and 3 (25%) patients were the Hunt–Hess grade 3. Forty-three (65.2%) aneurysms were originated from the intradural vertebral artery, 15 (22.7%) aneurysms were originated from the basilar artery, and 8 (12.1%) aneurysms were originated from the vertebrobasilar artery junction. The maximal median diameter of the aneurysms was 13.2 (IQR 11.0–12.2) (range: 10.0–29.8) mm in the cohort. FD was administrated in 24 (36.4%) patients (FD group) and 42 (63.6%) patients underwent SAC treatment (SAC group). The main baseline characteristics of the SAC and FD groups are as follows: mean age was 56.7 ± 9.0 years in the SAC group and 53.2 ± 8.9 years in the FD group, median aneurysm size was 13.2 (IQR 11–16) mm and 13.3 (IQR 11.8–21) mm, respectively, anterior inferior cerebellar artery (AICA) or posterior inferior cerebellar artery (PICA) was involved in 10 (23.8%) aneurysms in the SAC group and 3 (12.5%) aneurysms in the FD group, and all 12 (28.6%) ruptured aneurysms were treated with SAC. All the parent arteries were normal, without stenosis, tortuosity, or difficult vascular access. In addition to the rate of aneurysm rupture cases ($P = 0.010$), no other obvious differences of baseline characteristics of patients and aneurysms were observed between the groups and detailed characteristics are given in **Table 1**.

Procedures

Of the 42 aneurysms in the SAC group, 26 (61.9%) aneurysms were treated with overlapping stent-assisted coiling and 16 (38.1%) aneurysms were treated with single stent-assisted coiling. The median number of coils used in the SAC group was 8.5 (IQR 5.0–12.3). Twenty-six FDs were used to treat 24 aneurysms, of which 1 (4.2%) aneurysm was treated with 3 overlapping FDs. All the aneurysms in the FD group were treated with FD alone without adjunctive coiling. Unilateral vertebral artery sacrifice was performed in 5 (7.6%) patients, of which 3 (7.1%) patients in the SAC group and 2 (8.3%) patients in the FD group. The details of the procedure-related data are shown in **Table 2**.

Comparison of Clinical Outcomes

All the patients' final clinical outcomes were available for analysis, with the median clinical follow-up time of 24.0 (IQR 12.0–45.0) months, including 35.5 (IQR 23.0–61.0) months in the SAC group and 13.0 (IQR 9.0–20.0) months in the FD group ($P < 0.001$). As shown in **Table 3**, a total of 13 (19.7%) patients experienced postprocedural neurological complications, of which 9 (13.6%) patients first occurred during the periprocedural phase and 4 (6.1%) patients first occurred during follow-up. The overall complication rate and periprocedural complication rate were both higher in the SAC group, but did not reach statistical significance [23.8 vs. 12.5%, relative risk (RR) = 1.91, 95% CI: 0.58–6.25, $P = 0.430$; 16.7 vs. 8.3%, RR = 2.00, 95% CI: 0.45–8.87, $P = 0.564$]. A total of 8 (12.1%) patients died during the follow-up. The mortality rates were similar between the groups (11.9 vs. 12.5%, $P = 1.000$). The proportion of favorable outcomes (mRS ≤ 2) at last follow-up were also similar (81.0 vs. 87.5%, $P = 0.731$). We found no differences in the rates of overall postprocedural ischemic complications (19.0 vs. 12.5%, $P = 0.731$) or hemorrhagic complications (4.8 vs. 4.2%, $P = 1.000$) between SAC and FD treatments. The details of the treatment and angiographic outcome of patients are shown in **Table 3**.

Complications

Among the 10 patients with postprocedural complications in the SAC group, one patient presented with one-sided motor weakness on the day after procedure and died due to the acute cerebral infarctions during the follow-up. Two patients presented with dysphagia postprocedurally and both died related to acute cerebral infarctions during the follow-up. Two patients experienced the persistent dizziness, of which 1 patient died due to the acute cerebral infarctions during the follow-up and the other patient improved after medication with the final mRS score of 1. One patient with ruptured aneurysms died due to the rerupture 3 days after the procedure. Two patients experienced one-sided motor weakness during the follow-up at 7 and 24 months, respectively, with the final mRS scores of 3 and 4, respectively. One patient experienced dysphagia and two-sided motor weakness on the day after procedure. The following brain MRI demonstrated the acute cerebral infarctions and the final mRS score was 4. Periprocedural symptomatic cerebellar hemorrhage occurred in one patient and the final mRS scores was 0.

TABLE 1 | Baseline characteristics of patients and aneurysms.

Characteristics	FD group ($n = 24$)	SAC group ($n = 42$)	*P*-value
Male, *n* (%)	17 (70.8)	25 (59.5)	0.358
Age (years) (m ± SD)	53.2 ± 8.9	56.7 ± 9.0	0.126
Risk factors, *n* (%)			
Hypertension	14 (58.3)	23 (54.8)	0.779
Diabetes mellitus	1 (4.2)	3 (7.1)	1.000
Smoking	9 (37.5)	11 (26.2)	0.336
Alcohol abuse	7 (29.2)	15 (35.7)	0.587
Presented with ischemic symptoms, *n* (%)	7 (29.2)	8 (19.0)	0.345
Presented with hemorrhage, *n* (%)	0	12 (28.6)	0.010
Aneurysm location, *n* (%)			0.128
VBJ	5 (20.8)	3 (7.1)	
BA	3 (12.5)	12 (28.6)	
VA	16 (66.7)	27 (64.3)	
Aneurysm size (mm) (IQR)	13.3 (11.8, 21.0)	13.2 (11.0, 16.0)	0.292
Aneurysm size classification, *n* (%)			0.845
Large (10-15 mm)	16 (66.7)	27 (64.3)	
Very large or giant (>15 mm)	8 (33.3)	15 (35.7)	
Side branch involved, *n* (%)	3 (12.5)	10 (23.8)	0.430

FD, flow diversion; SAC, stent-assisted coiling; SD, standard deviation; BA, basilar artery; VBJ, vertebrobasilar junction; VA, vertebral artery; IQR, interquartile range.

TABLE 2 | Endovascular procedure details.

Procedure details	Number of patients
FD	$n = 24$ patients
Single PED	22
Single PED and unilateral vertebral artery sacrifice	1
PED × 3 and unilateral vertebral artery sacrifice	1
SAC	$n = 42$ patients
Single EP assisted coiling	9
EP × 2 assisted coiling	3
EP + LVIS assisted coiling	17
EP + LVIS assisted coiling and unilateral vertebral artery sacrifice	1
EP + LVIS × 2 assisted coiling	1
EP + LVIS × 2 assisted coiling and unilateral vertebral artery sacrifice	1
EP × 2 + LVIS assisted coiling	1
Single LVIS assisted coiling	5
Single LVIS assisted coiling and unilateral vertebral artery sacrifice	1
LVIS × 2 assisted coiling	2
Solitaire assisted coiling	1

FD, flow diversion; PED, pipeline embolization device; SAC, stent-assisted coiling; EP, enterprise stent; LVIS, low-profile visualized intraluminal support.

In the FD group, one patient experienced acute cerebral infarctions on the day after the procedure, followed by cerebral hemorrhage: the mRS score at discharge was 4. The patient experienced another cerebral infarction during the follow-up and finally died due to the aneurysm rupture (**Figure 1**). One patient developed acute parent artery occlusion directly after the procedure and the intra-arterial urokinase was then performed. The patient died due to acute cerebral infarctions during the follow-up, though the mRS score at discharge was 0. The other one patient died due to the acute in-stent thrombosis 5 months after the procedure (**Table 3**).

Comparison of Angiographic Outcomes

Angiographic outcomes were available for 46 patients at the median follow-up time of 7.0 (IQR 6.0–14.0) months, including 10.5 (IQR 6.0–24.0) months in the SAC group and 6.5 (IQR 6.0–10.0) months in the FD group ($P = 0.061$). The overall complete occlusion rate was 71.7% (33/46). A numerically higher complete occlusion rate in the SAC group (82.1 vs. 55.6%, RR = 1.48, 95% CI: 0.95–2.31, $P = 0.051$), and similar adequate aneurysm occlusion rates between the groups (85.7 vs. 83.3%, $P = 1.000$) were found. Two (7.1%) aneurysms in the SAC group received the retreatment. One (5.6%) mild in-stent stenosis and one (5.6%) fatal in-stent thrombosis were found in the FD group.

Factors Associated With Complications

In the univariate Cox regression analysis, we found that older age (≥60 years old) ($P = 0.012$), aneurysms involved basilar artery ($P = 0.002$), patients with ischemic onset ($P = 0.004$), and unilateral vertebral artery sacrifice ($P < .001$) were related to postprocedural complications. In the multivariate Cox regression analysis, the following factors were associated with overall postprocedural complications statistically significantly: ischemic onset [hazard ratio (HR): 4.48, 95% CI: 1.29 to 15.61; $P = 0.019$], unilateral vertebral artery sacrifice (HR: 7.81, 95% CI: 1.72 to 35.53; $P = 0.008$), and older age (HR: 4.22, 95% CI: 1.14–15.67; $P = 0.031$) (**Figure 2** and **Table 4**).

TABLE 3 | Treatment and angiographic outcome of patients.

Characteristics	SAC group	FD group	RR (95% CI)	*P*-value
Number of patients with clinical FU	42	24	-	-
Median clinical FU (m) (IQR)	35.5 (23.0–61.0)	13.0 (9.0–20.0)	-	P<0.001
Overall complications, *n* (%)*	10 (23.8)	3 (12.5)	1.91 (0.58–6.25)	0.430
Death	5 (11.9)	3 (12.5)	0.95 (0.25–3.64)	1.000
Ischemic complications	8 (19.0)	3 (12.5)	1.52 (0.45–5.21)	0.731
Hemorrhage	2 (4.8)	1 (4.2)	1.14 (0.11–11.95)	1.000
Periprocedural complications, *n* (%)†	7 (16.7)	2 (8.3)	2.00 (0.45–8.87)	0.564
Death	1 (2.4)	0	-	1.000
Ischemic complications	5 (11.9)	2 (8.3)	1.43 (0.30–6.81)	0.970
Hemorrhage	2 (4.8)	1 (4.2)	1.14 (0.11–11.95)	1.000
Complications during FU, *n* (%)†	7 (16.7)	3 (12.5)	1.33 (0.38–4.68)	0.922
Death	4 (9.5)	3 (12.5)	0.76 (0.19–3.12)	1.000
Ischemic complications	7 (16.7)	3 (12.5)	1.33 (0.38–4.68)	0.922
Hemorrhage	0	1 (4.2)	-	0.364
mRS at discharge, *n* (%)				0.758
0–2	38 (90.5)	23 (95.8)	0.94 (0.83–1.07)	
3–6	4 (9.5)	1 (4.2)	2.29 (0.27–19.30)	
mRS at last FU, *n* (%)				0.731
0–2	34 (81.0)	21 (87.5)	0.93 (0.75–1.14)	
3–6	8 (19.0)	3 (12.5)	1.52 (0.45–5.21)	
Number of patients with angiographic FU	28	18	-	-
Median angiographic FU (m) (IQR)	10.5 (6.0–24.0)	6.5 (6.0–10.0)	-	0.061
Aneurysm angiographic finding, *n* (%)				
Complete occluded	23 (82.1)	10 (55.6)	1.48 (0.95–2.31)	0.051
Adequate occluded	24 (85.7)	15 (83.3)	1.03 (0.80–1.33)	1.000
In-stent stenosis/thrombosis	0	2 (11.1)	-	0.148
Retreatment	2 (7.1)	0	-	0.513

SAC, stent-assisted coiling; FD, flow diverter; RR, relative risk; CI, confidence interval; FU, follow-up; IQR, interquartile range; mRS, modified Rankin Scale.

**One patient in the FD group experienced the ischemic and hemorrhagic events.*

† Four patients in the SAC group and one patient in the FD group experienced two ischemic events, one within periprocedural period and one during the follow-up; One patient in the FD group experienced the ischemic and hemorrhagic events within periprocedural period, and ischemic and hemorrhagic events during the follow-up.

DISCUSSION

Intradural VBA aneurysms are relatively rare as compared to anterior circulation aneurysms. In the International Study of Unruptured Intracranial Aneurysms (ISUIA) (1), vertebrobasilar or posterior cerebral artery aneurysms account for only about 8% of all the aneurysms. However, such aneurysms presented a higher risk of rupture than aneurysms in other location and the diameter of aneurysm $\geq$10 mm was more likely to rupture than smaller ones. As reported by Mizutani et al. (13), once the rupture of VBA aneurysms occurred, if untreated, about 70% of patients subsequently underwent rerupture and about half of them subsequently died. Open surgical procedures, including trapping, clipping, and parent artery occlusion along with bypass, have been attempted to treat intradural VBA aneurysms in the past (14, 15). However, due to the limited surgical accessibility and relatively high mortality of open surgical procedures, endovascular reconstructive therapies, including SAC and FD, have been increasingly used. FD has been attempted to apply in the treatment of intradural large VBA aneurysms, but the results regarding the safety and efficacy remain controversial, as compared to SAC (7, 16, 17). We aimed to compare the treatment outcomes of FD and SAC for the treatment of intradural large VBA aneurysms.

Our results revealed a trend toward lower overall complication rate and periprocedural complication rate in the FD cohort. Intra-aneurysmal partial thrombosis is a common phenomenon in intradural large VBA aneurysms. The intra-aneurysmal mechanical manipulation may cause thrombus detachment from the aneurysm, which may cause the distal vessel occlusion or branch vessel occlusion, leading to ischemic complication or ischemia-reperfusion hemorrhage (7, 18, 19). In this study, all the patients in the FD group were treated with FD alone without adjunctive coiling. The nonintra-aneurysmal mechanical manipulation may associate with a lower complication rate in the FD group. A relatively high coil packing density in the SAC group may increase the risk of ischemic and hemorrhagic complications (20). In addition, the coil embolization in the SAC group may also increase the procedure time and endovascular mechanical

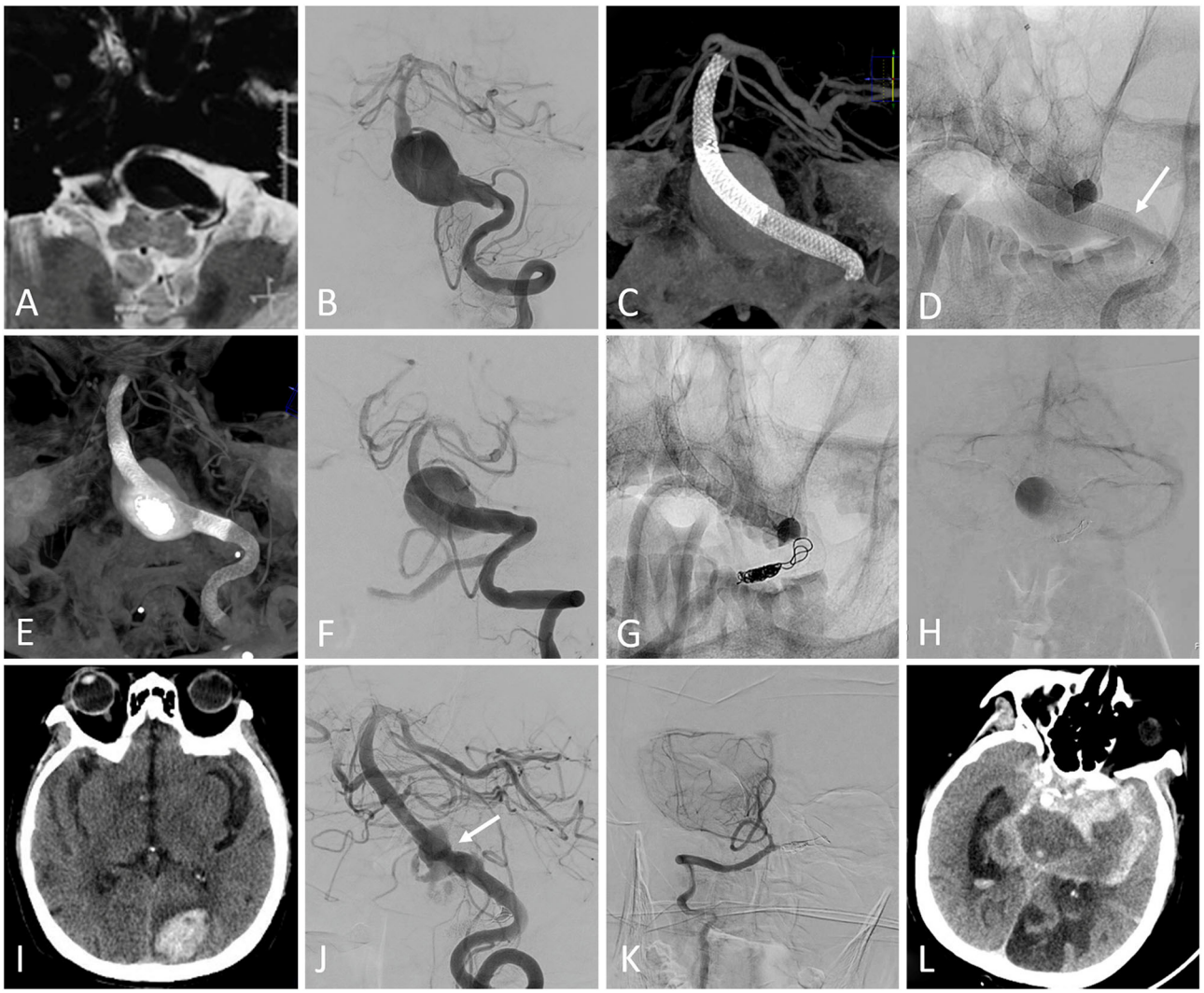

FIGURE 1 | (A) MRI showed a large lesion extending from the medulla oblongata to the pons. **(B)** Pretreatment digital subtraction angiography (DSA) demonstrated a basilar artery aneurysm. **(C)** Two overlapping Pipeline embolization devices (PEDs) were deployed without adjunctive coiling. **(D)** The second PED shortened after the complete deployment (the arrow showed the proximal end of the second PED). **(E)** A third PED was deployed. **(F)** The DSA showed the patency of the parent artery. **(G)** The contralateral vertebral artery was occluded using coils and the blood flow detained to the venous phase was detected on postprocedural DSA **(H)**. The patient experienced right-sided motor weakness on the day after the procedure and the following CT did not show any hemorrhage. The motor weakness temporarily resolved after the administration of tirofiban and low-molecular weight heparin, but the left occipital lobe intraparenchymal hemorrhage was detected on CT 2 weeks after the procedure **(I)**. The patient experienced left-sided motor weakness 18 months after the procedure and the follow-up DSA showed the partial residual of the aneurysm, with mild in-stent stenosis (arrow) **(J)**. The right posterior inferior cerebellar artery remained patency **(K)**. The aneurysm ruptured 2 days after the angiography **(L)** and the patient finally died.

manipulation, increasing the risk of vascular endothelial injury, atherosclerotic plaque detachment, and platelet aggregation (19).

This study demonstrated a complete occlusion rate of 55.6% for intradural large VBA aneurysms treated with FD, slightly lower than the complete occlusion rate for the overall posterior circulation aneurysm cohort, which was around 65% (10). Larger aneurysm size in our cohort could be a potential reason, which has been demonstrated to be associated with incomplete occlusion after FD treatment (21, 22). In addition, the results of this study showed a numerically higher complete occlusion rate in the SAC group (82.1 vs. 55.6%), but the adequate aneurysm occlusion rates were similar (85.7 vs. 83.3%). Published studies have reported the adjunctive coiling in patients with large or giant aneurysms treated with FD that could promote the thrombosis formation and aneurysm occlusion (23, 24). However, on one hand, the adjunctive coiling increased the cost of the procedure; on the other hand, the risks of procedure-related complication, procedure time, and fluoroscopy time also increased. Moreover, a relatively high coil packing density could also lead to the persistence of the mass effect of the aneurysms. In this study, no

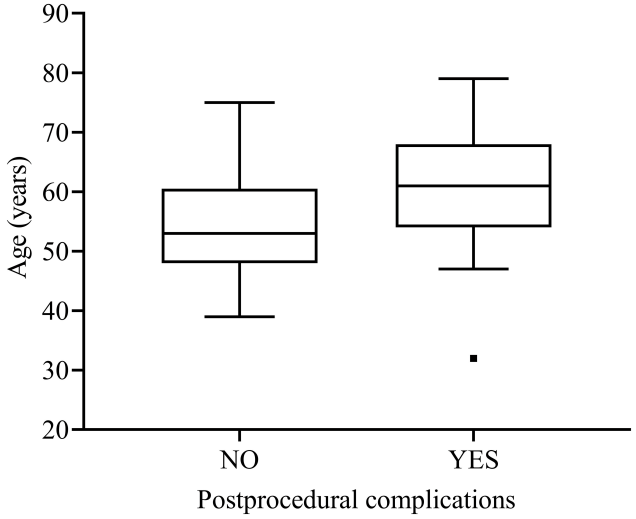

FIGURE 2 | Box plot for age and postprocedural complications.

TABLE 4 | The univariate and multivariate Cox regression analysis for postprocedural complications.

Variable	Hazard ratio	95% confidence interval	*P*-value
Univariate analysis			
Age, (≥60 years)	4.53	1.40–10.21	0.012
Incorporation of the branch vessel	1.20	0.33–4.37	0.786
Sex (male)	0.92	0.30–2.82	0.885
Aneurysms involved basilar artery	7.65	2.10–28.00	0.002
Ruptured aneurysms	0.76	0.17–3.45	0.725
Hypertension	2.74	0.75–9.95	0.126
Ischemic onset	5.09	1.69–15.34	0.004
Unilateral vertebral artery sacrifice	11.65	3.07–44.20	<0.001
Diabetes mellitus	1.34	0.17–10.30	0.779
Smoking	0.40	0.09–1.79	0.229
Alcohol abuse	1.20	0.39–3.66	0.755
Flow diversion	0.56	0.15–2.03	0.373
Aneurysm size (>15 mm)	2.25	0.76–6.70	0.145
Multivariate analysis			
Age, (≥60 years)	4.22	1.14–15.67	0.031
Aneurysms involved basilar artery	2.12	0.46–9.86	0.337
Ischemic onset	4.48	1.29–15.61	0.019
Unilateral vertebral artery sacrifice	7.81	1.72–35.53	0.008

aneurysm in the FD group was treated with adjunctive coiling, which may be associated with a relatively low complete occlusion rate during follow-up. Furthermore, more than a half of patients in the SAC group underwent overlapping LVIS stents technique or LVIS-within-enterprise technique, which has been reported to be associated with less risk of aneurysm recurrence (25, 26). But, satisfactorily, the adequate aneurysm occlusion rates were similar between the groups, which were also similar to the results of meta-analysis by Domingo et al. on the treatment of intracranial aneurysms with FD and SAC (27).

We found that patients with ischemic symptoms before procedure were a risk factor of postprocedural complications in this study, which indicated that patient with ischemic onset still at risk of ischemic complication or ischemia-reperfusion hemorrhage after procedure. Similar result has been shown by Flemming et al. (28), who reported the natural history of vertebrobasilar nonsaccular aneurysms and found that the risk of recurrent cerebral infraction was 6.7% per year in patients presenting initially with ischemic infraction. They also found that the risk of cerebral infraction due to the target aneurysm increased from 2.7 at 1 year to 11.3% at 5 years and 15.9% at 10 years. In addition, this study revealed that unilateral vertebral artery sacrifice might increase the postprocedural complication rate. Due to both the vertebral arteries are converged at the vertebrobasilar junction and the occlusion site was located at the vertebrobasilar junction, we did not conduct the balloon occlusion test (BOT) on the premise of ensuring the patency of PICA. However, despite successful BOT, there was still a risk of delayed ischemic complications described by published studies and unpredicted hypoperfusion may be the possible reason (28, 29). After the occlusion, organized thrombus in the occluded artery may dislodge at any time due to the clot propagation. The gradual contraction of the occluded artery may eject the thrombus into the side branches and leads to delayed ischemic complication or ischemia-reperfusion hemorrhage (29).

Older age (≥60 years) was associated with postprocedural complications in this study. In the ISUIA, older age has also been demonstrated to be the only risk factor of poor clinical outcome for patients who underwent surgical treatment (1). The intra-arterial mechanical manipulation during the procedure may cause the arterial injuries and the delayed endothelial healing may increase the risk of postprocedural ischemic events. Gennaro et al. (30) found that the impairment of reendothelialization was age dependent and aging could negatively regulate endothelial healing after injury. The comorbidities, such as atherosclerotic, and impairment of reendothelialization after endovascular procedure in the elderly may be associated with poor outcomes.

There are some limitations to this study. The sample size in this study was relatively small and the CIs are wide when analyzing the potential risk factors of overall complications, resulting in lower power for statistical analysis. In addition, 30.3% of patients were lost to angiographic follow-up, which might impact the evaluation of aneurysm healing. Also, due to the retrospective, nonrandomized design, the baseline data were not totally balanced and the potential bias (selection bias and so on) inherent to all the retrospective studies is unavoidable. Thus, a randomized controlled trial with large sample size would be of great interest.

CONCLUSION

This study showed a trend toward lower complication rate and lower complete occlusion rate for intradural large VBA aneurysms following FD as compared to SAC. FD and SAC have

comparable mortality rates, favorable outcomes, and adequate aneurysm occlusion rates. Moreover, ischemic onset, unilateral vertebral artery sacrifice, and older age could increase the risk of complications.

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 Harbin 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

QW, CL, HS, and PW contributed to study conception and design. QW, CL, SX, CW, ZJ, JQ, YL, and BS contributed to data acquisition and data interpretation. QW and CL contributed to the data analysis and drafted the manuscript. HS and PW contributed to the major revision of the manuscript. HS, PW, SX, CW, ZJ, and JQ contributed to the significant intellectual content. All authors have made a significant contribution to this study including, manuscript preparation, critically revised the article, and approved the final version of the manuscript.

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Treatment of Blood Blister Aneurysms of the Internal Carotid Artery With Pipeline-Assisted Coil Embolization: A Single-Center Experience

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Background: Blood blister aneurysm (BBA) is a complex and rare aneurysm that presents significant treatment challenges. The application of pipeline embolization device (PED)-assisted coiling in the treatment of ruptured BBA remains controversial. This study aimed to report on our experience and assess the safety and efficacy of this strategy.

Methods: Between February 2019 and February 2021, 12 patients with ruptured BBAs underwent PED-assisted coil embolization. We collected detailed data about each patient, including demographic information, aneurysmal data, technical details, antiplatelet strategy, operation-related complications, and follow-up outcomes.

Results: A total of 12 BBA patients were treated with single PED-assisted coil embolization. One patient experienced intraoperative rupture that was controlled by rapid coiling without clinical consequences. All the patients demonstrated complete occlusion on postoperative angiography. A total of three patients had postoperative complications: left hemiparesis, Broca's aphasia, and right hemiplegia due to vasospasm, and transient hemiparesis. Follow-up angiography revealed that all BBAs were completely occluded, except one with neck residue. All patients had favorable outcomes at discharge and the most recent clinical follow-up (mRS score $\leq$ 2).

Conclusion: Endovascular treatment of BBAs of the internal carotid artery using PED-assisted coil embolization is a safe and effective strategy. This has contributed to the understanding of BBA therapy and provides a potentially optimal treatment option for this intractable lesion.

Keywords: blood blister aneurysm, pipeline embolization device, internal carotid artery, coil embolization, subarachnoid hemorrhage

INTRODUCTION

A blood blister aneurysm (BBA) is a rare type of aneurysm. It accounts for approximately 0.3–1% of intracranial aneurysms and 0.9–6.5% of ruptured aneurysms (1). It is characterized by thin-walled broad-based aneurysms that lack an identifiable neck and have a high risk of rupture (2). Unlike a saccular aneurysm, a BBA typically originates from the non-branching sections of the supraclinoid

portion of the internal carotid artery (ICA) (3). This complex character poses significant challenges for treatment.

Although the efficacy of microsurgical treatment of BBA has been demonstrated, the endovascular intervention has gradually become the preferred alternative for BBA treatment, owing to its lower complication rate and better prognosis (4, 5). While there are numerous interventional techniques in the treatment of BBA, including various intracranial stents with or without coiling, endovascular ICA trapping, and a combination of other procedures, the invention of the flow diverter (FD) represents a milestone in the history of aneurysm treatment (6–8). The pipeline embolization device (PED), the most often used FD, promotes intra-aneurysmal occlusion by reconstructing the blood flow in the parent artery. At present, more reports have focused on the use of PED alone for BBA treatment. Complications, such as delayed occlusion, resulting in recurrence or possibly re-rupture, raise concerns and restrict its application (6, 7). Using PED combined with coil embolization may be a reasonable and feasible strategy. However, few studies have reported the effects of PED-assisted coil embolization in BBA treatment. Therefore, this study aimed to evaluate the safety and efficacy of this strategy, enhance our understanding of BBA therapy, and provide a potentially optimal treatment option for intractable lesions.

METHODS

Data Sources and Variables

Between February 2019 and February 2021, 12 consecutive patients with subarachnoid hemorrhage (SAH) due to ruptured BBA of the ICA were treated with PED-assisted coil embolization at West China Hospital of Sichuan University. Three-dimensional angiography was performed to confirm all BBAs. PED was used to treat BBA only in the absence of hydrocephalus, severe vasospasm, cerebral infarction, and the Hunt and Hess grade lower than III. Detailed information was extracted from the medical records of each patient, including patient demographics, aneurysmal data, technical details, antiplatelet strategies, operation-related complications, and follow-up outcomes. The safety and efficacy of this treatment modality were also evaluated. Safety was assessed based on perioperative complications and follow-up neurological function. Postoperative and follow-up occlusions were considered the criteria for efficacy. This study was approved by the Ethics Committee of the West China Hospital of Sichuan University.

Technical Details

The procedure was performed under general anesthesia, and systemic heparinization was administrated before the procedure. A triaxial guide-catheter system, including 9F short femoral sheath (Terumo, Tokyo, JPN), 7F 90 cm long sheath (COOK, Indiana, USA), and 5F 115 cm Navien (Medtronic, California, USA) intermediate catheter, were introduced into the left or right femoral artery. The 7F sheath was inserted into the C1 segments of the ICAs using a 125 cm vertebral catheter (Terumo, Tokyo, JPN). The Navien intermediate catheter was advanced into the C2 segment to complete the parent artery angiography and three-dimensional (3D) rotational angiography. To choose a suitable PED (Medtronic, California, USA) and coil size, the diameters of the proximal and distal parts of the parent vessel, aneurysm, and neck were measured. The Marksman (Medtronic, California, CA) microcatheter was navigated to the M2 segment through the Navien catheter. After that, a steam-shaped Echelon-10 microcatheter (Medtronic, California, USA) was delivered to the aneurysmal sac *via* the 7F long sheath located next to the Navien catheter. The Echelon-10 microcatheter was removed from the aneurysm sac to the parent artery, after confirming whether it has the suitable shape to navigate to the aneurysm sac easily. A suitable PED was then semi-deployed to the distal of the aneurysm neck, subsequently, the Echelon-10 microcatheter was navigated to the aneurysm sac again, and some loops of coils were inserted into the aneurysm sac. After the aneurysm cavity was completely embolized, the PED was fully deployed. Digital subtraction angiography (DSA) was performed immediately after PED placement to evaluate the degree of embolization, stent positioning, and patency of the branch and parent arteries. Vasospasms and operation-related complications were recorded.

Perioperative Management

After admission, all patients received specialist care and systemic treatment to withstand the surgery. Tirofiban (0.2 μg/kg/min) was administered immediately following successful stent placement. One day after the procedure, tirofiban was discontinued after a loading dose of 225 mg clopidogrel and 300 mg aspirin for 6 h. All patients continued aspirin 100 mg/day for 6 months and clopidogrel 75 mg/day for at least 3 months, beginning the next day.

Follow-Up

We conducted clinical and imaging follow-ups for all patients. The modified Rankin score (mRS) was used to assess neurological outcomes at discharge and at the most recent clinical follow-up. An mRS score of 0–2 indicated that the patient had a positive neurological prognosis. Imaging follow-up was performed 3–6 months postoperatively using DSA to assess aneurysmal occlusion, which was quantified using the simplified Reymond grade (grade 1, complete occlusion; grade 2, neck remnant; grade 3, residual sac) (8). Additionally, the patency of the branch and parent vessels, degree of embolization, and position of the PED were documented. Two neurointerventional specialists assessed these findings.

RESULTS

This study involved 12 patients (six women and six men) who had acute SAH due to BBAs. The mean age of the patients was 44.2 years (range, 34–56 years). On admission, nine patients had a Hunt and Hess classification of II, and III in three patients. The Fisher grade was 3 in six patients, 2 in five patients, and 1 in one patient. The BBAs were located at the C6 segment of the

Abbreviations: BBA, blood blister aneurysm; PED, pipeline embolization device; FD, flow diverter; 3D, three-dimensional; DSA, digital subtraction angiography; mRS, modified Rankin Score; PFT, platelet function testing.

ICA in five patients and C7 in seven patients, ranging from 1.4 × 1.3 mm to 5.9 × 3.9 mm. The average duration from disease onset to treatment was 5.8 days (range, 2–16 days). The baseline clinical and imaging characteristics are shown in **Table 1**.

All enrolled patients were treated with single PED-assisted coil embolization. Of the 12 cases, complete occlusion (Raymond grade I) was confirmed using immediate angiography after the operation. Intraoperative angiography revealed vasospasm in five patients. None of the patients in our study underwent extraventricular drainage or other surgical procedures. None of the patients experienced intraoperative complications, except for one patient (Patient 1) who experienced an aneurysm rupture that was successfully treated with urgent dense coiling. Three patients experienced adverse post-procedural complications related to vasospasm. Patient 1 developed left limb hemiplegia due to vasospasm. Patient 4 developed Broca's aphasia and right hemiplegia. The patient was discharged from the hospital with an mRS score of 2, which improved to 1 without aneurysm recurrence at 28 months visit. Furthermore, patient 8 developed transient hemiparesis. After the symptomatic therapy, no neurological deficits were observed at discharge.

Follow-up angiography after the endovascular procedure was available for 12 patients with an average of 7.1 months (range 3–30 months). Overall, 11 of 12 BBAs (91.2%) had Raymond grade I, and only one patient (Patient 2) demonstrated neck residue (Raymond II). Two angiographic results from another hospital showed no progression in the residue. The patient maintained an mRS score of 0 at the 34-month postoperative follow-up. Additionally, the imaging results revealed stent shortening in four patients (Patients 1, 4, 8, and 10). Neurological outcomes were available for all 12 patients. Ten patients had an mRS score of 0 at discharge and at the latest clinical follow-up. Although Patient 4 sustained motor aphasia and hemiplegia, her mRS score increased from 2 at discharge to 1 at 28 months follow-up. The mRS score of Patient 1 remained at 1 from discharge to the last follow-up. The mean follow-up was 25.3 months (range, 11–36 months). Descriptions of the periprocedural and follow-up information are summarized in **Table 2**.

Typical Case

Patient 8: A 44-year-old man was admitted to our hospital with a severe headache (Hunt-Hess grade 2). Brain CT revealed diffuse SAH in the suprasellar cistern (Fisher grade 2) (**Figure 1A**). One day after the onset, diagnostic DSA confirmed a BBA (3.4 × 3.0 mm) in the lateral wall of the supraclinoid left ICA (**Figure 1B**). After two days, one-stage PED-assisted coil embolization was performed. During the operation, we selected an appropriate PED (4.75 × 20 mm) according to the diameter of the proximal ICA. After placing the Marksman microcatheter, an Echelon-10 coil embolization microcatheter was inserted into the aneurysmal sac. After filling the aneurysmal sac, we loosely covered the neck with some loops of the coil (2.5 mm × 5 cm) bulging into the ICA and fully deployed the PED to compact the coil. The DSA performed immediately revealed a complete obliteration (**Figure 1C**). The patient experienced transient hemiparesis due to vasospasm after surgery. There were no neurological deficits at discharge after symptomatic treatment. He was discharged from the hospital four days later and continued to receive dual antiplatelet therapy. The CT scan was reviewed one month later and showed that the SAH had been fully absorbed (**Figure 1D**). Follow-up angiography at 6 months revealed that the BBA was occluded without stenosis of the ICA. However, we found that the distal end of the PED moved toward the proximal part of the parent artery and retained complete coverage of the aneurysmal neck (**Figures 1E,F**). The patient had no neurological deficits at discharge or at the latest follow-up (mRS 0).

DISCUSSION

Blood blister aneurysms are complex and challenging vascular lesions that lack an identifiable neck, and they have a high risk of rupture (9). Owing to the intricate histopathological features and urgent SAH manifestations, aggressive treatment must be adopted once diagnosed. Although the efficacy of microsurgical, interventional, and combined methods for BBAs have been demonstrated, no one-fit-all solution exists (10–16). Successful microsurgical treatment of BBA has been demonstrated, including clipping, wrap-clipping, suturing, and extracranial-intracranial bypass (4, 17). Wrap-clipping, in comparison to wrapping and clipping, has been shown in several studies with low recurrence and re-rupture rates (18, 19). However, unbefitting clip-wrapping had a negative effect on therapeutic effect, resulting in arterial stenosis, perforator injury, and ischemic consequences (13, 20). Thus, microsuturing may be able to resolve the issue of ICA stenosis, and some literature has documented surprising results (14, 21). Significantly, the fact that technical requirements, complications at the suture site, and atherosclerosis in some cases may influence the results of microsuturing. Besides, extracranial-intracranial bypass is also a prospective approach for ruptured BBAs. Balik et al. revealed in a meta-analysis that the bypass strategy is superior to non-bypass in terms of safety and efficacy (22). In addition, the ischemic risk associated with BBAs treated with extracranial-intracranial bypass, as well as the timing and selection of procedure, should be rationally assessed.

With the introduction of various intracranial stents, endovascular therapy has gradually become the primary strategy in the treatment of BBA (19). The treatment paradigm has changed from simple coil embolization to guiding blood flow away from the aneurysm and reconstructing the parent artery. In recent years, the use of Willis covered stents for BBA treatment has yielded promising results (23, 24). However, the difficulty in delivery, endoleakage, and occlusion of branches limit its application. While stent-assisted coil embolization demonstrated high rates of immediate occlusion, the final obliteration was indistinguishable from other endovascular treatment techniques (25, 26). In addition, bleeding recurrence due to insufficient flow diversion raised concerns about this technique (27). Therefore, the presence of multiple overlapping stents combined with coiling embolization contributes to a significant reduction in bleeding recurrence and an increase in aneurysm occlusion rates (26, 28, 29). In a multicenter study of 221 patients, Fang

TABLE 1 | Baseline clinical and imaging characteristics.

Case no.	Sex/Years	Presentation	Other disease	H&H	FGS	Aneurysm location	Aneurysm size (mm)	Aneurysm neck (mm)	DT (day)
1	M/34	SAH	N	2	2	R-C7	3.3 × 2.6	3.5	8
2	F/47	SAH	asthma	2	3	L-C7	4.3 × 3.6	4.3	2
3	F/47	SAH	N	2	3	L-C6	1.6 × 1.4	1.9	4
4	F/46	SAH	hypertension	3	3	L-C7	3.7 × 3.4	7.2	5
5	F/49	SAH	N	2	3	R-C7	1.4 × 1.3	1.3	16
6	M/53	SAH	N	2	1	R-C6	3.5 × 2.0	3.5	5
7	F/36	SAH	pneumonia	2	2	R-C7	5.9 × 3.9	5.3	4
8	M/44	SAH	N	2	2	L-C7	3.4 × 3.0	3.1	3
9	M/56	SAH	N	3	2	R-C6	2.9 × 2.1	3.1	4
10	F/39	SAH	hypertension	3	3	L-C7	3.4 × 3.2	3.7	5
11	M/43	SAH	N	2	2	L-C6	4.7 × 3.3	5.4	7
12	M/37	SAH	N	2	3	L-C6	5.3 × 4.2	6.1	6

F, female; M, male; H&H, Hunt and Hess grade; FGS, Fisher grade scale; SAH, subarachnoid hemorrhage; DT, Diagnosis to treatment.

TABLE 2 | Summary of clinical and angiographic outcomes of patients treated by PED-assisted coil embolization.

Case no.	PED size	Treatment	Im-DSA	Intra- complication	Post-complication	Follow-up angiography	PED shortening (Y/N)	mRS at Discharge	mRS at latest FU	Latest FU time (mos)
1	PED-375-20	PED + coil	1	Rupture, vasospasm	Left hemiparesis	CO (6 months)	Y	1	1	36
2	PED-475-20	PED + coil	1	N	N	NR*(30 months)	N	0	0	34
3	PED-325-30	PED + coil	1	Vasospasm	N	CO (5 months)	N	0	0	30
4	PED-300-18	PED + coil	1	Vasospasm	Right hemiplegia; Broca aphasia;	CO (3 months)	Y	2	1	28
5	PED-500-20	PED + coil	1	N	N	CO (3 months)	N	0	0	27
6	PED-400-16	PED + coil	1	N	N	CO (10 months)	N	0	0	21
7	PED-350-18	PED + coil	1	N	N	CO (3 months)	N	0	0	18
8	PED-475-20	PED + coil	1	Vasospasm	Transient hemiparesis	CO (6 months)	Y	0	0	11
9	PED-475-20	PED + coil	1	N	N	CO (3 months)	N	0	0	25
10	PED-400-16	PED + coil	1	Vasospasm	N	CO (6 months)	Y	0	0	31
11	PED-375-20	PED + coil	1	N	N	CO (4 months)	N	0	0	14
12	PED-325-30	PED + coil	1	N	N	CO (6 months)	N	0	0	29

*PED, Pipeline embolization device; Intra, Intraoperative complication; Post, post operation complication; mRS, modified Rankin Scale; RS, Raymond grade; Im, immediate; FU, follow-up; CO, complete occlusion; NR, neck remnant. *The latest angiography showed no progression of the residue.*

et al. demonstrated that the complete occlusion rates of BBAs treated with a single stent, two stents, and three or more stents were 42.9%, 78.4%, and 88.2%, respectively. Furthermore, the recurrence rates were 38.1%, 13.5%, and 5.9%, respectively (30). However, deploying a second stent is not always feasible because of the procedure complexity.

The introduction of FDs represents a paradigm shift in therapeutic approaches from intra-sac embolization to vessel reconstruction (31). This strategy has proven to have a lower retreatment rate than microsurgery and other endovascular treatment (18). As the most commonly used FD, PED has been approved to treat unruptured aneurysms. Nonetheless, its application in ruptured aneurysms is limited owing to delayed occlusion, with only a few reports of ruptured BBAs being treated. In this study, all patients with BBAs underwent single PED-assisted coil embolization. During angiographic follow-up, 12 patients achieved complete embolization, but one developed a neck residue. During a mean follow-up of 25.3 months, 12 patients maintained good neurological function (mRS score $\leq$ 2). Accordingly, we demonstrated that PED-assisted coil embolization is a safe and effective strategy for BBA treatment.

There is controversy over using a coil in conjunction with PED for BBA treatment. In a multicenter study of 45 patients, Mokin et al. demonstrated that a single PED is a safe and effective modality, and the use of coils is not associated with eventual occlusion (7). Besides, several small sample studies have also reported success with PED alone in the treatment of BBAs (11, 32, 33). Overall, these studies indicate that a single PED may be sufficient for BBA treatment. However, incomplete or delayed occlusion and persistent aneurysm growth during thrombosis

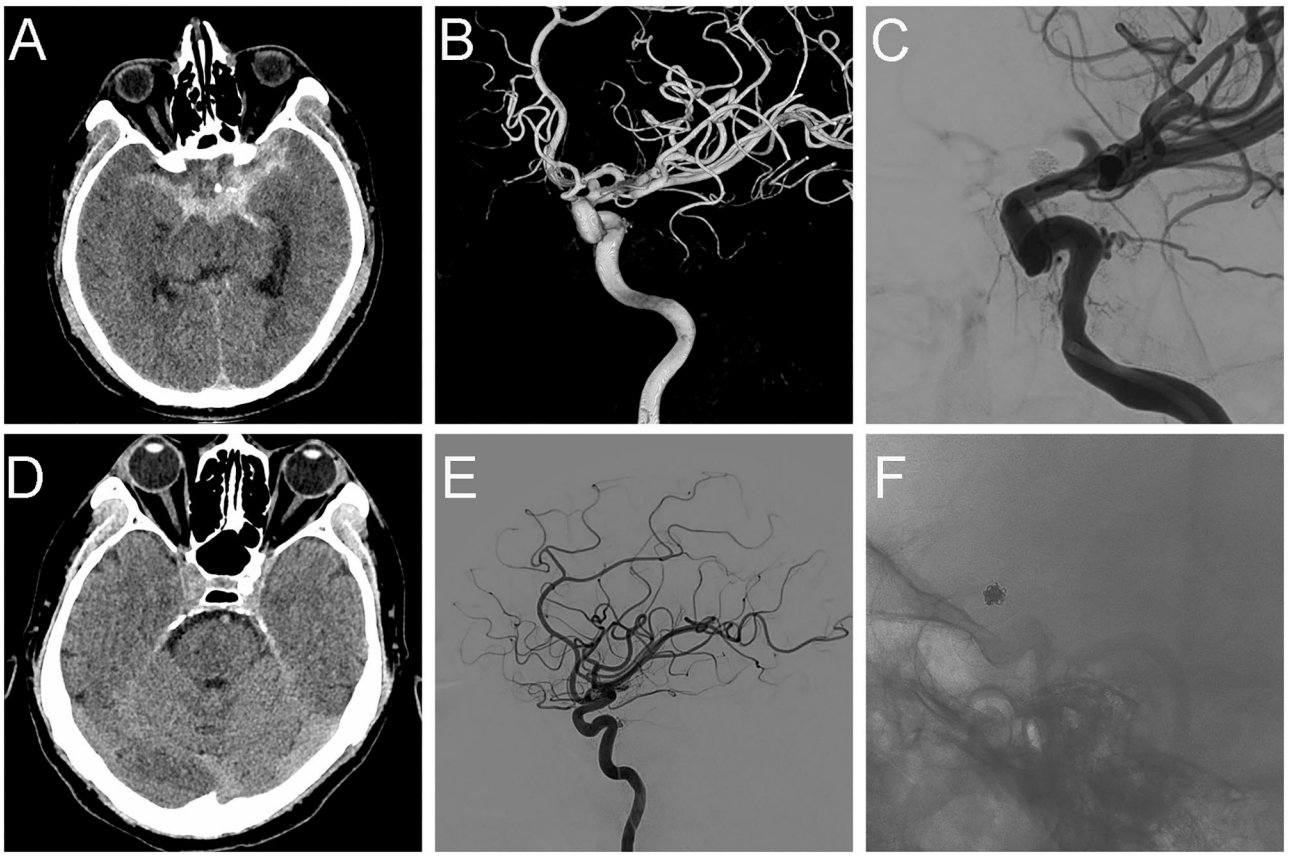

FIGURE 1 | Typical case images. **(A)** CT scan showing SAH in suprasellar cistern before operation. **(B)** Preoperative DSA showing BBA at C7 segment of the left ICA. **(C)** Intraoperative DSA showing complete occlusion of the BBA using PED+ coils. **(D)** CT scan at 1-month follow-up. **(E,F)** DSA and Xper-CT at 6 months follow-up.

in the aneurysm sac have increased, which is uncommon in traditional endovascular procedures. Ryan et al. reported 16 BBAs; none of the aneurysms was completely occluded on the day of treatment, and only 31% were completely occluded at three months follow-up (34). Some studies have also reported aneurysm growth and catastrophic re-rupture following a single PED deployment, leading to death (6, 35, 36). In addition, although intraoperative contrast stasis and decreased blood flow were observed in the aneurysm sac after PED placement, this finding did not suggest a decrease in pressure. Computational hemodynamic research conducted by Cebral et al. (37) illustrated that increased intra-aneurysmal pressure after FD deployment was associated with re-rupture.

These cases indicate that early intravascular embolization may be a reasonable strategy for avoiding re-rupture. Therefore, some studies advocate for a therapeutic strategy using coil embolization followed by PED to re-establish blood flow in the parent artery (6, 10, 38, 39). The coil was used to embolize the aneurysm cavity, loosely pack the aneurysm neck, and assist the PED in repairing the parent artery. Thus, the parent artery was reconstructed simultaneously with the embolization of the aneurysm. Our patient showed favorable outcomes. Immediate postoperative angiography revealed that all BBAs were successfully achieved one-stage embolization. However, this modality involves intraluminal surgery, which theoretically increases the risk of intraoperative aneurysm rupture. Contrast leakage occurred during coil packing in Patient 1, and re-rupture of the aneurysm was contemplated. The aneurysmal sac was rapidly filled with coils, and the PED was opened without any leakage. Based on this experience, we selected coils smaller than the measured diameter and adopted a more cautious approach to reduce the probability of intraoperative rupture in other patients.

The stability and shape of the microcatheter as well as the coiling microcatheter delivery timing into the aneurysm cavity are critical for this surgery. The PED deployment may cause the fluctuation of the coaxial system, which may cause the coiling microcatheter to move. The coiling microcatheter could either enter the aneurysm cavity so as to rupture the aneurysm or drop out of the aneurysm cavity and thus extending the operating time and increasing the risk of stent thrombosis. Furthermore, the time of the PED in the semi-deployed state should be reduced to prevent stent thrombosis. The PEDs were successfully deployed in all the patients in our study. In Patient 2, the PED was failed to be fully expanded despite the wire being swayed gently. Finally, the PED was fully opened with the assistance of a balloon. In addition to these two operations, re-deployment

following PED recycling is an effective solution to solve issues, such as stent malposition. All the patients achieved complete obliteration at the follow-up angiography, except one patient with slight neck residue. It may be associated with the formation of an intractable wedge-shaped space between the PED and aneurysm neck. At the 7 and 30-month angiography follow-up, two angiographic results from a different hospital demonstrated no progress in the residue. At the 34-month clinical follow-up, this patient maintained an mRS score of 0. Therefore, further invasive therapy was not necessary because of the expected low risk of re-bleeding from such a minimal residue. If progression is observed during subsequent imaging examination, then a second PED may be considered.

In our center, we also adopted the technique of "endovascular patch embolization" to repair the fragile neck, which is one of the challenges in BBA therapy (40). The advantage of this technique is that embolization of the aneurysm neck can be achieved using coils and staged-deployed PED. After filling the aneurysmal sac, we used a few loops of coil herniation into the parent vessel to loosely cover the neck and fully deploy PED to compact the coil. Our practice has proved the safety and efficacy of this patching technique.

Imaging follow-up also revealed stent shortening in four patients, which was thought to be a key factor influencing treatment success. Wang et al. indicated that this is relative stent shortening due to changes in the parent vasculature during BBA formation. After PED deployment, the shortened parent arteries reverted to their original length, resulting in the appearance of a shorter PED. However, this does not preclude the possibility of stent shortening, as the PED is entirely expanded (41). A review of our intraoperative findings of vasospasm in these four patients supports this viewpoint. Notably, this "shortening" did not cause aneurysmal recanalization. Accurate assessment of the aneurysm and parent artery, proper PED size, and adequate anchoring length around the BBA are crucial for preventing stent migration and shortening. The size of PED used was selected based on the diameters of the ipsilateral distal and proximal non-vasospasm segments or the relatively normal contralateral artery.

Because the BBA is typically located in the supraclinoid of the ICA, occlusion of the branch vessels is unavoidable, causing ischemic complications. However, despite coverage of the ICA branches and anterior cerebral artery, no associated problems were detected in this study. In their meta-analysis, Cagnazzo et al. included 757 ophthalmic arteries, and 196 posterior communicating arteries demonstrated that none of the patients had symptoms related to decreased blood flow or occlusion. In 199 prechoroidal arteries, the pooled results indicated that only 1% of patients experienced transient neurological symptoms (42). Bhogal et al. analyzed 147 aneurysms treated with FDs and illustrated that the side-branch occlusion rate of the ICA was 20%. However, none of the patients showed clinical symptoms of arterial occlusion (43). Although FD covers the collateral vessels, the strong collateral circulation system may explain lower occlusion rates and rare manifestations. Therefore, we do not have to worry about branch patency when using FD.

Currently, there is no consensus on the timing and duration of antiplatelet therapy using PED to treat ruptured BBA (34, 39, 44). An ideal protocol should effectively prevent in-stent thrombosis while minimizing the risk of drug-related bleeding. Combining ASA and clopidogrel has become the most commonly used strategy, despite the different regimes. However, in five cases of ruptured BBAs treated *via* PED, Tanburoglu et al. demonstrated that single antiplatelet therapy is safe and effective (45). In this study, antiplatelet treatment was not administered before the procedure. The protocol for promptly administering tirofiban and bridging loading doses of aspirin and clopidogrel was successful. No ischemic or hemorrhagic complications were associated with antiplatelet therapy during the perioperative period. This demonstrated the safety and efficacy of this modified strategy. This favorable outcome may be explained by the decreased risk of re-rupture caused by coiling embolization, and the modified antiplatelet strategy used to avoid thrombosis. Saber et al. (46) reviewed 2,002 patients treated with PED and found performing platelet function testing (PFT) did not 229 predict hemorrhagic and ischemic events. Besides, some studies have demonstrated that patients undergoing PFT have an increased risk of hemorrhagic complications (47, 48). Therefore, PFT was not performed at our center. In summary, additional prospective studies on antiplatelet strategies after PED placement are needed.

Limitation

Limitations of this study include its retrospective design, single-center sample size, lack of a defined control group, and a small number of patients involved (12 patients). All of which may have contributed to the selection and reporting bias. Given the rarity of BBAs and the scarcity of reports on PED-assisted coil embolization, this study provides strong evidence for advocating this technique.

CONCLUSION

The favorable outcomes from this study suggest that PED in conjunction with coils is safe and efficacious in the treatment of ruptured BBAs. It has enhanced our understanding of BBA therapy and provided a potentially optimal option for this intractable lesion. However, further evidence from prospective and multicenter studies is necessary.

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

LL, CW, and XX contributed to the study design. PL, SL, and TW performed the clinical follow-up. PL and LL performed the literature search, data collection, and drafted the manuscript. LZ, TW, XX, and CZ contributed to data analysis and interpretation. XX, SL, and CW contributed to editing and revision of the manuscript. All authors read, edited, and approved the final version of the manuscript.

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Feasibility and Safety of Flow Diversion in the Treatment of Intracranial Aneurysms *via* Transradial Approach: A Single-Arm Meta-Analysis

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Background: While studies have confirmed that flow diversion (FD) can treat intracranial aneurysms *via* transradial approach (TRA), it remains unclear whether their treatment ultimately impacts safety and feasibility. We aim to conduct a systematic review and meta-analysis assessing the safety and feasibility after FD treatment of intracranial aneurysms *via* TRA.

Methods: PubMed, EMBASE, and Web of Science were systematically reviewed. The primary outcomes were the success rate and the access-related complications of deploying FD *via* TRA. Meta-analysis was performed using a random or fixed effect model based on heterogeneity. And the publication bias was evaluated using a funnel plot. This study was registered with PROSPERO, number CRD42021244448.

Results: Data from 8 studies met inclusion criteria (250 non-duplicated patients). The success rate was 93% (95% confidence interval [*CI*] 0.86–0.98; $I^2 = 61.05\%$; $p = 0.01$). The access-related complications rate was 1% (95% *CI* 0–0.03; $I^2 = 0.00\%$; $p < 0.01$). The mainly access-related complications included radial artery spasm (85.7%) and radial artery occlusion (14.3%). The TRA convert to transfemoral approach (TFA) was 7% (95% *CI* 0.02–0.14; $I^2 = 61.05\%$; $p = 0.01$).

Conclusions: Although TFA is still the main access for FD in the treatment of intracranial aneurysms, the TRA also has a higher success rate and lower access-related complications rate. With the improvement of future experience and equipment, the TRA may become the main access for FD which has more advantages. Future studies should design prospective, multicenter randomized controlled studies for long-term follow-up.

Keywords: endovascular procedures, flow diversion, transradial approach, intracranial aneurysms, meta-analysis

INTRODUCTION

In interventional cardiology, the advantages of the TRA are more and more obvious than that of the TFA (1, 2). Meanwhile, TRA gradually began to pay attention to the field of neurointervention (3–5).

With the development of Interventional Neurology, flowdiversion (FD) has become an important complementary treatment for coils and stents (6). Although some studies have shown that FD is effective and safe for the treatment of intracranial aneurysms *via* TRA, its data are limited. There were only some meta-analyses of diagnostic cerebral angiography and mechanical embolectomy (7, 8). Therefore, we conducted the first meta-analysis to illustrate the feasibility and safety of FD in the treatment of intracranial aneurysms *via* TRA. This study may be helpful to provide benchmark numbers to guide surgeons choose the appropriate access when using FD to treat intracranial aneurysms.

Abbreviations: FD, flow diversion; CI, confidence interval; TRA, transradial approach; TFA, transfemoral approach; LCCA, left common carotid artery; AC, anterior circulation; PC, posterior circulation; ICA, internal carotid artery; NA, not available.

METHODS

This study was performed following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (9).

Search Strategy

We conducted a comprehensive literature search of the PubMed, EMBASE, and Web of Science databases for studies published from their dates of inception to May 2021. The title and abstract were searched using combinations of the following search terms: (divert OR diverts OR diversion OR flow-diverter OR flow diversion OR pipeline embolization device OR PED OR pipeline OR flow diverters OR diverters) AND (Intracranial Aneurysm OR Aneurysms, Intracranial OR Intracranial Aneurysms OR Aneurysm, Intracranial OR Brain Aneurysm OR Aneurysm, Brain OR Aneurysms, Brain OR Brain Aneurysms OR Cerebral Aneurysm OR Aneurysms, Cerebral OR Cerebral Aneurysms OR Aneurysm, Cerebral) AND (Radial Artery OR Arteries, Radial OR Artery, Radial OR Radial Arteries OR transradial OR radial OR transradial access OR transradial approach).

Selection Criteria

The inclusion criteria were (1) treatment of aneurysms with FD *via* TRA; (2) ≥5 patients with an aneurysm; (3) and the clinical or angiographic outcomes of aneurysms reported. The exclusion

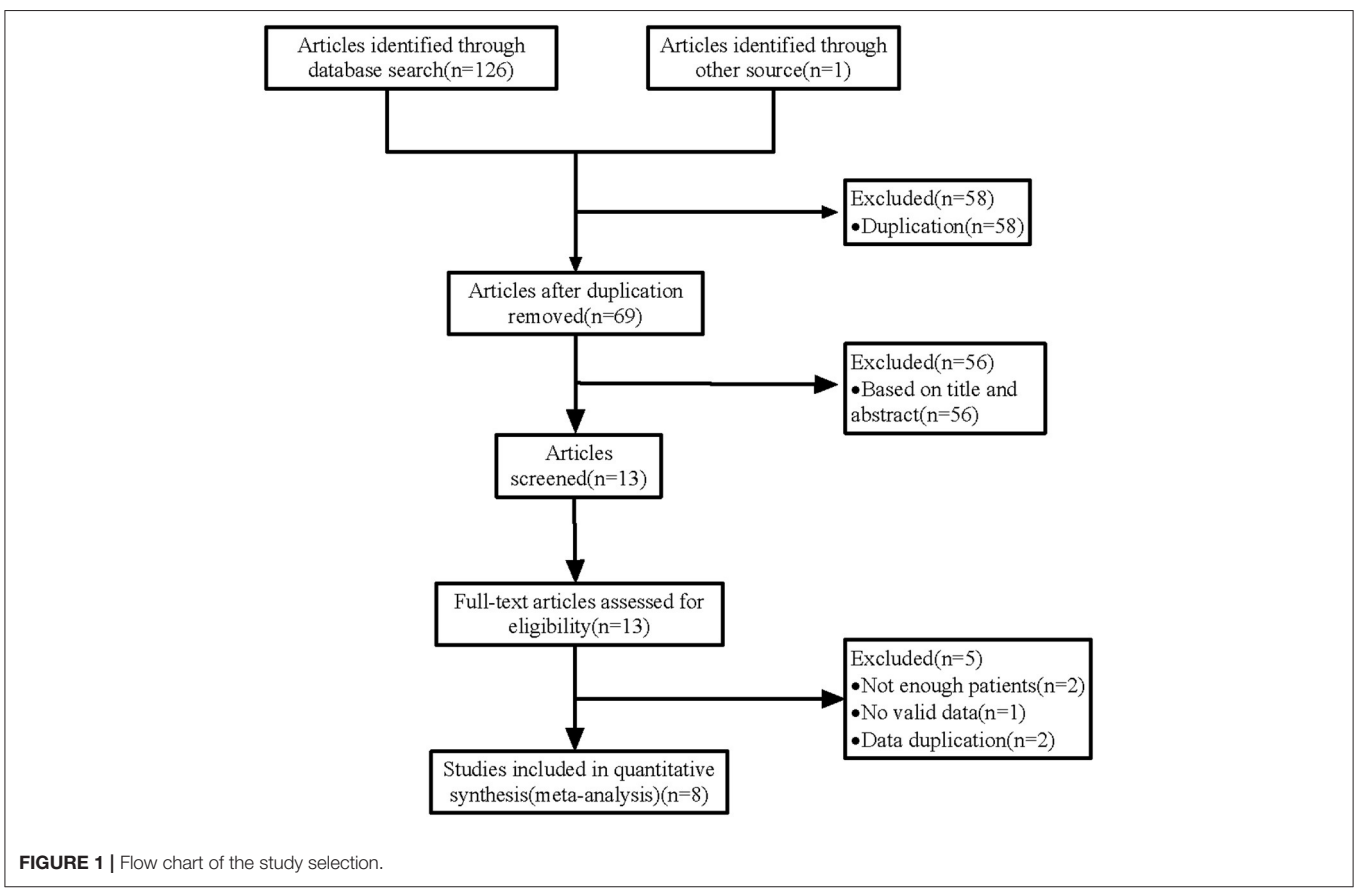

FIGURE 1 | Flow chart of the study selection.

TABLE 1 | Evaluation of the included studies using the criteria described by Murad et al. (10).

Study	Selection	Ascertainment		Causality		Reporting
	Does the patient(s) represent(s) the whole experience of the investigator (center)?[a]	Was the exposure adequately ascertained?	Was the outcome adequately ascertained?[b]	Were other alternative causes that may explain the observation ruled out?	Was follow-up long enough for outcomes to occur?	Is the case(s) described with sufficient details?[c]
Khandelwal et al. (12)	Yes	Yes	Yes	Yes	NR	Yes
Kühn et al. (14)	Yes	Yes	Yes	Yes	Yes	Yes
Waqas et al. (13)	Yes	Yes	Yes	Yes	Yes	Yes
Weinberg et al. (11)	Yes	Yes	Yes	Yes	Yes	Yes
Chen et al. (17)	Yes	Yes	Yes	Yes	NR	Yes
Snelling et al. (16)	No	Yes	Yes	Yes	NR	Yes
Sweid et al. (15)	Yes	Yes	Yes	Yes	Yes	Yes
Goland et al. (18)	No	Yes	Yes	No	NR	Yes

NR means not reported.

[a] *This criterion is to report only FD for intracranial aneurysms.*

[b] *This criterion does not meet the definition of access-related complications or there is no reason for approach conversion.*

[c] *This definition explains the procedure technique in detail.*

TABLE 2 | The characteristics of FD in the treatment of intracranial aneurysm *via* TRA.

Study	No. procedures	Mean Age (yr)	Side	Location	No. success (*n*%)	No. access-related Complication	Conversion (radial-femoral)	Reasons for conversion
Khandelwal et al. (12)	29	55	R:15 L:14	AC:29	26 (90%)	3	3	Radial artery spasm 3
Kühn et al. (14)	74	57.5	NA	AC:80 PC:6	71 (96%)	1	3	vessel tortuosity 2 aberrant right subclavian artery 1
Weinberg et al. (11)	32	56.7	R:11 L:20 M:1	AC:30 PC:2	32 (100%)	0	0	0
Waqas et al. (13)	35	62.1	L:16	AC:29 PC:6	33 (94%)	0	2	vessel tortuosity 2
Chen et al. (17)	49	57.8	L:32 R:17	AC:44 PC:5	39 (80%)	2	10	LCCA angle of origin 4 LCCA/ICA tortuosity 4 Radial artery spasm 2
Snelling et al. (16)	11	NA	L:9 R:2	AC:10 PC:1	8 (73%)	1	3	Radial artery spasm 1 vessel tortuosity 2
Sweid et al. (15)	18	57.7	NA	AC:16 PC:2	17 (94%)	0	1	inadequate support 1
Goland et al. (18)	5	58.2	L:1 R:4	NA	5(100%)	0	0	0

AC, Anterior circulation; PC, posterior circulation; LCCA, left common carotid artery; ICA, Internal carotid artery; NA, Not Available.

criteria were as follows: (1) unextractable or unclear data; (2) duplicated reports; (3) meta-analyses, reviews, comments, letters, and non-English language studies.

Data Extraction and Item Definition

The following information was extracted from the included studies: first author, publication year, the number of procedures treated by FD *via* TRA, baseline patient information, the number of stents successfully placed *via* the TRA, the access-related complications, and the number of the conversion from the TRA to the TFA. Data extraction was performed by Xiang Liu and Wenzhang Luo. Any disagreement during article selection was resolved by a discussion with a third author (Changren Huang). The success rate refers to the successful placement of FD *via* TRA rather than *via* TFA. The access-related complications include radial artery spasm, radial

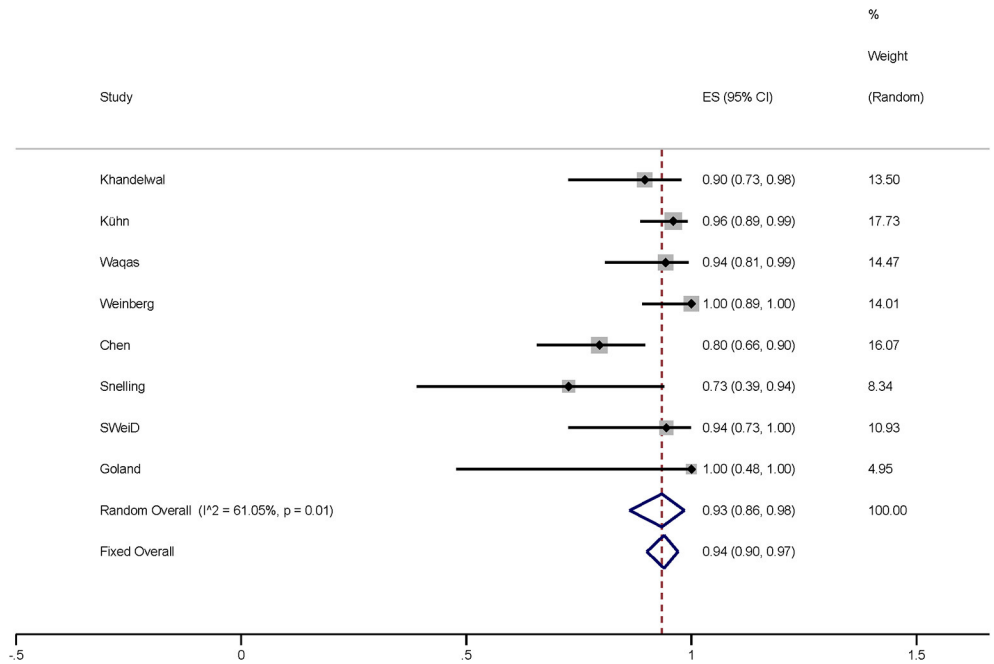

FIGURE 2 | Plot showing the success rate of 265 FD-treated intracranial aneurysms *via* TRA, reported by eight studies. FD, flow diversion; TRA, transradial approach; *CI*, confidence interval.

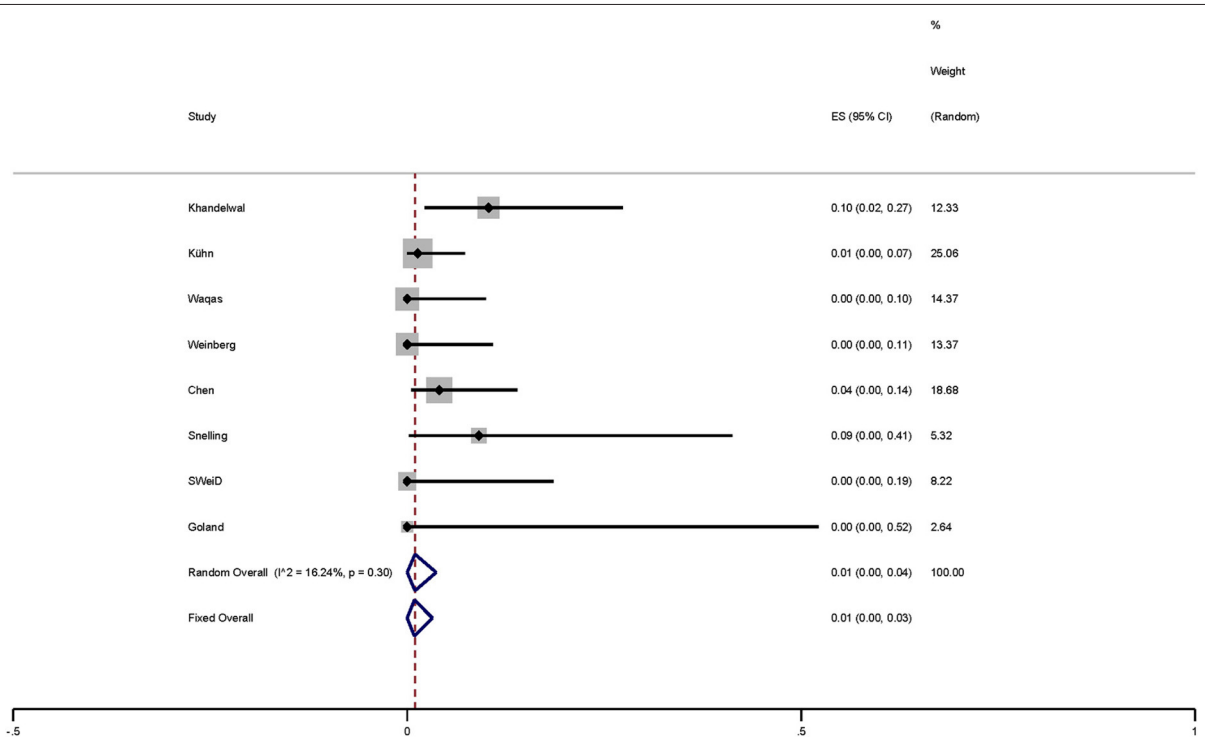

FIGURE 3 | Plot showing the access-related complications of FD-treated intracranial aneurysms via TRA.

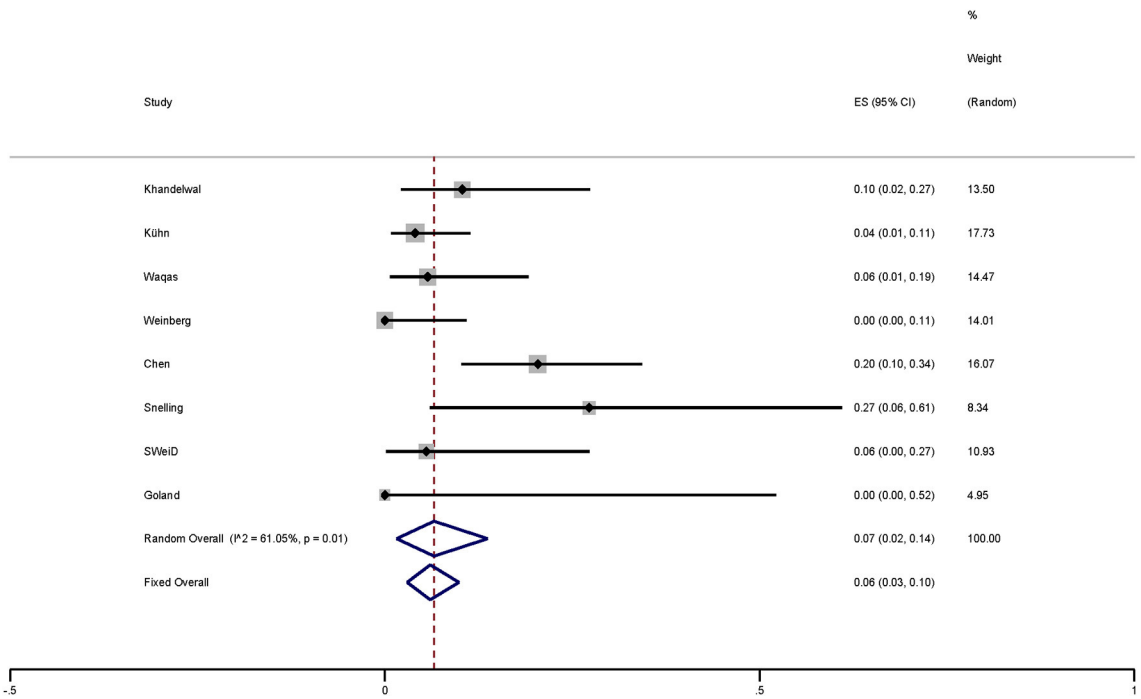

FIGURE 4 | Plot showing the from TRA to TFA of FD-treated intracranial aneurysms via TRA.

artery occlusion, forearm hematoma, and forearm osteofascial space syndrome.

Critical Appraisal

The study quality was assessed using the modified Newcastle–Ottawa scale for case series (10). It mainly includes selection, ascertainment, causality, and reporting.

Statistical Analysis

This meta-analysis was performed using Stata, version 14.0 (StataCorp, College Station, Texas, USA). The main outcome was the success rate of procedures and the access-related complications. The secondary result was the conversion rate of TRA. Continuous variables are presented as mean values. Dichotomous variables are presented as efficient with 95% confidence intervals (*CI*). The statistical heterogeneity was assessed using I^2. A fixed-effects model was used if $I^2 < 50\%$ and a random-effects model was used if $I^2 > 50\%$. An alpha level of significance was set to 0.05 and 95% *CI*.

RESULTS

Search Results

Our search rendered 127 studies (**Figure 1**). After duplicate removal and abstract screening, 13 studies remained for full-text screening. After reading the full text, we included 8 studies (11–18) in the meta-analysis. The 8 studies involved 265 FD-treated aneurysms *via* TRA in 250 patients. All studies were single- or multi-center retrospective analyses. **Table 1** shows the quality evaluation of 8 studies and their characteristics are summarized in **Table 2**.

Clinical Characteristics

The average age of the 8 studies included was 55–62.1 years. Six studies (11–13, 16–18) reported the laterality of aneurysms, 57.1% (92/161) of which were located on the left side and 7 studies (11–17) reported that 91.5% (238/260) of aneurysms were located in the anterior circulation. The 8 studies described in detail the use of drugs and operative procedures before operation.

Procedural Success

In this meta-analysis, 253 cases of intracranial aneurysms were treated with FD *via* TRA, of which 231 cases were successful. Based on the meta-analysis of random effects, the total effect amount of 8 studies was 93% (95% *CI* 0.86–0.98; $I^2 = 61.05\%$; $p = 0.01$; **Figure 2**). The funnel plot showed there was no significant publication bias.

Complications

The access-related complications include radial artery spasm and radial artery occlusion. Complications occurred in four of these studies (12, 14, 16, 17). Based on the meta-analysis of fixed effects, the access-related complications rate was 1% (95% *CI* 0–0.03; $I^2 = 0.00\%$; $p < 0.01$; **Figure 3**). These complications included radial artery spasm (85.7%, 6/7) and radial artery occlusion (14.3%, 1/7). The funnel plot showed there was no significant publication bias.

Conversion (Radial-Femoral)

Based on the meta-analysis of random effects, the conversion rate is 7% (95% *CI* 0.02–0.14; $I^2 = 61.05\%$; $p = 0.01$; **Figure 4**). The vessel tortuosity was the most common reason (45.5%), followed by radial artery spasm (27.3%), left common carotid artery (LCCA) angle of origin (18.2%), and inadequate support (4.5%) and aberrant right subclavian artery (4.5%). In one study (14), two cases were converted to femoral artery pathway because of vascular tortuosity and insufficient support. We think that it was caused by vascular tortuosity.

DISCUSSION

We present the first meta-analysis demonstrating the success rate and the access-related complications rate of FD *via* TRA for the treatment of intracranial aneurysms. Our results demonstrate that the success rate was 93% (95% *CI* 0.86–0.98; $I^2 = 61.05\%$; $p = 0.01$) and the access-related complications rate was 1% (95% *CI* 0–0.03; $I^2 = 0.00\%$; $p < 0.01$).

The concept of "endovascular flow diversion" was proposed on the assumption that the stent can block the blood flow in the aneurysm while preserving the flow into the parent vessel and adjacent branches (19). This device has higher surface coverage and lower porosity, which can slow down the blood flow to the aneurysm, gradually form thrombosis and promote the formation of new endothelium at the neck of the aneurysm (20). With the development of materials, FD has not only been confined to the original indications, but also has been applied to acutely rupture aneurysms, posterior circulation aneurysms, carotid-cavernous fistulas, distal anterior circulation aneurysms, and blister aneurysms (21, 22). At present, FD is the most commonly used access for the treatment of intracranial aneurysms *via* TFA. However, with the advantages of TRA becoming more and more prominent, some studies began to treat intracranial aneurysms with FD *via* TRA.

Dietrich et al. (23) first reported that a large cavernous internal carotid artery aneurysm was treated with Pipeline Embolization Device (PED) *via* TRA due to a complex aortic arch. Other previous studies had also reported that FD in the treatment of intracranial aneurysms *via* TRA was mainly suitable for type III aortic arch or bovine arch configurations (24, 25). At present, it has been the preferred access in some institutions with rich experience in the treatment of intracranial aneurysms with FD *via* TRA (11, 13, 15). When the radial artery is less than 2.0–2.5 mm on ultrasound, some studies suggest that TFA should be chosen. Even if you want to use TRA, 071″ systems (Envoy DA with 058″ Navien or 044″ DAC) or triaxial system should be selected (17, 23). In terms of materials, the research had shown that the system suitable for TFA is also suitable for radial artery (16). At the same time, some studies suggested Barbeau testing to evaluate palm blood circulation before operation and exclude patients with a D-shape of Barbeau testing when deploying FD *via* TRA (16, 17). However, some studies suggested that there was no additional benefit of preoperative Barbeau testing or Allen testing for hand ischemic complications (26, 27). In our meta-analysis, only 1 case had an access-related complication of asymptomatic radial artery occlusion. In addition, all researchers performed radial artery punctures under the guidance of ultrasound in the literature we included, which significantly improved the success rate of punctures. The TRA with Ultrasound Trial (RAUST) confirmed that ultrasound guidance was helpful for the success rate and efficiency of radial artery catheterization. Compared with palpation, fewer attempts for successful puncture with the guidance of ultrasound (mean: 1.65 ± 1.2 *vs.* 3.05 ± 3.4, $p < 0.0001$) (28). After a puncture, immediately 2.5–5 mg verapamil and 200 μg nitroglycerin will be paid to prevent radial artery spasm, and some studies will also be given 5 mg nicardipine (11, 15). In our meta-analysis, the incidence of radial artery spasm was 85.7% and 27.3% turned to TFA because of radial artery spasm. Therefore, how to prevent radial artery spasm is also one of the problems that TRA will become the main access for the treatment of aneurysms with FD in the future. There are also reports of forearm hematoma and forearm osteofascial space syndrome during interventional operation *via* TRA (29, 30). A short sheath of 6F was routinely inserted after the puncture, and the target artery was entered through Simmons-II. An appropriate multiaxial system was supposed to place FD according to the diameter of the radial artery. Because the deployment of FD requires a larger vessel diameter, it not only increases the risk of radial artery spasm but also makes surgeons reluctant to deploy FD *via* TRA. The triaxial system was utilized for patients with radial artery diameter > 2.5 mm and the biaxial or triaxial system was used for patients with radial artery diameter <2.5 mm in a multicenter study. The overall success rate was 91% (122/134) and compared with TFA, which has higher access-related complications (2.48 *vs.* 0%, $p = 0.039$) (30). Their research also believed that the deployment of FD *via* TRA is safe and feasible. Patel et al. (31) believed that the biaxial systems could replace the triaxial systems to place FD. In our meta-analysis, the incidence of access-related complications is only 1% (95% *CI* 0–0.03; $I^2 = 0.00\%$; $p < 0.01$). On the other hand, the most important reason is that the access conversion is 63.7% owing to the vessel tortuosity and LCCA angle of origin. In the future, the development of neurointervention materials and the progress of technology may improve this situation.

Deploying FD needs to take a large dose of dual antiplatelet therapy, which increases the risk of femoral artery bleeding, prolonged compression time, and pseudoaneurysm *via* TFA (32). The radial artery is shallow, which is easier to stop bleeding by compression. At the same time, the TRA will not lead to the patient's bed for a long time, and will also reduce the incidence of lower extremity deep venous thrombosis (15, 33, 34). Secondly, several studies had shown that neurointerventional *via* TRA can reduce the discomfort of patients after interventional surgery, and reduce the cost of surgery, and length of hospital stay compared to TFA (3, 11, 35–37). Especially for patients taking anticoagulants, pregnant women, patients with severe iliac atherosclerosis, bovine arch, type II/III aortic arch, the TRA should be the main access for FD in the treatment of intracranial aneurysms (11, 38, 39).

Although the deployment of FD *via* TRA has more benefits for patients with intracranial aneurysms, it also has a high success rate in our meta-analysis. However, we cannot ignore the causes of his conversion to TFA and its complications. We should

choose the appropriate access based on maximizing the interests of patients.

Limitations

Our study has some limitations. We only included a small number of cases without a control group which lead to selection bias, and this result is not suitable for comprehensive promotion. Further, we were unable to analyze the location of the failed aneurysm, aortic arch angles, and catheter system because of the lack of stratification. Moreover, given the lack of long-term follow-up in the included studies, we were not able to consider the cases of access-related complications that may have been missed.

CONCLUSIONS

Although TFA is still the main access for FD in the treatment of intracranial aneurysms, the TRA also has a higher success rate and lower access-related complications rate. With the improvement of future experience and equipment, the TRA may become the main access for FD which has more advantages. Future studies should design prospective, multicenter randomized controlled studies for long-term follow-up.

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.

AUTHOR CONTRIBUTIONS

Guarantor of integrity of entire study, manuscript revision and review, manuscript final version approval, and manuscript definition of intellectual content: KB and CH. Study concepts: XL and MW. Study design and data acquisition: XL and WL. Literature research: MW. Data analysis/interpretation and statistical analysis: XL, WL, and KB. Manuscript preparation: XL. All authors contributed to the article and approved the submitted version.

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Outcomes of reconstructive endovascular treatment of vertebrobasilar dissecting aneurysms with intramural hematoma

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Background: Vertebrobasilar dissecting aneurysms (VBDAs) with an intramural hematoma (IMH) usually cause symptoms because of mass effect and grow in size over time. Clinical outcomes are generally poor.

Objective: This study aimed to examine outcomes of reconstructive endovascular treatment (EVT) in patients with VBDAs with IMH. Safety and effectiveness were compared between flow diverters (FDs) and conventional stents.

Methods: We retrospectively analyzed the clinical and radiological data of 36 VBDAs with IMH in 36 patients who underwent EVT with either FDs or conventional stents from January 2012 to December 2020 at our institution.

Results: Among the 36 study patients, 20 were treated with FDs and 16 with conventional stents. Incidence of procedure-related complications did not significantly differ between the two stents. IMH growth occurred after EVT in a significantly higher proportion of conventional stent group aneurysms (zero vs. 31.3% [5/16]; $p = 0.012$). Among the five aneurysms with IMHs that grew, all recurred. Change in IMH size after EVT was significantly lower in the FD group (−2.7 vs. +8.1%, p = 0.036). However, after the recurrent aneurysms were removed from the conventional stent group, change in IMH size did not significantly differ between the two groups (−2.7 vs. +1.0%, $p = 0.332$). The proportion of patients who experienced an improvement in mRS score after EVT was significantly higher in the FD group (60 vs. 25%, $p = 0.036$).

Conclusion: IMHs in VBDAs stop growing after successful reconstructive EVT. Although both FD and conventional stent treatment are effective, FD treatment may be superior based on clinical outcomes and effect on IMH size.

KEYWORDS

intracranial aneurysm, dissection, intramural hematoma, vertebrobasilar artery, endovascular treatment

Introduction

Spontaneous intracranial vertebrobasilar dissecting aneurysm (VBDA) is an important cause of subarachnoid hemorrhage (SAH) and posterior circulation ischemic stroke in young and middle-aged adults (1, 2). Digital subtraction angiography (DSA) is the gold standard for VBDA diagnosis and follow-up; however, it is associated with complications such as iatrogenic arterial dissection and is relatively limited in showing arterial wall characteristics such as intramural hematoma (IMH) (3). In contrast, magnetic resonance imaging (MRI) can depict IMH and other findings associated with dissection (4, 5). IMH appears to be crucial for dissection progression and generation of symptoms (6).

At present, there are two main hypotheses regarding IMH formation. One theory stipulates that the hematoma begins as circulating blood enters the arterial wall after sudden disruption of both the inner elastic plate and tunica media; another hypothesizes that it originates from the vasa vasorum (7). Aneurysms with IMH will continue to progress, which can be neurologically devastating or even fatal. Although surgery for these aneurysms is theoretically more effective, the operation is high-risk and technically difficult (6, 8). Endovascular treatment (EVT) is generally considered the first-line option in VBDA management; however, its effect on IMH growth in these aneurysms remains unclear (9). This study aimed to examine outcomes in patients with VBDAs with IMH who underwent reconstructive EVT. We also aimed to compare safety and effectiveness between treatment with flow diverters (FDs) and treatment with conventional stents.

Materials and methods

Patient selection and data collection

This retrospective study was approved by the ethics committee of Beijing Tiantan Hospital. We searched our aneurysm database, which includes patients diagnosed with intracranial aneurysms between January 2012 and December 2020, and identified patients with VBDA with IMH. Patients who met the following criteria were eligible for study inclusion: (1) VBDA confirmed by DSA and MRI; (2) unequivocal evidence of IMH on MRI (IMH >5 mm in the plane perpendicular to the long axis of the vessel); (10) (3) EVT was performed; and (4) follow-up MRI was performed at least 6 months after treatment. We excluded patients with arteritis, fibromuscular dysplasia, underlying malignancy, iatrogenic aneurysm, pseudoaneurysm, or VBDA that had been previously treated. We also excluded those who had no clinical follow-up. The study flow chart is shown in Figure 1. Hospital records and radiological studies were reviewed. Recorded data included patient age, sex, comorbidities, smoking and alcohol history, and symptoms; treatment strategy; modified Rankin scale (mRS) score at presentation, discharge and follow-up; and size of aneurysm and IMH. IMH size was defined as the maximum diameter of the IMH on axial MRI.

Endovascular treatment strategy

Treatment for each patient was discussed and rendered after consensus was reached among the neurointerventionalists at the daily peer-reviewed endovascular conference in our hospital. Decisions were based on imaging parameters and clinical symptoms. Patients scheduled for reconstructive treatment received dual antiplatelet therapy (75 mg of clopidogrel and 100 mg of aspirin daily) for 5 days before treatment. Endovascular procedures were performed under general anesthesia. Full heparinization was used during the procedures to maintain an activated clotting time 2.5 times greater than baseline. In the early stage of the study, FDs were not available in our hospital. During that period, we preferred to place coils in the aneurysmal lumen after conventional stent placement if possible; if there was not sufficient space in the lumen for coiling, we treated with conventional stenting alone. Multiple devices were used in patients with long lesions or large aneurysms. The following conventional stents were used: Enterprise (Cerenovus, Raynham, Massachusetts, USA), LVIS (MicroVention, Tustin, California, USA), Neuroform EZ (Stryker Neurovascular, Fremont, California, USA), and Solitaire (Covidien, Irvine, California, USA). The stent delivery catheter was placed distal to the dissection and a microcatheter was placed within the VBDA. After deploying coils, the stent was released. The FD used was the Pipeline embolization device (Medtronic, Minneapolis, MN, USA). In patients who underwent FD placement, a microcatheter was placed into the aneurysm lumen for coil placement under microwire guidance. A triaxial support system was used to access the aneurysm with the FD introduced through a Marksman microcatheter (EV3, Irvine, California, USA). FDs were delivered to satisfactorily reconstruct the parent artery and then deployed. In patients undergoing treatment with FDs, we used the stent–jailing technique to coil the aneurysm or eccentric lumen if the diameter of the aneurysm or eccentric lumen exceeded 10 mm. One side of the vertebral artery was occluded to reduce aneurysm flow and avoid postoperative bleeding for giant vertebrobasilar junction aneurysms. After EVT, patients in the conventional stent group received 75 mg clopidogrel daily for 6 weeks and 100 mg aspirin daily for 6 months; those in the FD group received clopidogrel for 3 months and will continue taking aspirin for life.

Follow-up and clinical outcomes

Patient data was obtained from hospital and outpatient records and *via* telephone. Clinical outcome was measured using the mRS score. Favorable clinical outcome was defined as mRS

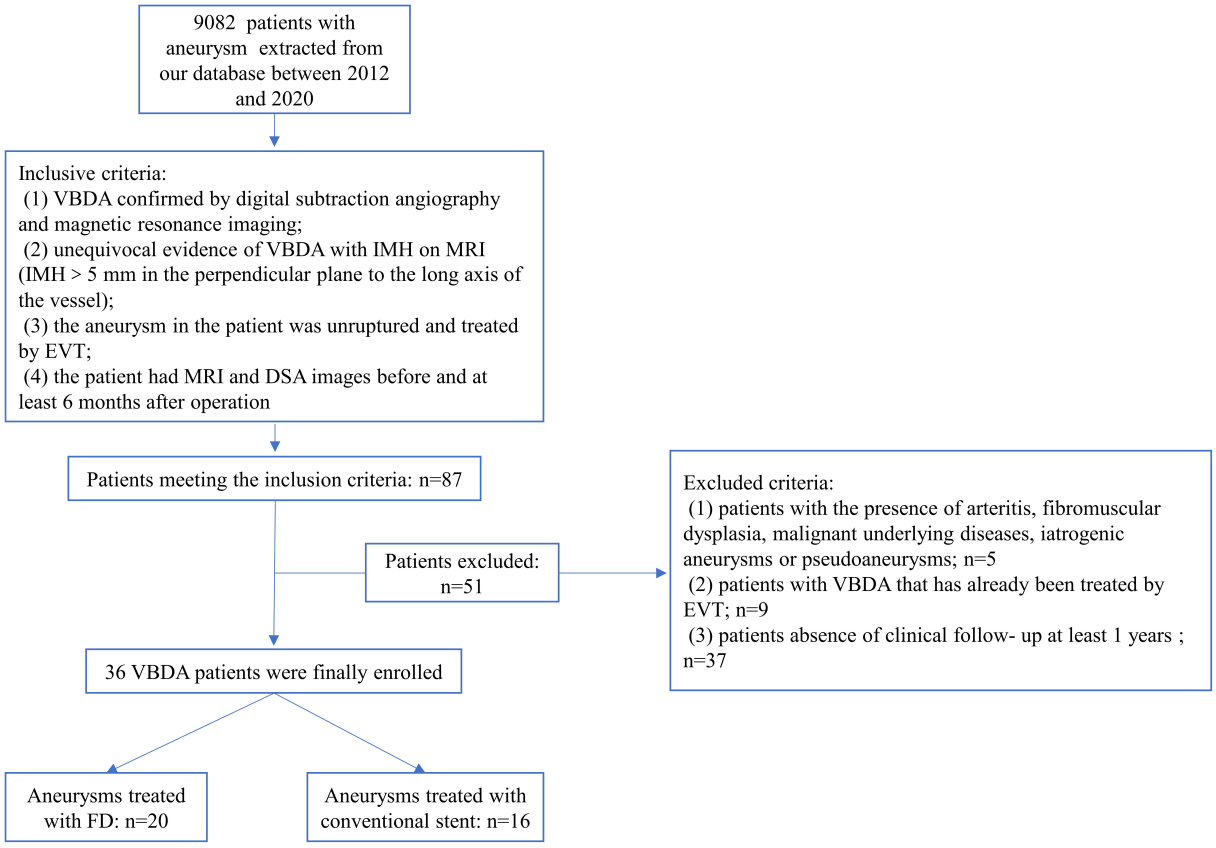

FIGURE 1
Study flowchart.

score 0–2; poor clinical outcome was defined as mRS score 4–6. Angiographic results were determined immediately after the procedure and during follow-up. DSA follow-up was scheduled between 3 and 6 months after EVT. Results were classified using the O'Kelly–Marotta (OKM) grading scale (A, total filling; B, subtotal filling; C, entry remnant; D, no filling). Favorable angiographic outcome was defined as OKM grades C and D; unfavorable angiographic outcome was defined as OKM grades A and B. Aneurysm recurrence during follow-up was defined as an increase in contrast filling within the aneurysm. MRI follow-up was scheduled 1, 2, and 5 years after EVT. A >10% increase in IMH size was defined as IMH growth (a change <10% may be due to manual error or imaging artifact).

Statistical analysis

Statistical analyses were performed using SPSS software version 25 (IBM Corp., Armonk, NY, USA). Continuous variables are presented as means with standard deviation. Categorical variables are reported as proportions. The Shapiro–Wilk test was used to assess normality of variables. Patients and aneurysms were grouped according to type of treatment (conventional or FD stent). Group comparisons were performed using the independent samples *t*-test, χ^2 test, or Fisher exact test as apprpriate. $P < 0.05$ was considered significant.

Results

Patient characteristics

In total, 36 VBDAs with IMH in 36 patients who underwent reconstructive EVT were included for analysis. All patients were symptomatic at the time of treatment and all aneurysms were unruptured. Twenty were treated with FDs and 16 with conventional stents. Mean patient age in the FD and conventional stent groups was 47.1 and 55.8 years, respectively; the difference was not significant. Similarly, the groups did not significantly differ in terms of other baseline characteristics. One patient in each group had an unfavorable mRS score at admission: the FD group patient presented with left limb

TABLE 1 Patient and aneurysm characteristics.

	FD group	Conventional stents group	Significance (*P*-Value)
Patients	20	16	
Mean age (yrs)	47.1 ± 16.7	55.8 ± 7.3	0.063
Female, *n*(%)	5 (25%)	1 (6.3%)	0.147
Co-morbidities, *n*(%)			
Hypertension	10 (50%)	11 (68.8%)	0.32
Diabetes	2 (10%)	1 (6.3%)	1
Smoking	8 (40%)	7 (43.8%)	1
Drinking	6 (30%)	3 (18.8%)	0.7
Presentation, *n*(%)			
Headache	9 (45%)	9 (56.2%)	
Dizziness	3 (15%)	3 (18.8%)	
Brainstem compression	5 (25%)	2 (12.5%)	
Stroke	3 (15%)	2 (12.5%)	
Mean aneurysm diameter	18.4 ± 8.3	17.3 ± 7.0	0.697
Aneurysm size, *n*(%)			0.935
Small (<10 mm)	2 (10.5%)	2 (12.5%)	
Large (10-25 mm)	13 (68.4%)	10 (62.5%)	
Giant (>25 mm)	4 (21.1%)	4 (25%)	
Location, *n*(%)			0.702
BA	2 (10%)	2 (12.5%)	
VBA	3 (15%)	1 (6.3%)	
VA	15 (75%)	13 (81.3%)	
Mean IMH size (mm)	15.5 ± 7.3	17.9 ± 10.0	0.406

FD, flow diverter; BA, basilar artery; VBA, vertebrobasilar artery; VA, vertebral artery; IMH, intramural hematoma.

TABLE 2 Angiographic and clinical outcomes.

	FD group	Conventional stents group	Significance (*P*-Value)
Complication, *n*(%)	3 (15%)	1 (6.3%)	0.613
Clinical follow-up time (Mean, months)	42.1	51.3	0.063
MRI follow-up time (Mean, months)	24.4	24.7	0.958
Angiographic follow-up time (Mean, months)	9.7	14.3	0.198
Treatment modality, *n*(%)			**0.041**
Stents alone	13 (65%)	4 (25%)	
Stents with coils	7 (35%)	12 (75%)	
Number of stents implanted, *n*(%)			
1	17 (85%)	5 (31.3%)	**0.002**
2	2 (10%)	6 (37.5%)	0.103
3	1 (5%)	5 (31.3%)	0.069
Immediate angiographic	20	16	**0.004**
Favorable results, *n*(%)	2 (15%)	10 (66.7%)	
Unfavorable results, *n*(%)	17 (85%)	5 (33.3%)	
Last angiographic	15	14	0.390
Favorable results, *n*(%)	13 (86.7%)	10 (71.4%)	
Unfavorable results, *n*(%)	2 (13.3%)	4 (28.6%)	
Recurrence, *n*(%)	0 (0%)	5 (31.3)	**0.044**
Change of IMH size, *n*(%)	−2.7%	8.1%	**0.036**
Follow-up of clinical outcome	20	16	0.637
Favorable results, *n*(%)	18 (90%)	13 (81.3%)	
Unfavorable results, *n*(%)	2 (10%)	3 (18.8%)	
Change in mRS score, *n*(%)			
Improved	12 (60%)	4 (25%)	**0.036**
No change	6 (30%)	8 (50%)	0.307
Worsened	2 (10%)	4 (25%)	0.374

FD, flow diverter; IMH, intramural hematoma; mRS, modified Rankin scale. Boldface type indicates statistical significance.

weakness, facial asymmetry and weakness, adverse speech, and tinnitus with mRS score 4; the conventional stent group patient presented with dizziness and unstable gait with mRS score 3. Patient and aneurysm characteristics are shown in Table 1.

Postprocedural angiographic and clinical results

EVT was successful in all patients. Thirteen patients (65%) in the FD group were treated with stenting alone and seven (35%) with stent-assisted coiling. In the conventional stent group, four patients (25%) were treated with stenting alone and 12 (75%) with stent-assisted coiling. The difference in type of EVT between groups was significant ($p = 0.023$). In the FD group, 17 patients (85%) were treated with one stent, compared with only five patients (31.3%) in the conventional stent group ($p = 0.002$). On immediate postoperative angiography, the rate of favorable angiographic outcome (OKM grades C and D) was significantly lower in the FD group than the conventional stent group (15 vs. 66.7%, $p = 0.004$). At hospital discharge, no patient in the FD group had a poor clinical outcome; one conventional stent patient did.

Procedure-related complications occurred in three FD group patients (15%) and one conventional stent group patient (6.3%); however, the difference was not significant ($p = 0.613$). The complications were two hemorrhages and one ischemic event in the FD group and one hemorrhage in the conventional stent group. Angiographic follow-up was available in all patients. Mean angiographic follow-up was 9.7 months in the FD group and 14.3 months in the conventional stent group. At last follow-up, the proportion of patients who achieved favorable angiographic outcome (OKM grades C and D) was higher

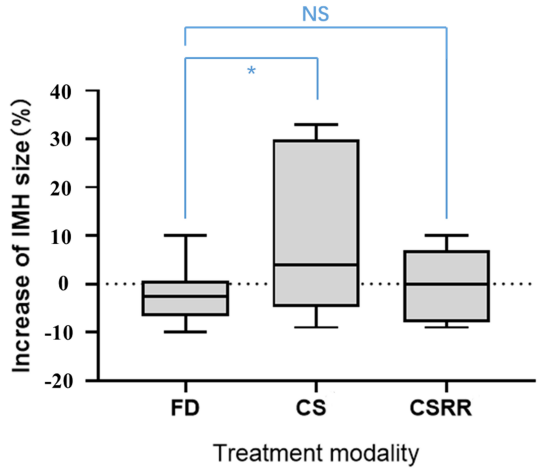

FIGURE 2
Increase in intramural hematoma size according to treatment group. CS, conventional stent group; CSRR, conventional stent group excluding recurrent aneurysms; NS, no significant difference; *significant difference.

in the FD group than the conventional stent group, but the difference was not significant (86.7 vs. 71.4%, $p = 0.390$). Clinical follow-up was available in all patients. Mean clinical follow-up was 42 months in the FD group and 51 months in the conventional stent group. Favorable clinical outcome (mRS score 0–2) was achieved at last follow-up in 18 patients (90%) in the FD group and 13 patients (81.3%) in the conventional stent group ($p = 0.637$). The proportion of patients who experienced an improvement in mRS score after EVT was significantly higher in the FD group (60 vs. 25%, $p = 0.036$). Angiographic and clinical outcomes are shown in Table 2.

Description of change in IMH size

Before EVT, IMH size did not significantly differ between the FD and conventional stent groups (15.5 mm vs. 17.9 mm; $p = 0.406$). Mean MRI follow-up was 24.5 months (range, 3–80). IMH growth occurred after EVT in a significantly higher proportion of conventional stent group aneurysms (zero vs. 31.3% [5/16], $p = 0.012$). Among the five aneurysms with IMHs that grew, initial IMH size was >20 mm and all recurred after treatment. Change in IMH size after treatment was significantly lower in the FD group than the conventional stent group (−2.7% vs. +8.1%, $p = 0.036$). However, after the recurrent aneurysms were removed from the conventional stent group, change in IMH size did not significantly differ between the two groups (−2.7 vs. +1.0%, $p = 0.332$; Figure 2).

Illustrative cases

Case 1

A patient presented with a 6-month history of headaches. DSA showed a giant right vertebral artery dissecting aneurysm. MRI showed a 20.8 mm IMH. The patient was treated using three 4.5 mm × 37 mm Enterprise stents overlap without complication. Immediately after treatment, angiography showed satisfactory reconstruction of the vertebral artery and the patient's headache had improved. Two years after treatment, DSA showed aneurysm recurrence and MRI showed a 27 mm IMH, which had increased from 24.2 mm 1 year prior (Figure 3).

Case 2

A patient presented with a 10-month history of dizziness. DSA showed a large right vertebral artery dissecting aneurysm. MRI showed a 12.3 mm IMH. The patient was treated with a 4.5 mm × 35 mm Pipeline embolization device without complication. Immediately after treatment, angiography showed contrast stasis within the aneurysm and the patient reported symptom relief. One-year after treatment, DSA showed satisfactory arterial reconstruction and complete aneurysm obliteration. MRI showed no change in IMH size over 3 years of follow-up (Figure 4).

Discussion

Key results

This study examined a series of patients with VBDAs with IMH who underwent reconstructive EVT using FDs or conventional stents. In the FD group, the aneurysm recurrence rate was lower and the proportion of patients who experienced improvement in mRS score after treatment was higher than those in the conventional stent group. More importantly, IMH size continued to increase after conventional stent treatment in five patients and the aneurysm in all of these patients recurred. In both the FD and conventional stent groups, the IMH in aneurysms that did not recur stopped growing. Therefore, angiographic aneurysmal occlusion after reconstructive EVT may impair or prevent IMH growth.

Natural history of the IMH in VBDAs

IMH usually results from extensive damage to the internal elastic lamina, rupture of neovessels, or penetration of blood into the vessel wall (11). Despite numerous pathological studies, the mechanism of aneurysmal IMH growth remains unknown. Growth may be related to bleeding from the vasa vasorum (VV), parent arterial inflow, and/or inflammation. Krings et al. suggested a mechanism of repeated subadventitial hemorrhage

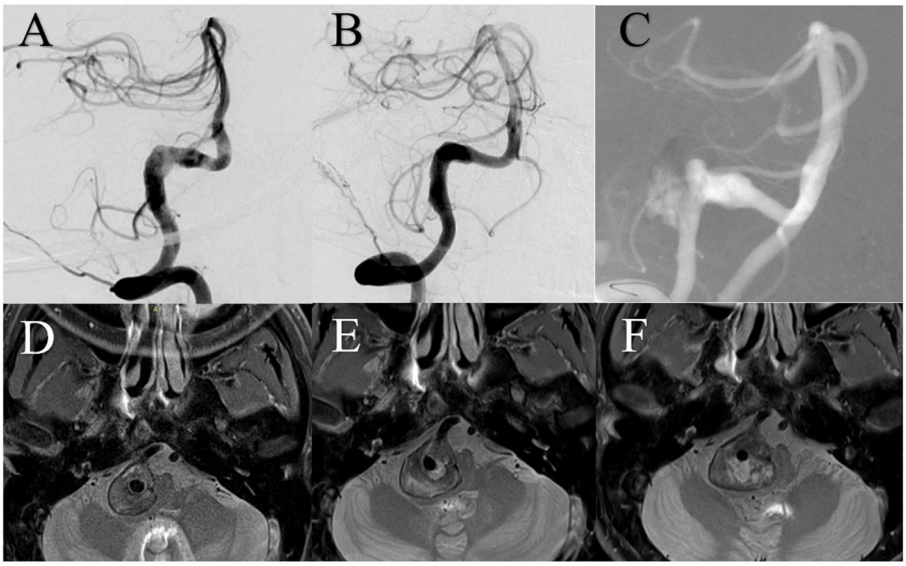

FIGURE 3
(A) Digital subtraction angiography (DSA) showed the right vertebral artery aneurysm. **(B)** DSA immediately after treatment showed satisfactory arterial reconstruction. **(C)** DSA 2 years after treatment showed aneurysm recurrence. Magnetic resonance imaging demonstrated intramural hematoma growth from before treatment **(D)** to 1 year **(E)** and 2 years **(F)** after.

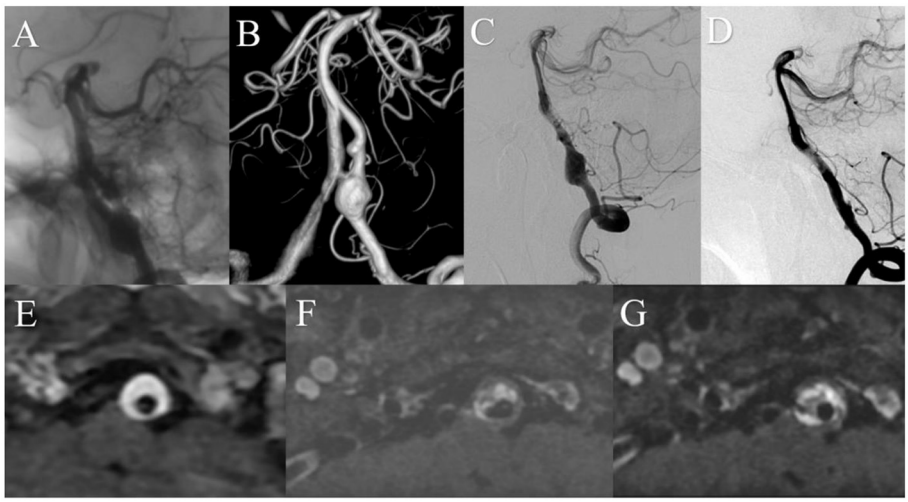

FIGURE 4
Preoperative anteroposterior **(A)** and three-dimensional reconstruction **(B)** digital subtraction angiography (DSA) showed a left vertebral artery aneurysm. **(C)** DSA immediately after treatment showed that contrast stasis within the aneurysm. **(D)** One year after treatment, DSA showed satisfactory arterial reconstruction and complete aneurysm obliteration. Magnetic resonance imaging demonstrated stability of the intramural hematoma over time [**(E)** before treatment; **(F)** 1 year after; **(G)** 3 years after].

from the VV (12). The VV are composed of small arteries, capillaries, and veins that supply the walls of large vessels and serve as a conduit for macrophages and inflammatory, angiogenic, and other factors (13, 14). One postmortem study suggested that the VV are more developed in vessels with a thick wall to meet their higher metabolic needs; the same study also reported that approximately half of disease-free intracranial arteries have VV and that they are frequently found in the vertebrobasilar artery (15), which may explain why IMHs are common in VBDAs.

Nagahiro et al. reported different findings: their examination of VBDAs with large IMH showed no evidence of hemorrhage

around the vessels in the aneurysmal wall; however, intrathrombotic vascular channels were observed. Therefore, blood flow between the parent artery and the intrathrombotic vascular channels may explain continuous IMH growth (16). This agrees with prior studies that found recanalizing vessels within the thrombus (6). Yasui et al. reported similar findings of numerous clefts in old thrombus near the wall of the distal aneurysmal neck that seemed to connect the parent artery lumen with the most peripheral fresh hemorrhage (17). Ferracci et al. also reported that parent arterial inflow rather than VV may be the cause of IMH and that shear stress on the edge of the aneurysm neck or at the vessel dissection point might drive dissection, leading to recurrent intramural hemorrhage (18). Furthermore, inflammation is involved in thrombus organization, vessel dissection, and neovascularization (12, 19, 20).

In our study, IMH growth stopped after successful reconstructive EVT but continued in aneurysms that recurred. This supports the hypothesis that parent arterial inflow contributes to IMH growth. Vascular remodeling may block parent arterial inflow; however, blood from the aneurysmal neck can penetrate into the vessel wall when aneurysms recanalize.

Treatment strategy for VBDAs with IMH

Aneurysms with IMH progress without exception in a relatively short time, which usually leads to a poor outcome (6). Considering the potentially fatal consequences, early intervention is necessary. Before the development of EVT, surgical treatment was the mainstay. Drake et al. reported outcomes in 56 surgically treated patients with fusiform posterior circulation aneurysms. Treatments included aneurysm clipping, wrapping, or proximal ligation with or without bypass surgery. Thirteen died and four had severe neurologic deficits (21). Considering the high morbidity and mortality of surgical treatment, EVT has become widely preferred. The introduction of FDs has enabled endovascular reconstruction treatment and vascular remodeling for complex dissecting aneurysms with IMH. Treatment with FDs results in a high complete aneurysm occlusion rate. However, limited information is available regarding IMH outcome after reconstructive EVT. Moreover, the safety and effectiveness of FDs in the treatment of these aneurysms is unclear and has not been compared with conventional treatment.

We found similar favorable clinical outcome rates in patients treated using FDs and conventional stents (90 and 81.3%, respectively; $p = 0.637$). This is in line with favorable outcome rates of 85.7 and 92.0% reported in two recent studies of reconstructive EVT for VBDAs (22, 23). Considering that all aneurysms in our study had a large IMH, the efficacy of both FDs and conventional stents was acceptable. The rate of favorable angiographic outcome was significantly lower in the FD group than the conventional stent group immediately after treatment (15 vs. 66.7%, $p = 0.004$); however, at last angiographic follow-up, the same rate was actually higher in the FD group (86.7 vs. 71.4%, $p = 0.390$) but the difference was not significant, possibly because of the small sample size. This finding agrees with prior studies that reported higher long-term occlusion rates in the FD group (24). In addition, we found that the recurrence rate was higher in the conventional stent group (zero vs. 31.3%, $p = 0.044$). Jeon et al. (25) studied 47 patients with VBDAs who underwent stent-assisted coil embolization with conventional stents; recurrence occurred in 10 (21.2%). In another study of posterior circulation aneurysms treated with FDs, the retreatment rate was 8.4% (26).

Compared to conventional stenting (even with adjunctive coiling), FD treatment is superior in terms of the long-term occlusion rate, primarily because FDs completely seal the aneurysm neck and divert flow away from the aneurysm, which leads to aneurysmal thrombosis and shrinkage (27, 28). The major concern with use of FDs for posterior circulation aneurysms is their high complication rate. Nonetheless, some studies have shown favorable outcomes. Zhang et al. (29) compared the incidence of complication between FD and stent-assisted coiling treatment of unruptured posterior circulation non-saccular aneurysms; the two groups did not differ in terms of periprocedural complications, technical events, or delayed complications. In a study of large or giant non-saccular vertebrobasilar aneurysms, similar results were obtained (24). Natarajan et al. (30) reported 11 patients with posterior circulation aneurysms who underwent FD treatment; only one experienced a perforator stroke while the others had a good outcome. They suggested that flow diversion is evolving to become a safer treatment option.

VBDAs with IMH usually present with progressive mass effect because of IMH growth. The true lumen may become more stenotic in the presence of an IMH, which may lead to embolic ischemic events (10, 31, 32). Therefore, recurrence of these aneurysms may be more dangerous. Our study also illustrates this point: five patients treated with conventional stenting experienced aneurysm recurrence. The IMH continued to grow in all five and two of them died. Considering the lower recurrence rate and better symptom improvement in the patients treated with FDs, early FD treatment of these aneurysms should be highly considered.

Hypothesis of IMH outcome for symptom improvement

In the present study, the proportion of patients who experienced improvement in mRS score at last follow-up was significantly higher in the FD group (60% vs. 25%, $p = 0.036$). This result is not unexpected considering that previous studies

have reported that the rate of symptom improvement is high in patients with dissecting posterior circulation aneurysms after FD treatment (26, 33). Our results also suggest that IMH size did not increase in patients with aneurysms that did not recur. We speculate that the improvement in symptoms is attributed to several factors.

First, symptoms may improve owing to the "water-hammer effect." In fluid dynamics, the water- hammer effect occurs when high-velocity fluid rapidly changes momentum, which erodes or destroys the surface with which it contacts. A basilar aneurysm study suggested that aneurysms with a wide neck or those that incorporate a major arterial branch are subject to constant arterial pulsations that cause motion of the IMH, which results in increased mass effect from the aneurysm (34). Tomokiyo et al. (35) suggested that a persistent water-hammer effect against the aneurysmal lumen as well as an IMH-induced increase in aneurysmal volume may contribute to the development of perianeurysmal edema. We therefore hypothesize that blood flow in the aneurysm transmits pulsations and gradually aggravates neurological symptoms because of the development of mass effect and perianeurysmal edema. After reconstructive EVT, pulsations decrease and the IMH stops growing, which alleviates mass effect and perianeurysmal edema and improves patient symptoms. Furthermore, FDs can promote endothelialization of the aneurysm neck and combat the water-hammer forces (36).

Inflammation may be another factor related to symptom improvement. Suzuki et al. (37) suggested that microvascularization owing to microbleeds and inflammation from microvessels occur in a vicious cycle, which causes neurological symptoms. Moreover, repeated hemodynamic insults after dissecting aneurysm formation leads to periods of inflammation and thrombosis, which exacerbates this cascade. However, with reconstructive EVT, the aneurysmal neck is completely covered by a layer of long slender cells resembling endothelium three to 12 months after treatment and there is little inflammatory cellular reaction in the aneurysm dome (38). Therefore, early EVT may reduce patient symptoms. As mentioned above, FDs may be a better choice than conventional stents because they are superior at promoting endothelialization of the aneurysm neck and eliminating intra-aneurysmal inflammation. However, our speculations regarding IMH size and clinical improvement require further study.

Limitations

Our study has several limitations. It is retrospective in nature and was conducted in a single center. Given the rarity of VBDAs with IMH, our sample size was small. In addition, the study time period was long, during which technical nuances of treatment changed. Therefore, both selection and treatment bias may have been introduced. Moreover, the follow-up period was short and MRI measurements of IMH may have been affected by manual errors and imaging artifact from metal devices (coils or stent).

Conclusion

IMHs in VBDAs stop growing after successful reconstructive EVT but continue to grow in aneurysms that recur. Successful vascular remodeling may block penetration of parent arterial flow into the aneurysm. Although both FD and conventional stent treatment are effective, FD treatment may be superior based on clinical outcomes and effect on IMH size.

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 Institutional Review Board of Beijing Tiantan Hospital. The patients/participants provided their written informed consent to participate in this study.

Author contributions

YZha and QP collected the clinical data, performed the statistical analysis, and wrote the manuscript. YZho, CW, and LZ helped collect the clinical data. XY and SM helped revise the manuscript, designed the research, and handled funding and supervision. 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.

Publisher's note

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Use of flow diverter device in basilar artery for aneurysm treatment: Case series and literature review

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Background: Flow diverters (FDs) for the treatment of basilar artery (BA) aneurysms remain controversial. In this study, we report our initial experience of flow diversion for treatment of this pathology.

Methods: Consecutive patients with an aneurysm of the BA that was treated by implantation of the FD were included in our retrospective study. Procedural complications, aneurysm occlusion, and a functional outcome were evaluated. FD placement in BA for aneurysm treatment reported in the literature was also reviewed and summarized.

Results: Sixteen patients with 16 BA aneurysms were treated by FD implantation with ($n = 8$) or without ($n = 8$) adjunctive coiling. The Tubridge was used in 13 (81.3%) and Pipeline in 3 (18.8%) procedures. Average aneurysm size was 15.7 mm. Four aneurysms were located at the basilar apex, six at the basilar trunk, and six at the vertebrobasilar junction. Three patients experienced procedural complications (18.8%), including two ischemic strokes and one hydrocephalus, with resultant mortality in one case (6.3%). Median follow-up was 7.7 months and available for 15 aneurysms. Complete/near-complete occlusion was seen in 13 (86.7%) aneurysms.

Conclusion: In our initial experience, flow diversion is feasible and safe in the treatment of BA aneurysms with promising occlusion rates at mid-term follow-up. Larger cohort studies are required to validate these results.

KEYWORDS

flow diverter, intracranial aneurysm, basilar artery, endovascular treatment, literature review

Introduction

Posterior circulation aneurysms remain an ongoing challenge to treat by either endovascular or surgical strategies due to the complexity of these lesions (1). Overall, endovascular methods have yielded slightly better results than microsurgery and were considered to be the primary treatment modality (2). Recently, flow diverters (FDs)

have become reliable tools used to treat complex aneurysms. Many of these devices appear in studies on off-label use in basilar artery (BA) for aneurysm treatment, but published series are still limited and report heterogeneous results (3–5). Among the most commonly used is the Pipeline FD (Medtronic-Covidien, USA), as well as the Flow-Redirection Endoluminal Device (FRED; Microvention-Terumo, USA), Surpass (Stryker Neurovascular, USA), Silk (Balt Extrusion, France), p64 (Phenox, Germany), while others, such as the Tubridge (MicroPortNeuroTech, China), have not yet appeared in studies with such locations (6–9).

To date, two kinds of FDs have been commercially available in China: Tubridge and Pipeline. The Tubridge FD has proved to be a safe and effective device in managing complex aneurysms of anterior circulation, and its use was approved by the Chinese Food and Drug Administration in 2018 (10). We have used Tubridge and Pipeline devices to treat BA aneurysms since 2018. Herein, we present a single-center case series of patients with aneurysms located in the BA that were treated by flow diversion using the Tubridge and Pipeline. In addition, we present a comprehensive literature review focused on the safety and efficacy of FD placement in BA for aneurysm treatment.

Materials and methods

Study design

We performed a retrospective review of all the patients who underwent FD implantation in BA for aneurysm treatment between April 2018 and April 2021. This study was conducted with the approval of our Institutional Review Board. Given that patient data were collected in a deidentified manner and posed no risk to the patients, individual informed consent was not required or sought. Indications for using FDs include aneurysms with a high risk of failure with conventional endovascular or surgical methods, with recurrences, and fusiform, dissecting and large aneurysms with mass effect. Dolichoectatic aneurysms were not included in this treatment cohort. Patient demographic data, clinical presentation, aneurysm morphology, therapeutic strategy, complication, immediate angiographic and clinical result, and clinical and radiological follow-up information were determined from the electronic medical records.

Procedure details

The patients were started on dual antiplatelet therapy with aspirin 100 mg daily and clopidogrel 75 mg daily at least 3 days before their scheduled procedure. Platelet function testing was performed routinely using thrombelastograms (TEG Hemostasis System, Haemoscope Corporation, USA) before the procedure. Ticagrelor (a loading dose of 180 mg followed by 90 mg two times daily) was substituted for the patients non-responsive to clopidogrel. After the procedure, dual antiplatelet therapy was continued at least 3 months, followed by a lifelong use of aspirin 100 mg daily. Additional periprocedural Tirofiban was used at the discretion of the operators based on procedural findings.

The Tubridge and Pipeline procedures were performed in the manner previously described (10–12). Transfemoral access was routinely used in all cases. Access through both femoral arteries was used when a "jailed" catheter was required for adjunctive coil placement or the plan was to sacrifice one of the vertebral arteries (VAs) in cases in which there was flow from the other VA directly into the aneurysmal sac. The decision of whether to use coils in combination with FD was considered in specific scenarios (i.e., for very large aneurysms, if the FD was prone to herniate into the aneurysm without coiling protection, or when persistent inflow jet impingement to the aneurysm dome existed before treatment). Overlapping FD devices implantation was considered in case that inflow jet into the aneurysm remained after single-device deployment or the single device was not sufficient to cover the entire lesion segment of dissecting and fusiform aneurysms. For FDs with poor adherence, a micro-guidewire was used in combination with a microcatheter to "massage" the FD device, or a balloon was used to expand the FD device. The type of FDs used during the procedure was determined by the operators.

Procedural assessment and follow-up

Procedure-related complications, including hemorrhagic and thromboembolic events, were recorded. Symptomatic complications were defined as those associated with transient or permanent neurological deficits. A clinical outcome was evaluated at the baseline (presentation), discharge, and during follow-up according to the modified Rankin Scale (mRS) score.

Aneurysm occlusion was graded as completely occluded (100%), near-completely occluded with neck remnant (>90%), or incompletely occluded (<90%). Follow-up was performed regularly by digital subtraction angiography (DSA) at 3–12 months after treatment. If the patient declined DSA, cross-sectional imaging (CT angiography or MR angiography) was performed instead. Patency of parent arteries and jailed branches were also evaluated on follow-up angiogram.

Literature review

The literature was reviewed based on a PubMed search of all cases with the use of FDs in the BA for aneurysm treatment, including the following keywords, singly and in combination: flow diverter, basilar artery, posterior circulation, aneurysm. We excluded literature with a small volume of cases and case reports.

Data from large series (≥10 cases with FD placement in BA) published were selected and summarized.

Statistical analyses

Statistical analyses were performed using SPSS 19.0 (SPSS, Chicago, IL, USA). Normally distributed continuous variables are presented as means and ranges. Categorical variables are presented as numbers with frequency.

Results

Baseline patient and aneurysm characteristics

A total of 16 BA aneurysms were treated with FD devices in 16 patients. The individual overview about the baseline, aneurysm, and procedural characteristics is presented in Table 1. The average age was 47 years old, and majority (62.5%) of the patients were men. Common presenting symptoms included headache or dizziness (50%), retreatment for recurrence (18.8%), ischemic stroke (12.5%), mass effect (6.3%), while 12.5% were incidental. Three recurrent cases had previously undergone endovascular treatment, including conventional stent assisted with coiling ($n = 2$) and PED implantation with coiling ($n = 1$) at outside hospitals. Of the 16 patients, 14 were mRS 0, one was mRS 1, and one was mRS 3 at presentation. Aneurysm morphology was classified as dissecting (50%), fusiform (31.3%), or saccular (18.8%), and the median aneurysm diameter was 15.7 mm, with 25% of aneurysms >20 mm. Four aneurysms were located at the basilar apex, six at the basilar trunk, and six at the vertebrobasilar junction. Platelet function testing was performed in 14 (87.5%) patients, and three clopidogrel non-responders were found and were substituted with ticagrelor.

Procedural details and angiographic outcome

Procedural success was achieved in all cases. In eight patients (50%), aneurysms were additionally coiled. Most (87.5%) aneurysms were treated by single FD placement using 11 Tubridge and three Pipeline devices, while the remaining two cases were treated with two Tubridge devices, one of which was treated with an overlapping technique and the other telescoping (Figure 1). No obvious difficulties with device delivery or deployment were encountered. Balloon angioplasty was performed before or after FD deployment in two cases, respectively. There were 26 covered branches after implantation of the FD, including nine anterior inferior cerebellar arteries (AICAs), twelve superior cerebellar arteries (SCAs), and five posterior cerebral arteries (PCAs). At the end of the procedure, no acute occlusion of covered branches was found.

During a mean follow-up of 7.7 months (range 3–12 months), angiographic follow-up was available for 15 of 16 aneurysms at different time intervals. Thirteen patients were followed-up with DSA, one with MRA, and one with CTA. Complete or near-complete aneurysm occlusion was observed in nine (60%) and four (26.7%) aneurysms, respectively. The remaining two aneurysms with incomplete occlusion revealed progressive occlusion at follow-up. Aneurysm recanalization was not observed. At the follow-up, of all 26 vessels covered by the device, 22 were patent, while other four branches were occluded asymptomatically, including two PCAs and two SCAs. Figure 2 shows a representative case illustration of a patient successfully treated with a Tubridge device for a large basilar trunk aneurysm.

Procedural complications and clinical outcome

Procedural complications developed in three patients (18.8%), including two ischemic strokes and one progressive hydrocephalus, resulting in one mild neurologic deficit, one severe neurologic deficit, and one death (6.3% mortality). There were zero intracranial hemorrhages or SAH. No inhospital mortality occurred. One patient was found dead at 12-month telephone follow-up (Case 4). This patient initially presented with vertigo and limb numbness. MR imaging found infarctions at thalamus and cerebellum. DSA demonstrated a 20-mm fusiform vertebrobasilar aneurysm involving bilateral vertebral artery. This patient was noted to have extensive atherosclerosis and aneurysmal ectasia. Uneventful single Tubridge placement with adjuvant coiling of the aneurysm lumen was performed, and the left vertebral artery was also sacrificed. After that, the patient missed MRI/angiography follow-up due to non-compliance. This patient was also non-compliant with antiplatelet drugs. 5 months after treatment, the patient suffered a loss of consciousness and coma. Emergent CT showed a massive brainstem infarction, but no further details were available. We speculate that stent occlusion secondary to antiplatelet non-compliance may be a contributing factor. This patient died ultimately in a local hospital.

One delayed thromboembolic event developed in an additional patient (Case 3) who experienced hemiplegia and hypoesthesia 3 months after treatment of a 10-mm basilar trunk aneurysm using single Tubridge deployment. Emergent DSA demonstrated a patent basilar artery and visible perforators. MRI disclosed pontine infarction and the patient was discharged home with an mRS score of 1.

TABLE 1 Patient demographics, aneurysm characteristics, and treatment details.

Pt #	Age, y (Sex)	Presentation	mRS		Aneurysm characteristics		Treatment details				Angiographic FU				
				Previous Treatment	Location	Diameter, mm	Number and Type of FDs used	Additional Devices applied	Jailed Major Branches	Complications	Time	Modality	Occlusion Grade	Jailed Branches	mRS at FU
1	46 (M)	Dizziness	0		VBJ	20.2	2 TB	Coils	2 AICA		12	DSA	CO	Patent	0
2	56 (M)	Dizziness	0		VBJ	14.5	1 TB	Coils			6	DSA	NC		0
3	67 (M)	Incidental	0		Trunk	10.2	1 TB		1 AICA	Ischemic stroke	9	MRA	CO	Patent	1
4	66 (M)	Ischemic stroke	1		VBJ	20.4	1 TB	Coils		Mortality					6
5	57 (M)	Finding tandem BA aneurysms after infarction	0	LEO	Trunk	11.8	1 TB	Post-dilation with Scepter balloon	2 AICA		5	DSA	CO	Patent	0
6	8 (F)	Recurrence after previous treatment	0	LEO + coils	Tip	27.4	2 TB	Pre-dilation with Gateway balloon, Coils	1 PCA and 2 SCA		12	DSA	CO	All occluded	0
7	28 (F)	Recurrence after previous treatment	0	PED + coils	VBJ	17.5	1 TB	Coils			7	DSA	NC		0
8	68 (F)	Dizziness	0		Trunk	11.1	1 TB		1 AICA		7	DSA	IC	Patent	0
9	52 (F)	Dizziness	0		Tip	9.1	1 TB		2 SCA		7	DSA	CO	Patent	0
10	56 (M)	Dizziness	0		Trunk	13.6	1 TB		1 AICA		10	DSA	CO	Patent	0
11	38 (F)	Headache	0		Trunk	5.8	1 TB		1 PCA and 2 SCA		7	DSA	NC	Patent	0
12	65 (M)	Headache	0		VBJ	18.1	1 TB	Coils	2 AICA		9	DSA	NC	Patent	0
13	27 (F)	Incidental	0		Trunk	10.5	1 TB	Coils	1 PCA and 2 SCA		7	DSA	CO	Patent	0
14	25 (M)	Headache	0		VBJ	9.7	1 PED				6	CTA	CO		0
15	77 (M)	Progressivebrainstem compression syndrome	3		Tip	32.6	1 PED	Coils	1 PCA and 2 SCA	Progressive hydrocephalus	3	DSA	IC	Patent	4
16	36 (M)	Recurrence after previous treatment	0	LVIS + coils	Tip	18.3	1 PED		1 PCA and 2 SCA		9	DSA	CO	1 PCA occluded	0

BA, basilar artery; CO, complete occlusion; EP, enterprise stent; FD, flow diverter; FU, follow-up; IC, incomplete occlusion; LV, LVIS stent; NC, near-complete occlusion; PCA, posterior cerebral artery; PED, pipeline; Pt, patient; SCA, superior cerebellar artery; TB, Tubridge; UE, upper extremity; VBJ, vertebrobasilar junction. #, number.

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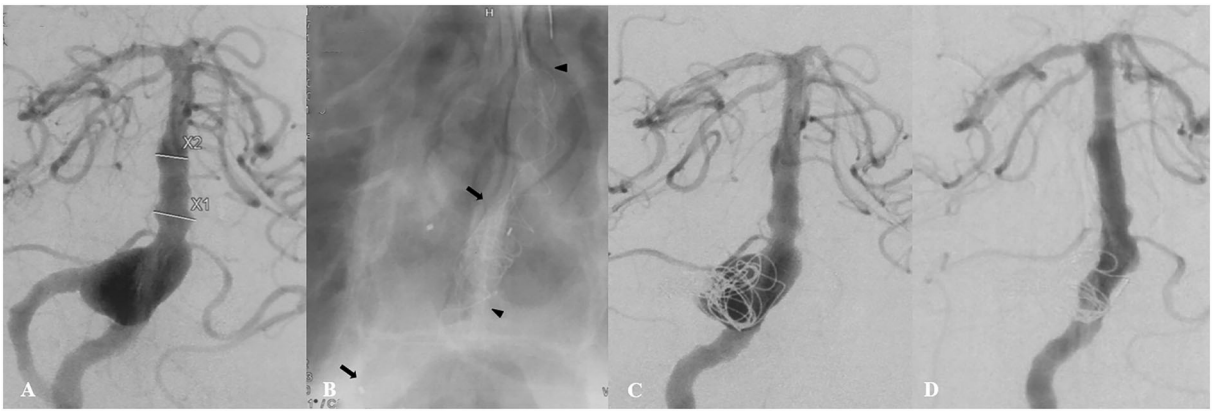

FIGURE 1
A 46-year-old patient (Case 1) presented with a 2-month history of dizziness. Preoperative angiography showed a large fusiform vertebrobasilar junction aneurysm **(A)**. This patient underwent placement of two telescoping Tubridge devices (the arrow and the arrowhead), along with coiling and right vertebral artery sacrifice **(B,C)**. Follow-up angiography 12 months later showed complete aneurysm occlusion **(D)**.

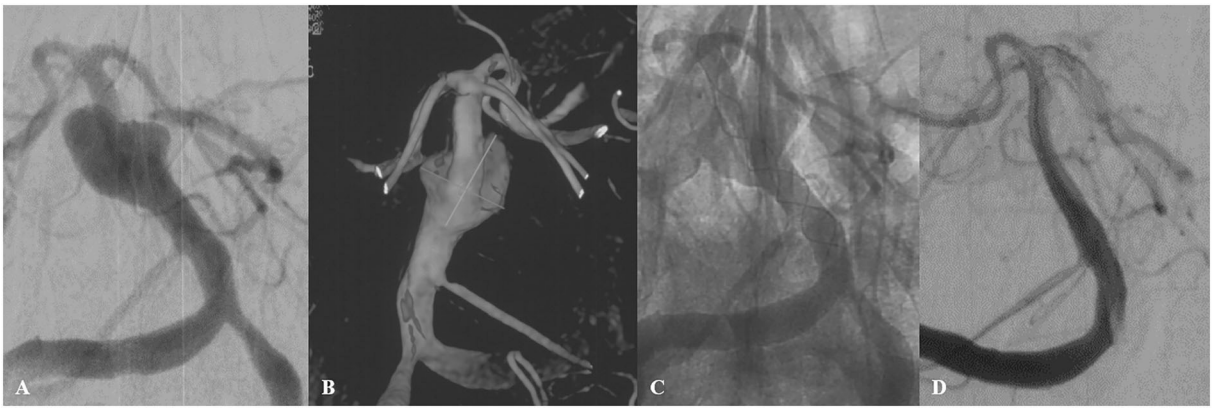

FIGURE 2
A 56-year-old male patient (Case 10) with a large basilar trunk aneurysm presented with dizziness. Preoperative angiography **(A)** with 3-dimensional reconstruction **(B)** demonstrated an irregular dissecting aneurysm at the middle basilar trunk. A single Tubridge device was placed in the basilar trunk **(C)**. 10-month follow-up angiography demonstrated complete obliteration of the aneurysm **(D)**.

A 77-year-old male patient (Case 15) presented with dizziness and unsteady gait on admission and was found with a giant basilar tip aneurysm. The patient gradually became unconscious after implantation of a single Pipeline device and adjunctive coils. The CT scan conformed a third ventricular mass leading obstructive hydrocephalus. A ventriculoperitoneal shunt was inserted for the patient with an unfavorable outcome at discharge (mRS = 4).

Clinical follow-up at 8–18 months (mean, 12.2 months) was achieved in 15 patients because one patient died during follow-up. One patient suffering obstructive hydrocephalus after treatment was still disabled with an mRS score of 4 at 8-month clinical FU. Except this case, a favorable clinical outcome (mRS ≤2) was observed in other 14 patients (87.5%).

Literature review

A literature review regarding the use of FDs in BA identified 296 cases within 11 original case reports/case series (Table 2). The overall complication rate was 27%, mainly ischemic events (15.8%). The mortality rate was 11.8%. Among 164 cases with angiographic follow-up, 123 (75%) cases achieved complete or near-complete occlusion.

Discussion

In this study, we examined the feasibility, safety, and efficacy profile of the Tubridge and Pipeline FD

TABLE 2 A summary of large series (≥10 patients) with flow diverter implantation in the basilar artery for aneurysm treatment.

Author, published year	FD types	All BA cases	Complications (%)	Ischemic (%)	Hemorrhagic (%)	Mass effect (%)	Others (%)	Mortality (%)	CO/NC at FU (total FU cases, %)
Ge et al. (13)	PED	29	13 (44.8)	7 (24.1)	3 (10.3)	3 (10.3)	0 (0)	7 (24.1)	20 (23, 87)
Hellstern et al. (9)	p64	30	6 (20)	4 (13.3)	2 (6.7)	0 (0)	0 (0)	1 (3.3)	20 (26, 76.9)
Wallace et al. (15)	PED	15	2 (13.3)	1 (6.7)	0 (0)	0 (0)	1 (6.7)	1 (6.7)	10 (13, 76.9)
Bender et al. (16)	PED	25	4 (16)	3 (12)	0 (0)	1 (4)	0 (0)	2 (8)	NA
Dmytriw et al. (18)	PED/FRED	16	3 (18.8)	0 (0)	2 (12.5)	1 (6.3)	0 (0)	1 (6.3)	11 (16, 68.8)
Griessenauer et al. (19)	PED	68	21 (30.9)	NA	NA	NA	NA	8 (11.8)	50 (68,73.5)
Taschner et al. (7)	Surpass	26	NA	NA	NA	NA	NA	8 (30.8)	NA
Lopes et al. (20)	PED	44	9 (20.4)	6 (13.6)	1 (2.3)	1 (2.3)	1 (2.3)	5 (11.4)	NA
Wakhloo et al. (21)	Surpass	10	4 (40)	2 (20)	0 (0)	0 (0)	2 (20)	2 (20)	5 (6, 83.3)
Phillips et al. (22)	PED	21	6 (28.6)	4 (19.0)	2 (9.5)	0 (0)	0 (0)	0 (0)	NA
Kulcsár et al. (23)	SILK	12	5 (41.7)	5 (41.7)	0 (0)	0 (0)	0 (0)	0 (0)	7 (12, 58.3)
Sum		296							
Number (sum, %)			73 (270, 27)	32 (202, 15.8)	10 (202, 5)	6 (202, 3)	4 (202, 2)	35 (296, 11.8)	123 (164, 75)

FD, flow diverter; CO, complete occlusion; FU, follow-up; NA, data not available; NC, near-complete occlusion.

in the treatment of BA aneurysms. The FD device was successfully implanted in the BA for all 16 aneurysms. Procedural complications occurred in 18.8% of the patients. Complete or near-complete occlusion was achieved in 86.7% of aneurysms at follow-up of 7.7 months. There were no instances of aneurysm recurrence or retreatment. Our initial experience showed satisfactory results with acceptable clinical outcomes and high occlusion rates after mid-term follow-up.

The tubridge flow diverter device

The Tubridge FD is a braided, self-expanding device with flared ends, which has various features that seem to predetermine its use in the posterior circulation. The application of a nickel–titanium alloy allows for improved shape-holding memory and super-elasticity. The platinum–iridium material used for the radiopaque microfilaments improves visualization of the stent during deployment. More importantly, the large-size Tubridge (> 3.5 mm), which was mostly used in the posterior circulation, has more braided microfilaments, which decreases the shortening rate after its full opening and offers more appropriate pore attenuation (24).

Previously, a multicenter, prospective, randomized, controlled clinical trial (PARAT study) has verified the safety and efficacy of the Tubridge in unruptured large and giant intracranial aneurysms (10). In the Tubridge group with 82 enrolled subjects, the complete occlusion rates were 75.34% at 6-month imaging follow-up. Device-related morbidity and mortality occurred in 12.19 and 4.88% of the patients. Only 4 subjects with posterior circulation aneurysms were included in this study and were not discussed in detail. Subsequently, the application of Tubridge has been reported in other different subtypes, such as recurrent aneurysms, middle cerebral artery aneurysms, and cavernous carotid artery aneurysms (17, 25, 26). The safety and the efficacy of using Tubridge in BA aneurysms have not been evaluated.

In the current study, the Tubridege FD was mainly used, and the Pipeline was only used in three cases. Given the limitations of sample size, we were unable to make any direct comparison between the two groups. Nevertheless, our data showed the safety and the efficacy of the Tubridge in treatment of BA aneurysms. Symptomatic thromboembolic complications occurred in 15.5% (2/13) of the patients, resulting in one death, with a mortality rate of 7.7%. Complete or near-complete occlusion was achieved in 91.7% (11/12) of aneurysms at a median follow-up of 24 months. A favorable functional outcome was achieved in all cases.

Safety of flow diverters in basilar artery

Aneurysms in the basilar artery are characterized by complex neurovascular anatomy with life-sustaining perforating vessels arising from the lesion and the adjacent vessel along the brainstem. Placement of FDs inevitably results in coverage of these side branches, which further exposes the patient to thromboembolic and ischemic complications (27). As shown in our literature review, available studies reporting on the use of FDs in the BA show highly variable results, with complication rates ranging from 13.3 to 44.8%. One of the important observations from the overall outcomes is that the mean procedural complication rate appears to be still high (27%), which leads to the mean mortality rate of 11.8%. Thromboembolic events are the main source of poor outcomes. Ischemic stroke is mainly associated with invisible perforator infarction, jailed vessel occlusion, and stent occlusion. The occlusion of invisible perforator may be the most common cause of ischemia (16). In the present case series, the rates of procedural complications and mortality were 18.8 and 6.3%, respectively. Ischemic stroke was the most common complication, with an incidence rate of 12.5%, including perforator infarction and stent occlusion one patient each. Although two PCAs and two SCAs were invisible at the follow-up angiogram, these jailed branches were occluded asymptomatically.

Several factors associated with complications and outcomes have been identified. Firstly, FD may be more appropriate for asymptomatic patients or patients with mild symptoms due to the poorer outcomes related to the treatment of aneurysms in patients with higher baseline mRS scores (7). Secondly, implantation of multiple FD devices was prudent in the series, which helped to reduce thromboembolic complications (20). Longer devices with larger diameters were necessary for spanning of the fusiform segment, reliable opening, and improved apposition. Furthermore, rigorous platelet function testing and subsequent regimen adjustments were critical factors to mitigate neurologic complications from FD procedures (6, 14). In our study, platelet function was assessed in 87.5% of procedures, and the rate of antiplatelet regimen adjustment was 21.4%. Applying those principles in the current study may have explained the very favorable safety profile.

Hemorrhagic events are relatively uncommon. In the literature review, the pooled hemorrhagic complication rate among the 202 patients was 5%. In this study, no hemorrhagic event was occurred. Adjunctive coiling may provide protection from bleeding complications by altering intra-aneurysmal hemodynamics and controlling thrombosis (28). One patient who experienced progressive hydrocephalus postoperatively had symptoms of brainstem compression before FD treatment. Worsening of mass effect was less common in our pooled analysis, which demonstrated a rate of 3%. Several studies have shown that rapid thrombus formation after FD treatment and subsequent thrombus renewal, instead of thrombus organization, may induce an autolytic and inflammatory cascade, causing edema and further weakening the arterial wall, leading to IA expansion and aggravation of mass effect (29, 30).

Efficacy of posterior circulation aneurysms with flow diverters

The literature review looking at treatment of BA aneurysms with FDs reported complete/near-complete occlusion rates, ranging from 58.3 to 87% (mean, 75%). These findings are consistent with our results with an occlusion rate of 86.7%, following treatment with Tubridge and Pipeline devices. Still, our data are promising in terms of occlusion of some of the most challenging cerebral aneurysms. Also, follow-up was limited to 7.7 months on average; long-term follow-up would show higher occlusion.

Previous reports have summarized a variety of predictors of occlusion. A predictor of occlusion in BA aneurysms was age, with older aneurysms occluding less often (19). The use of adjunctive coils has been associated with increased occlusion rates (31). Aneurysms harboring large amounts of pre-treatment thrombus were associated with lower rates of complete occlusion (32). Large or giant aneurysm size correlated with aneurysm persistence for posterior circulation aneurysms (16, 19).

Our study has various inherent limitations. A major limitation is the retrospective design. There may have been a selection bias during patient sampling. More specifically, BA aneurysms are admittedly heterogeneous, while, in this study, several types were absent, such as acutely ruptured aneurysms, perforator aneurysms, and dolichoectatic aneurysms. The literature review was relatively simple; the relatively small sample size also precludes statistical analysis; therefore, an independent meta-analysis and larger-scale studies are needed. However, the results of our preliminary experience of the treatment of BA aneurysms using the Tubridge and Pipeline devices are encouraging.

Conclusion

Although no definitive conclusions can be drawn from this case series because of the small number of treated patients, the Tubridge and Pipeline FD seem to be safe and effective for the treatment of BA aneurysms at mid-term follow-up.

However, studies with a long-term follow-up and larger series are necessary to validate these 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

Written informed consent was obtained from the minor(s)' legal guardian/next of kin for the publication of any potentially identifiable images or data included in this article.

Author contributions

CW, DZ, and XX: analysis and interpretation of data. YZ, RZ, QL, PY, QH, and YX: review and editing. YF and JL: overall review and study design. CW: the draft of the work. 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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Flow diversion effect of the leo braided stent for aneurysms in the posterior and distal anterior circulations: A multicenter cohort study

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Background and purpose: The treatment of aneurysms located in the posterior and distal anterior circulations remains a challenge. Leo stents with a flow diversion (FD) effect may be a potential option, which needs to be clearly studied.

Methods: From January 2016 to October 2021, 133 patients with 145 aneurysms in the posterior and distal anterior circulations, treated with Leo stents, were retrospectively analyzed in three neurosurgical centers. Data on demographic information, aneurysm characteristics, procedural outcomes, postoperative course, and aneurysm occlusion were retrospectively analyzed.

Results: After immediate surgery, 90 aneurysms (60.1%) were in complete occlusion [Raymond-Ray Occlusion Class (RROC) 1 and O'Kelly Marotta (OKM) grade D], 29 aneurysms (20%) in good occlusion (RROC 2 and OKM grade C), 17.9% in incomplete occlusion (RROC 3a or OKM grade B), and no aneurysms in invalid occlusion (RROC 3b and OKM grade A). A total of 112 patients with 117 aneurysms received angiographic follow-up (mean 11.4 months), and the degree of occlusion showed a significant improvement ($Z = 3.900$, $p < 0.001$). The complete occlusion rate increased to 84.6% (99/117), while good and incomplete occlusion decreased to 6.8% (8/117) and 8.6% (10/117), respectively. A total of 14 cases (10.5%) presented narrowing of the parent artery, and nine cases (6.8%) had injured side branches. Cerebral hemorrhage occurred in four patients (3.0%), and symptomatic ischemic infarction occurred in six patients (4.5%). The final permanent morbidity (mCS $\geq$3) and mortality were 2.8% (3/133) and 0.8% (1/133), respectively. For 82 aneurysms treated by stent-assisted with coiling (SAC), large-sized, ruptured aneurysms ($\chi^2 = 7.767$, $p = 0.005$) occurred. For 63 aneurysms treated by LEO stent monotherapy (LSM), multiple aneurysms, fusiform aneurysms ($\chi^2 = 18.958$, $p < 0.01$), and/or small-sized aneurysms ($Z = -2.692$, $p = 0.007$) occurred.

Conclusions: Leo stents are safe and effective for aneurysms located in the posterior and distal anterior circulations. The overall degree of occlusion improved during a follow-up because of the FD effect of Leo stents. Aneurysms in these areas should be treated with personalized measures.

KEYWORDS

endovascular treatment, flow diversion, aneurysm, stents, multicenter study

Highlights

- About 133 patients with 145 aneurysms in the posterior and distal anterior circulations were retrospectively analyzed in multi-neurosurgical centers.
- The safety and efficacy of Leo stents were verified.
- The FD effect of Leo stents had improved aneurysm occlusion during a follow-up.
- Aneurysms with different characteristics should be treated with personalized measures.

Introduction

Endovascular treatment (EVT) of aneurysms located in the posterior and distal anterior circulations remains challenging and involves a high risk of regrowth, aneurysm rupture, and parent artery occlusion, leading to disastrous consequences, due to small, tortuous parent arteries and the vital blood supply areas (1, 2).

As self-expanding stents, the metal coverage of Leo plus and Leo plus baby is ∼14 and 18%, respectively, and between laser-cut stents and flow-diverting stents (3). Leo stents have been proven to have a flow diversion (FD) effect. In 2005, the Leo self-expanding stent was applied for the first time to treat a wide-neck intracranial aneurysm, with the advantage of greater artificial coverage of the aneurysm neck (4). Soon afterwards, Leo stents have been attempted as monotherapy with stent or stent-assisted with coiling (SAC), for complicated aneurysms in some tortuous segments (5, 6).

The flow velocity in the aneurysm and the wall shear stress are two important hemodynamic parameters associated with the growth and rupture of intracranial aneurysms (7, 8). Leo stent implantation produces hemodynamic and biological effects on the parent artery to promote aneurysm occlusion, which cannot only redirect blood flow and decrease wall stress in the aneurysm, but also induce neointimal proliferation in the parent artery (5, 9).

However, the FD effect of Leo stents still needs to be clearly studied, especially for those aneurysms located in the posterior and distal anterior circulations. We collected a retrospective series of 133 patients with 145 aneurysms covered by LEO stents at three neurosurgical centers and focused on the following questions: (1) the safety and clinical efficacy of Leo for aneurysms located in the posterior and distal anterior circulations; (2) remodeling effect of Leo stents; and (3) clinical characteristic between LEO stent monotherapy (LSM) and SAC.

Materials and methods

Study design

From January 2016 to October 2021, patients with aneurysms treated with Leo plus or Leo plus baby stent were consecutively enrolled and retrospectively analyzed at our three neurosurgical centers. Inclusion criteria were as follows: (1) patients diagnosed with intracranial aneurysm(s) by digital subtraction angiography (DSA); (2) patients more than 14 years old; and (3) deployment *via* Leo plus or Leo baby plus stent(s). Exclusion criteria were as follows: (1) presence of aneurysms located in the internal carotid artery segment; (2) deployment by other kinds of stents; and (3) loss to follow-up. Data on demographic information, aneurysm characteristics, procedural outcomes, postoperative course, and aneurysm occlusion were analyzed.

Perioperative drug management

For patients with unruptured aneurysm, aspirin (100 mg/day) and clopidogrel (75 mg/day) were administered for at least 3 days before the operation. For patients with acute subarachnoid hemorrhage, 300 mg of aspirin and 150 mg of clopidogrel were taken 4 h before EVT. Leo plus or Leo plus baby was deployed under intraoperative systemic heparinization (80 U/kg by intravenous injection at first and then 1,000 U/h). Aspirin (100 mg/day) and clopidogrel (75 mg/day) were continued for at least 3 months after EVT, and then aspirin (100 mg/day) was administered separately for at least 2 years or for life, according to the result of angiographic follow-up.

Endovascular therapy

Endovascular treatment was performed on the angiographic system (Artis zeego, Siemens AG, Healthineers, Forchheim,

TABLE 1 Characteristic of 133 patients.

Clinical information	Date ($n = 133$)
Age (years old)	54.0 ± 12.1
Female (*n*, %)	80, 60.2%
Cardiovascular risk factors (*n*, %)	
Smoking	4, 0.3%
Drinker	5, 0.38%
Hypertension	17, 12.8%
Diabetes	12, 9.0%
SAH	26, 19.5%
Cerebral infarction	6, 4.5%
Hunt-hess grade	
1	10, 7.5%
2	9, 6.8%
3	2, 1.5%
Number of aneurysms in a patient	
1	122, 91.7%
2	10, 7.5%
3	1, 0.8%
Endovascular methods	
LSM	51, 38.3%
SAC	82, 61.7%

SAH, subarachnoid hemorrhage; LSM, Leo stent monotherapy; SAC, stent-assisted with coiling.

Germany). After general anesthesia, a long femoral sheath and a 6F guiding catheter (Johnson & Johnson, NJ, USA) were deployed, then the microcatheter was introduced at the target location. Treatment planning was carefully determined by three-dimensional (3D) rotational angiography.

Leo plus (Balt Extrusion, Montmorency, France) has its own microcatheter, and the Leo plus baby stent was delivered *via* a 0.017″ microcatheter or Echelon 10 (Medtronic, Irvine, CA, USA). Tirofiban hydrochloride (Yuanda Pharmaceutical Co. LTD, China) was used for acute thrombus within the stent, and if the stent was poorly opened, microcatheter massage of the stent or balloon dilatation was considered. Intracranial hemorrhage was routinely ruled out after the procedure by flat detector computed tomography (FD-CT).

Clinical follow-up

The first angiographic follow-up was usually scheduled at 6 months or more after surgery. Without special conditions, magnetic resonance angiography (MRA) without contrast medium injection was suggested once a year. The occlusion status of aneurysms treated with LSM and SAC was evaluated using the O'Kelly Marotta (OKM) grading scale (10) and the Raymond-Ray Occlusion Class (RROC) (11), respectively. OKM grade D and RROC 1 were defined as complete occlusion, OKM grade C and RROC 2 as good occlusion, OKM grade B and RROC 3a as incomplete occlusion, and OKM grade B and RROC3b as invalid occlusion. Clinical neurological function was assessed using the modified Rankin scale (mRS).

Statistical analysis

Data were analyzed with the SPSS23.0 statistical software package (SPSS, Chicago, IL, USA). Normally distributed measurement data [shown as mean and standard deviation (SD)] were tested by *t*-test. Non-normally distributed measurement data (shown as median and quartile spacing) were tested using the rank sum test (Mann–Whitney *U*-test]. Categorical variables (shown as number and percentage) were tested using Fisher's exact test to compare rates between groups. Complication risks were analyzed using multivariate logistic regression analysis. A p-value of <0.05 was considered statistically significant.

Results

Demographic information

A total of 133 patients with 145 aneurysms were enrolled in our study (Table 1). There were 80 women and 53 men with an average age of 54.0 ± 12.1 years (19–76 years). Of 145 aneurysms, 86 (59.3%) were in the posterior circulation and 59 (40.7%) were in the distal anterior circulation; and 67 (47.6%) were saccular aneurysms and 76 (52.4%) were fusiform aneurysms. A total of 21 patients had a subarachnoid hemorrhage before treatment. Of these, 19 (90.5%) were mild (Hunt–Hess grades 1–2).

Angiographic outcomes

As shown by the immediate occlusion results, 90 aneurysms (60.1%) were in complete occlusion (RROC 1 and OKM grade D), 29 aneurysms (20%) in good occlusion (RROC 2 and OKM grade C), 26 (17.9%) in incomplete occlusion (RROC 3a or OKM grade B), and no aneurysms in invalid occlusion (RROC 3b and OKM grade A). After a mean of 11.4 months (6 to 17 months), 112 patients with 117 aneurysms received angiographic follow-up and the degree of occlusion improved significantly ($Z = -3.900$, $p < 0.001$). The rate of complete occlusion increased to 84.6% (99,117), while good and incomplete occlusion decreased to 6.8% (8/117) and 8.6% (10/117), respectively (Table 2).

TABLE 2 The outcomes of treatment.

	Rate
Angiographic outcomes	
Immediate surgery	
Complete occlusion	60.1% (90/145)
Good occlusion	20.0% (29/145)
Incomplete occlusion	17.9% (26/145)
Latest follow-up*	
Complete occlusion	84.6% (99/117)
Good occlusion	6.8% (8/117)
Incomplete occlusion	8.6% (10/117)
Complication	
Endovascular stenosis	10.5% (14/133)
Injured side branches	6.8% (9/133)
Clinical follow-up	
Cerebral hemorrhage	3.0% (4/133)
Symptomatic ischemic infarct	4.5% (6/133)
Poor neurologic outcome (mCS ≥3)	2.3% (3/133)
Treatment-related mortality	0.8% (1/133)

*The ratio of occlusion degree was statistically different between immediate result and latest follow-up ($Z = -3.900$, $P < 0.001$).

Clinical outcomes and complications

There was no parent artery occlusion in this cohort study. A total of 14 patients presented narrowing of the parent artery, and nine patients had side branch injuries after stent deployment. Finally, symptomatic cerebral infarction was caused by narrowing of the parent artery in six patients (4.5%). Periprocedural cerebral infarct (up to 7 days after the procedure) occurred in four patients (3.0%) and delayed cerebral infarct occurred in two patients (1.5%).

Two cases of acute hemorrhage happened during coil release, and one patient died of severe cerebral hemorrhage. Of the two cases with delayed hemorrhage, one occurred 2 days after treatment for a SAC middle cerebral artery (MCA) aneurysm, and the other occurred 3 days after treatment for a ruptured fusiform posterior inferior cerebellar artery (PICA) aneurysm *via* the left main stem (LMS; Hunt–Hess grade 1). Antiplatelet treatment was totally suspended when post-hemorrhage was found. Hemorrhage in the two patients remained stable, aspirin (100 mg/day) was used after 3 days, and clopidogrel (75 mg/day) was reused after a week. There was one case of death, but the rest of the hemorrhage cases were considered minor events and recovered before hospital discharge.

In this cohort study, the final permanent morbidity (mCS ≥3) and mortality were 2.8% (3/133) and 0.8% (1/133), respectively.

Difference of aneurysm between SAC and LSM

According to treatment options, there were 82 and 63 aneurysms in the SAC group and in the LSM group, respectively (Table 3). All multiple aneurysms were treated with LSM [($\chi^2 = 35.580$, $p < 0.01$). Ruptured aneurysms were likely to be treated with SAC ($\chi^2 = 7.767$, $p = 0.005$). There were more fusiform aneurysms ($\chi^2 = 18.958$, $p < 0.01$) and/or small-sized aneurysms ($Z = -2.692$, $p = 0.007$) in the LSM group.

SAC group

There were 52 saccular and 30 fusiform aneurysms in the SAC group. After immediate surgery, the angiographic result showed complete occlusions (RROC 1), neck remnants (RROC 2), and residual aneurysms (RROC 3a) in 50.0% (41/82), 25.6% (21/82), and 24.4% (20/82), respectively. The degree of occlusion of the 65 aneurysms at the last follow-up showed 80.0% aneurysms in RROC 1, 7.7% in RROC 2, and 12.3% in RROC 3a. Two aneurysms with RROC 2 at immediate surgery showed neck recurrence during a follow-up and received EVT again.

In this group, intra-stent stenosis occurred in nine patients (11.0%) and injured side branches occurred in five cases (6.1%). In the early period after surgery, the rates of procedure-related complication rates of cerebral hemorrhage and symptomatic ischemic infarction were 3.7% (3/82) and 4.9% (4/82), respectively. Only one case of death in our cohort study was in the SAC group.

LSM group

There were 17 saccular aneurysms and 46 fusiform aneurysms in the LSM group. Of the 46 fusiform aneurysms, the average diameter was 6.5 ± 3.8 mm (2.48–22.9 mm); and according to Zhang's modified classification of fusiform aneurysms (12), 28 (60.9%, 28/46) aneurysms were classified as type I, 15 (32.6%) were type II, 3 (6.5%) were type III, and no aneurysms were type IV. After immediate surgery, imaging revealed OKM grade D in 49 aneurysms (77.8%), OKM grade C in eight aneurysms (12.7%), and OKM grade B in six aneurysms (9.5%). As shown in the last follow-up angiogram of 52 patients, the rate of complete occlusion (OKM grade D) was 90.4%. Five aneurysms remained stable (three aneurysms in OKM grade C and two aneurysms in OKM grade B), and no aneurysms worsened.

Of eight patients with intra-stent stenosis or injured side branches, two developed symptomatic ischemic infarction. One patient with a ruptured fusiform aneurysm in PICA suffered a recurrence of cerebral hemorrhage 2 days after the deployment of a Leo plus stent and totally recovered with conservative treatment. At prolonged follow-up, morbidity was 1.9% (1/62).

TABLE 3 The clinical information between SAC and LSM.

	SAC	LSM	Test value	*P*-value
Age (mean ± SD, years)	54.3 ± 11.7	53.4 ± 12.6	0.436[a]	0.664
Ruptured aneurysm (*n*, %)	19.5% (16/82)	7.9% (5/63)	3.855[b]	0.050
Recurrent aneurysm (*n*, %)	4.9% (4/82)	11.1% (7/63)	1.974[b]	0.160
Multiple aneurysms (*n*, %)	0	36.5% (23/63)	35.580[b]	$P < 0.01$
Perforator involving aneurysm	29.3% (24/82)	41.3% (26/63)	2.271[b]	0.132
Aneurysm size			−2.692[c]	0.007
Small (≤7 mm)	43	47		
Middle size (7.1–9.9 mm)	34	14		
Large (10–24.9 mm)	4	2		
Giant (≥25 mm)	1	0		
Aneurysm shape			18.958[b]	$P < 0.01$
Saccular	52 (52/82)	17 (17/63)		
Fusiform	30 (30/82)	46 (46/63)		
Aneurysm location			−1.443[c]	0.149
Distal anterior aneurysm				
ACA	14	11		
MCA	15	19		
Posterior circulation				
PCA	10	8		
PICA	4	3		
AICA	2	3		
VA	22	11		
BA	12	6		
BT	3	2		
Embolic degree at last follow-up			−1.596[c]	0.110
Complete occlusion	80.0% (52/65)	90.4% (47/52)		
Good occlusion	7.7% (5/65)	5.8% (3/52)		
Incomplete occlusion	12.3% (8/65)	3.8% (2/52)		
Periprocedural complication				
Parent artery narrowing	11.0% (9/82)	7.8% (4/51)	0.350[b]	0.554
Side branches injured	6.1% (5/82)	7.8% (4/51)	0.152[b]	0.697
Cerebral hemorrhage	3.7% (3/82)	2.0% (1/51)	0.311[b]	0.577
Symptomatic ischemic infarct	4.9% (4/82)	3.9% (2/51)	0.067[b]	0.796
Poor neurologic outcome	2.4% (2/82)	2.0% (1/51)	0.033[b]	0.857
Treatment-related mortality	1.2% (1/82)	0	0.627[b]	0.429

[a]T value; [b]χ^2 value; [c]*Z* value; The normal distribution measurement data were showed by mean and standard deviation and the non-normal distribution measurement data were showed by median and quartile spacing. ACA, anterior cerebral artery; MCA, middle cerebral artery; PCA, posterior cerebral artery; PICA, posterior inferior cerebellar artery; AICA, anterior inferior cerebellar artery; VA, vertebral artery; BA, Basilar artery; BT, Basilar tips.

Discussion

Endovascular treatment of aneurysms in the posterior and distal anterior circulations remains a challenge for interventional neuroradiologists. Delivery of conventional stiff flow-diverting stents in small or tortuous arteries would be dangerous, and retrieval of the system could be challenging (13, 14). Leo, as an existing self-expandable stent, has been proven to have FD properties (5, 9). To the best of our knowledge, our cohort is the biggest to study the FD effect of Leo stents for such aneurysms and to analyze treatment strategies for different characteristic aneurysms.

Occlusion results

As the final angiographic results of our study showed that the rate of complete occlusion (RROC 1) was 80.0% in the

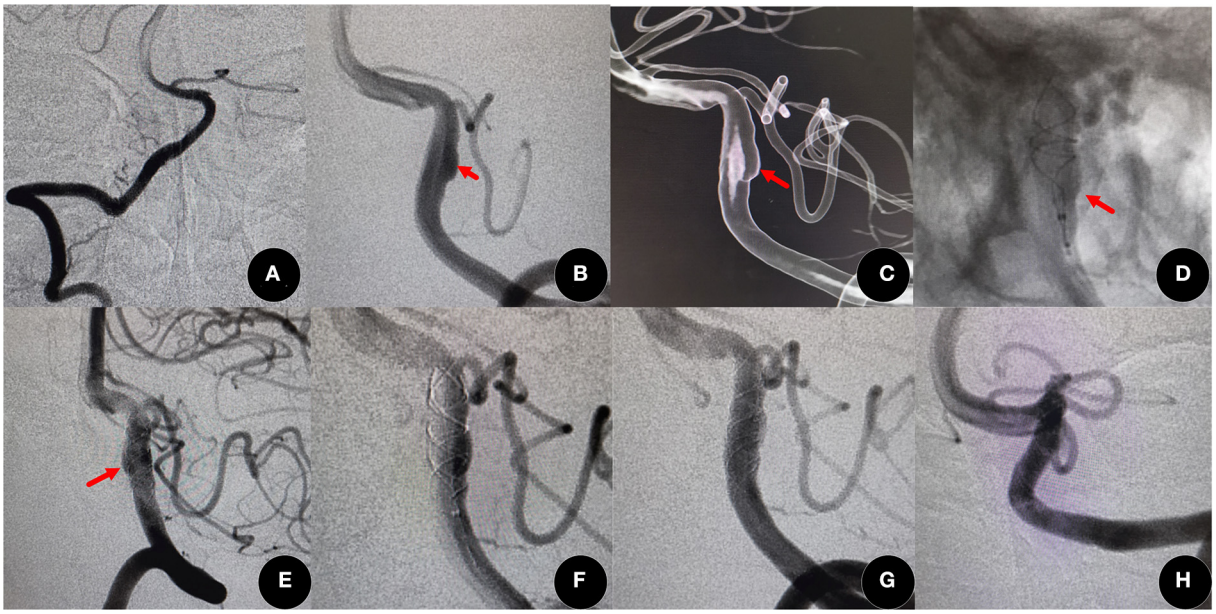

FIGURE 1
On routine examination, a fusiform aneurysm was found (60-year-old women). **(A)** Normal right vertebral artery. **(B,C)** Angiographic images showed a left fusiform vertebral artery (red arrow) **(D,E)** A Leo plus stent (3.5 mm × 25 mm) was deployed by telescopic technique (red arrow), and the aneurysm incomplete occlusion [O'Kelly Marotta (OKM) grade B]. **(F,G)** After the deployment of another Leo plus stent of the same size, flow into the aneurysm was obviously decreased and the degree of occlusion improved to good occlusion (OKM grade C). **(H)** The degree increased to complete occlusion (OKM grade D) at 14 months after surgery.

SAC group, which was similar to the main results of the last 10 years (from 70 to 88.9%) (15–21). In the LSM group, 90.3% of aneurysms in complete occlusion (OKM grade D) was the highest rate compared to the results from other LSM studies [70.0% (9), 73.7% (5)], even higher than TuBridge flow diverters (50% in OKM grades D and C) (22) or a meta-analysis of flow-diverting stents (78.7% in complete/near complete occlusion) (23) in MCA. For complicated aneurysms, the two-stage operation is accepted due to the high risk of rupture during coiling (24).

FD of leo stents

Pumar et al. found that the rate of complete occlusion (RROC 1) of wide-neck intracranial aneurysms after Leo stent deployment increased from 39.8% at immediate post-procedural angiography to 73.1% at year 5 (15). In our study, the degree of angiographic occlusion had improved significantly during a follow-up, similar to other studies (16, 25), again demonstrating that Leo stents have the ability to persistently promote thrombosis in the aneurysm due to the FD effect (Figure 1). Based on our clinical experience, overlapping stents (26) and telescopic technique (5) are also two important practical techniques of Leo stents to increase mesh density and improve the FD effect (Figure 2). Leo stents with favorable elasticity can easily be released and opened in small and tortuous distal parent arteries (Figure 3).

Procedure-related complications

Flow-diverting stents with high metal coverage may easily cause occlusion of the parent artery and injured side branches (2, 5, 13, 27, 28). A meta-analysis showed that more than 10% of covered arteries became occluded during a follow-up, with ∼16.3% thromboembolic events due to flow-diverting stents in MCA aneurysms (23). In this study, of 14 patients with parent artery narrowing or side branch lesions, four had developed a cerebral infarction.

Many related risks associated with the development of ischemia have been studied. Matteau et al. found that smoking was an independent risk factor for ischemic events and bleeding after stent implantation (29). Cagnazzo et al. showed that the rates of arterial narrowing and occlusion by Leo were close to 7 and 2%, respectively, and a longer radiologic follow-up and smoking are two independent factors associated with arterial narrowing and occlusion (9).

Delayed aneurysm rupture and distal intraparenchymal hemorrhage were the main causes of mortality in patients

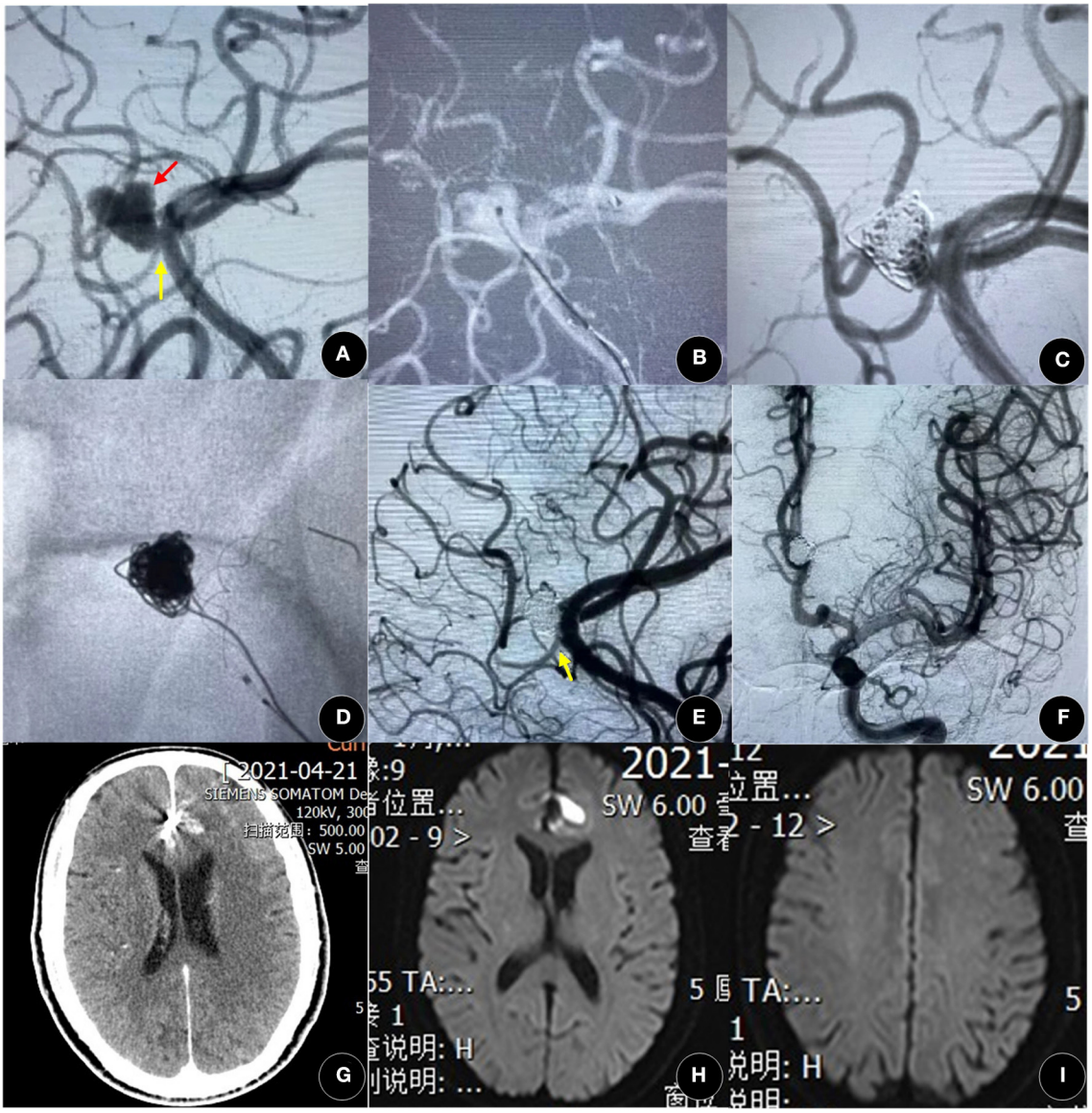

FIGURE 2
A 60-year-old woman presented with spontaneous SAH for 3 days. **(A)** The angiographic result showed a left lobular A3 aneurysm (black arrow) with a side branch (yellow arrow). **(B,C)** After coiling, the aneurysm was in incomplete occlusion [Raymond-Ray Occlusion Class (RROC) 3c]. **(D–F)** The aneurysm was achieved in complete occlusion (RROC 1) after the deployment of the Leo plus baby stent (2.5 mm × 18 mm), and the side branch was not affected (yellow arrow). **(G–I)** There was no new cerebral hemorrhage or infarction by computed tomography (CT) and magnetic resonance imaging (MRI). A3, the third segment of the anterior cerebral artery; SAH, subarachnoid hemorrhage.

with intracranial aneurysms treated with flow-diverting stents (30). In our cohort, four patients had procedure-related hemorrhage complications, of which two were caused by coiling, and one died at 2 weeks even after lateral ventricular drainage. Two patients suffered delayed hemorrhage, we will totally stop antiplatelet treatment for 3 days, if the hemorrhage stops and remains stable, monoclonal antibody will be used and if hemorrhage remains stable for a week, the double resistance will be reused. Although the incidence is not high, postoperative hemorrhage was still a nightmare for interventional neuroradiologists. In our study, most of the procedure-related complications had mild to moderate neurological deficits and disappeared within 3 months and we did not find any potential risk factors with procedure-related complications. Popularly, the intensity of antiplatelet therapy was decreased at 3 months after surgery (from 2 to 1) (17, 18) and terminated at 2 years after surgery.

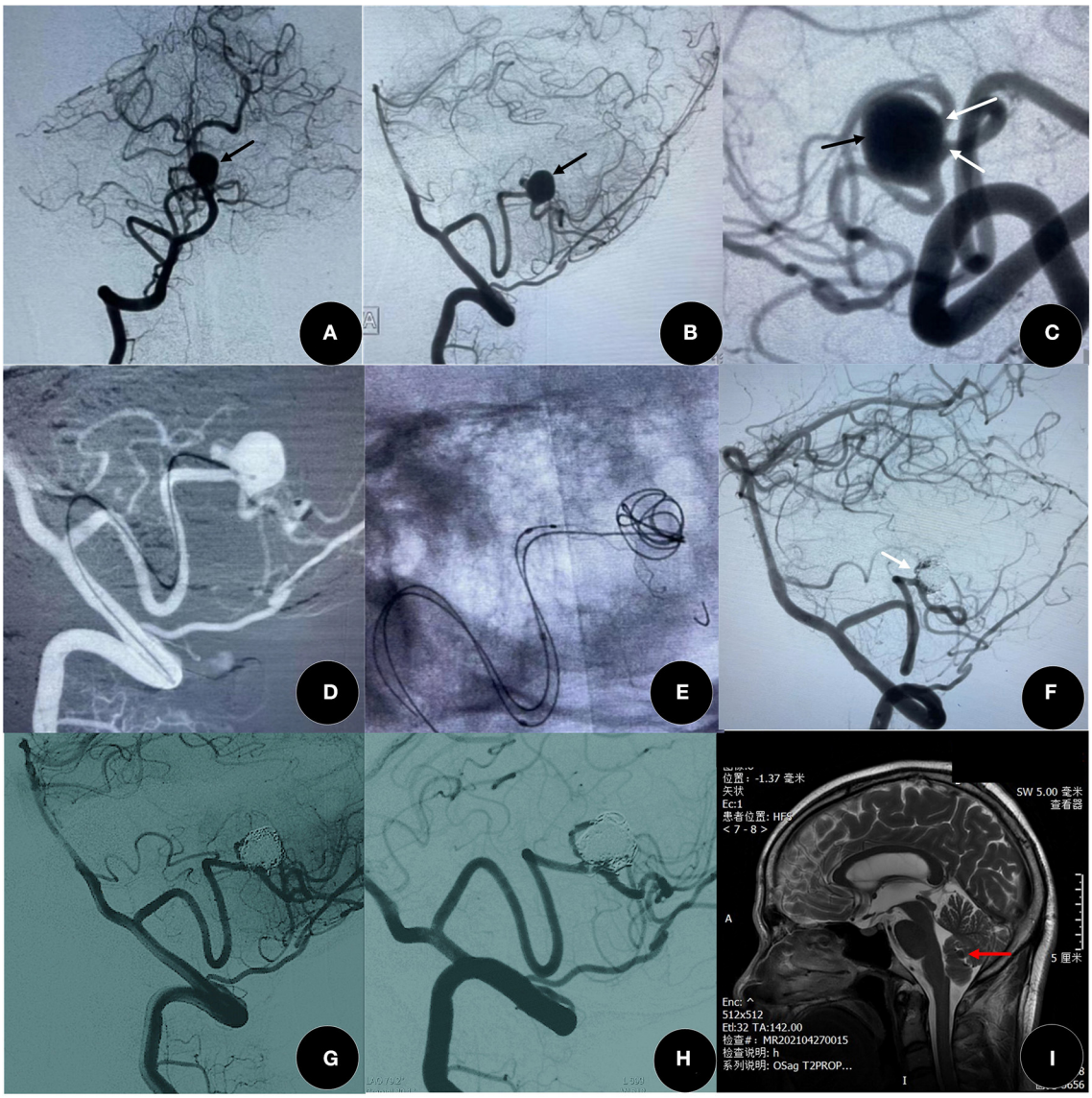

FIGURE 3
A 51-year-old woman presented with a headache for 1 year. **(A–C)** The angiographic result showed a distal posterior inferior cerebellar artery (PICA) aneurysm (black arrow) with two side branches (white arrow). **(D–G)** The aneurysm was in good occlusion (RROC 2) by Leo plus baby (2.5 mm × 18 mm) assisted coiling, and two branches were well-protected (white arrow). **(G,H)** The degree of occlusion increased to complete occlusion (RROC 2) at 9 months after surgery. **(I)** There is no new cerebral infarction after the confirmation of SAC by MRI, and red arrow indicates coils. SAC, stent-assisted coiling.

Therapeutic strategy

Although there was no significant difference in the degree of occlusion and postoperative complications, we proposed that SAC was still a priority, especially for irregularly shaped aneurysms (Figure 2) or ruptured aneurysms (Figure 4). Intraoperative aneurysm rupture is one of the significant risk factors for early serious complications (17), and the risk of intraprocedural rupture is significantly high during coiling, especially in heteromorphic or very small aneurysms (31, 32). Flow velocity in the aneurysm and wall shear stress are two important hemodynamic parameters associated with the growth and rupture of intracranial aneurysms (7, 8), and could be eliminated by coiling the aneurysm more intuitively (33, 34). In our study, two cases with acute cerebral hemorrhage were all in the SAC group, in our experience, complicated aneurysms treated with Leo-assisted coiling could not be packed too densely.

In 2008, a fusiform M_1 MCA aneurysm was satisfactorily treated with LSM, demonstrating that the Leo stent could cause

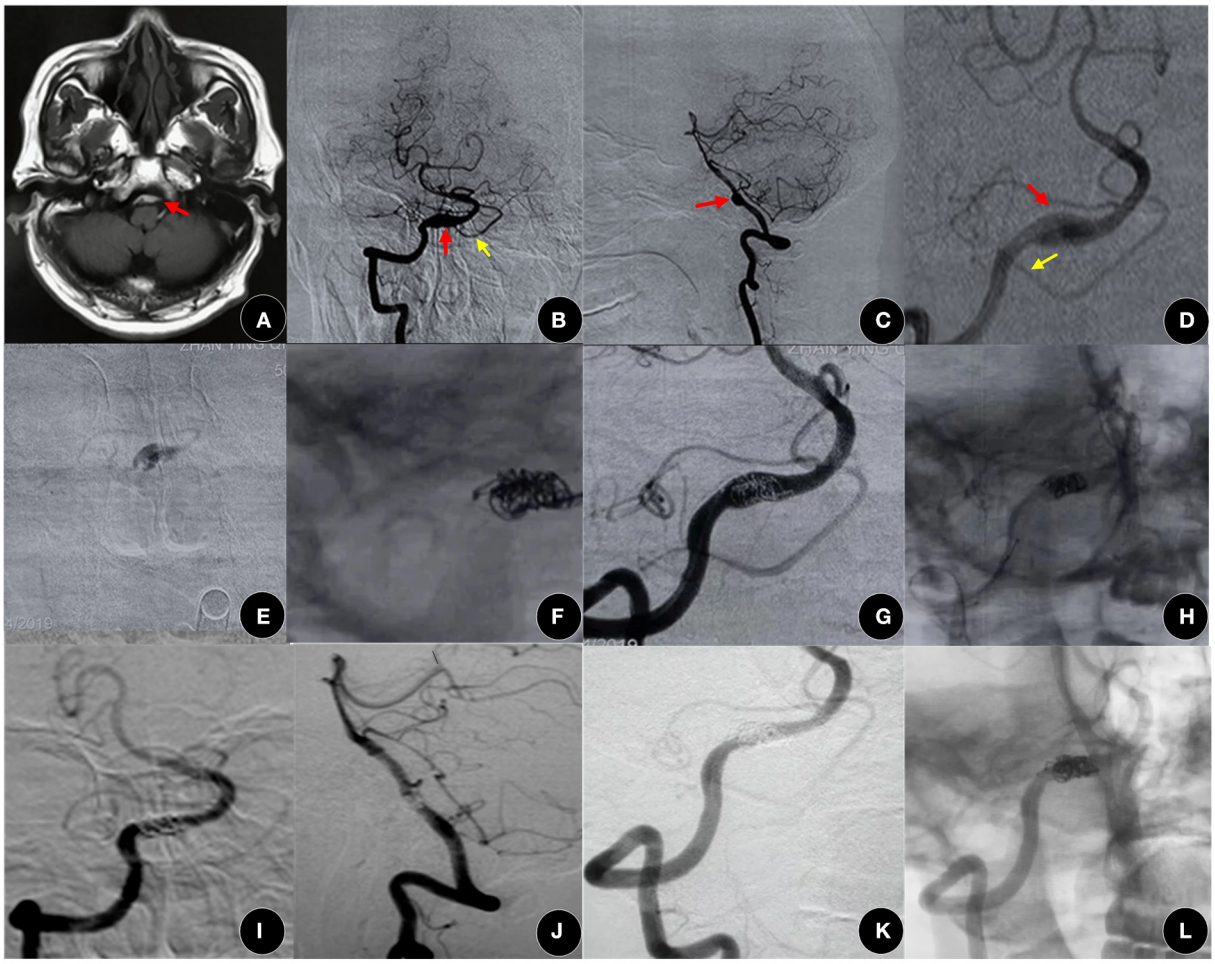

FIGURE 4
A 53-year-old man presented with SAH for 2 days. **(A–D)** MRI images indicated an aneurysm in the vertebrobasilar system (red arrow). **(B–D)** Angiographic images showed a vertebral artery dissecting aneurysm (red arrow) with a double aneurysmal cavity, located in the proximal posterior inferior cerebellar artery (yellow arrow). **(E)** It was confirmed that the microcatheter was in the aneurysmal cavity by the hand bolus injection contrast medium. **(F)** After releasing several coils, a Leo plus stent (3.5 mm × 25 mm) was deployed to press these coils evenly into the cavity, and then the other coils were continuously packed. **(G,H)** Good occlusion (OKM grade C) was achieved, and the VA and PICA were patented. **(I–L)** The embolism degree increased to complete occlusion (OKM grade D) and the modified Rankin scale (mRS) maintained a score of 0 at 13 months after surgery. VA, vertebral artery; PICA, posterior inferior cerebellar artery.

flow reduction and final thrombosis in the aneurysm without any additional treatment (35). Even without the expected occlusion, the fusiform aneurysms with Leo monotherapy could remain clinically and angiographically stable during a follow-up (36). As per our experience, sometimes the coil microcatheter would be difficult to introduce into the aneurysm located in the distal and tortuous artery, LSM was also demonstrated to be an important proposed alternative for saccular aneurysms and the incidence of intraprocedural rupture would decrease markedly without catheterization or a coil in the aneurysm. As we consider that small distal parent arteries have difficulty supporting three or more microcatheters simultaneously, many aneurysms are already achieved in complete occlusion after Leo stent deployment.

Limitations

The sample size in our cohort here was still not large. Of 133 patients, 21 (15.8%) had not received angiographic follow-up, which might lead to an attrition bias, and the follow-up was not long. In the future, as the number of cases increases, aneurysms located in the posterior and the distal anterior circulations should be analyzed individually with

longitudinal follow-up, and a prospective multicenter study may be performed.

Conclusion

Leo stents are safe and effective for aneurysms located in the posterior and distal anterior circulations. The degree of occlusion of aneurysms had persistently improved during a follow-up due to the FD effect of Leo stents. According to the different characteristics, those complicated aneurysms should be treated with personalized measures.

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 Huashan Hospital and Huadong Hospital, Shanghai Putuo District People's Hospital. Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin. 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

GC designed the study and performed surgery. YD wrote the article and analyzed the data. BX, RM, XQ, and JL assisted to finish part of surgery. YH and BZ collected the data. 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.

Publisher's note

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The evolution of intracranial aneurysm research from 2012 to 2021: Global productivity and publication trends

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Background: This study aimed to analyze the global research trends and map the knowledge network of intracranial aneurysm (IA) research in the last 10 years.

Methods: Publications related to IA from 2012 to 2021 were retrieved from the Web of Science core collection. Microsoft Excel 2010 and VOSviewer were used to characterize the largest contributors, including authors, journals, institutions, and countries. CiteSpace and VOSviewer were adopted to analyze the trends and knowledge network of IA.

Results: A total of 5,406 publications related to IA from 2012 to 2021 were identified, increasing from 344 in 2012 to 762 in 2021. Siddiqui, AH from the USA contributed the most publications. Papers published in the journal World Neurosurgery ranked first in quantity, while Stroke ranked first for total citations and citations per publication. The top three prolific institutions were Capital Medical University, Mayo Clinic, and the University Department of Neurology Utrecht from 2012 to 2021. Moreover, the USA held the greatest share in the field, and China was almost on par with the USA due to its rapid growth. Specifically, the most frequently covered topics over the recent decade were subarachnoid hemorrhage, endovascular treatment (EVT), clipping, vascular disorders, flow diverter, stent, delayed cerebral ischemia, inflammation, and hemodynamics.

Conclusion: The contribution made by different countries, institutions, journals, and authors for IA research over the past decade was demonstrated in the paper. The main topics include the choice of EVT or surgical clipping, particularly the application of flow diverter and associated complications, while themes such as the etiopathogenetic features of IA (e.g., inflammation and hemodynamics) deserve more attention.

KEYWORDS

intracranial aneurysm, bibliometric analysis, CiteSpace, VOSviewer, flow diverter, mechanism

Introduction

Intracranial aneurysm (IA) is characterized by cerebral artery dilation, with a prevalence of 3–5% in the general population, and can be life-threatening if ruptured (1). With the advances in medical imaging and quality of life, patients increasingly are being screened for unruptured IA, which brings anxiety to patients and increases the health care burden on society (2). Recent research studies focused on the understanding and treatment of IA, which advanced the knowledge of IA; however, the exact pathophysiological mechanisms are largely unknown (3). The bibliometric analysis, which has gained popularity in recent years, is used to determine the contribution made by different authors, journals, institutions, and countries and discover the trend and hot spots in a particular field (4). The application of bibliometric analysis in the field of IA is fruitful. To be specific, Kiraz et al. (5) explored the papers related to IA from 1980 to 2020 analyzed by VOSviewer, with the research area limited to the category "neuroscience and neurology" and the search item "aneurysm" in the title, which excluded numerous IA-focused publications. Lu et al. (6) elaborated on the characteristics, content, and changes of the most prominent unruptured IA from the 100 most cited articles. Despite the ballooning biomedical scientific literature due to the advances in science and technology (7), the trend and knowledge map of the IA field almost remained untouched over the past decade. Therefore, this study adopted CiteSpace and VOSviewer, the widely accepted bibliometric analysis tools (8), to comprehensively explore the field of IA based on the retrieved publications from the Web of Science Core Collection (WoSCC) from 2012 to 2021, especially uncovering the following research questions (RQs) in the field of IA over the recent decade.

RQ1. What is the publication trend in the field of IA?

RQ2. What are the most influential articles and key authors, institutions, countries, and journals in this field?

RQ3. Who are the potential collaborators (authors, institutions, and countries/regions) in this field?

RQ4. What are the major themes and research frontiers in this field?

Methods

Search strategy

To avoid bias introduced by the database updates, a computerized search was performed in WoSCC (Thomson Reuters, New York, USA) from 1 January 2012 to 12 December 2021. The Science Citation Index-Expanded database contains indexed and peer-reviewed articles and basic information, including authors, affiliations, citations, and references. The literature search was carried out using the following items ("cerebral aneurysm*," "intracranial aneurysm*," or "cerebral aneurysm*") in the title to filter out studies that focused on IA. Two investigators (Qian Zhang and Ling Weng) were responsible for the database search and filtering, while a senior neurosurgeon (Jian Li) was responsible for any discrepancies.

Data extraction and bibliometric analysis

Bibliometric parameters, including title, keywords, journal, publication date, total citations, citations per publication, authors, institutions, and countries, were extracted, and were then imported into Microsoft Excel 2010 (Redmond, Washington, USA) for the analysis of contribution. VOSviewer (Leiden University, Leiden, the Netherlands) was adopted to visualize the mapping of coauthor-authorship, coauthor-institution, coauthor-country, coauthor-journal, and keywords co-occurrence. The node size in VOSviewer indicates the number of articles, while the width of links between the nodes indicates the cooperation strength (9). CiteSpace (Version 5.8. R1) was used to identify the keyword bursting and co-cited reference bursting to present the evolution of this domain (10).

The search only included documents published in English. Relative research interest (RRI) was defined as the number of publications about IA divided by the total number of publications per year in WoSCC (11).

Results

Overall characteristics

Figure 1 illustrates the 5,406 publications identified in the field of IA, most of which were original articles (n = 4,833), accounting for 89.4% of the total. The number of publications showed an upward trend, from 340 in 2012 to 762 in 2021, with a decline in 2020 (n = 703 publications). The total number of citations was 64,853, and the number of citations per publication was 12. A total of 99 countries/regions, 4,095 institutions, 19,436 authors, and 720 journals made their contributions to the field of IA. Figure 2 shows the countries that published the most papers (USA, China, and Japan) over the past 10 years.

Countries/regions

Figure 3A displays the top 10 productive countries/regions, with the USA taking the lead (1,625 publications; 27,580 citations). Next, VOSviewer was adopted to demonstrate the international collaborative map with the minimum publication set to 100. Finally, 14 countries met our criteria. The USA, China, Canada, Japan, and Germany presented as the center node. As seen in Figure 3B, the USA had the highest degree of

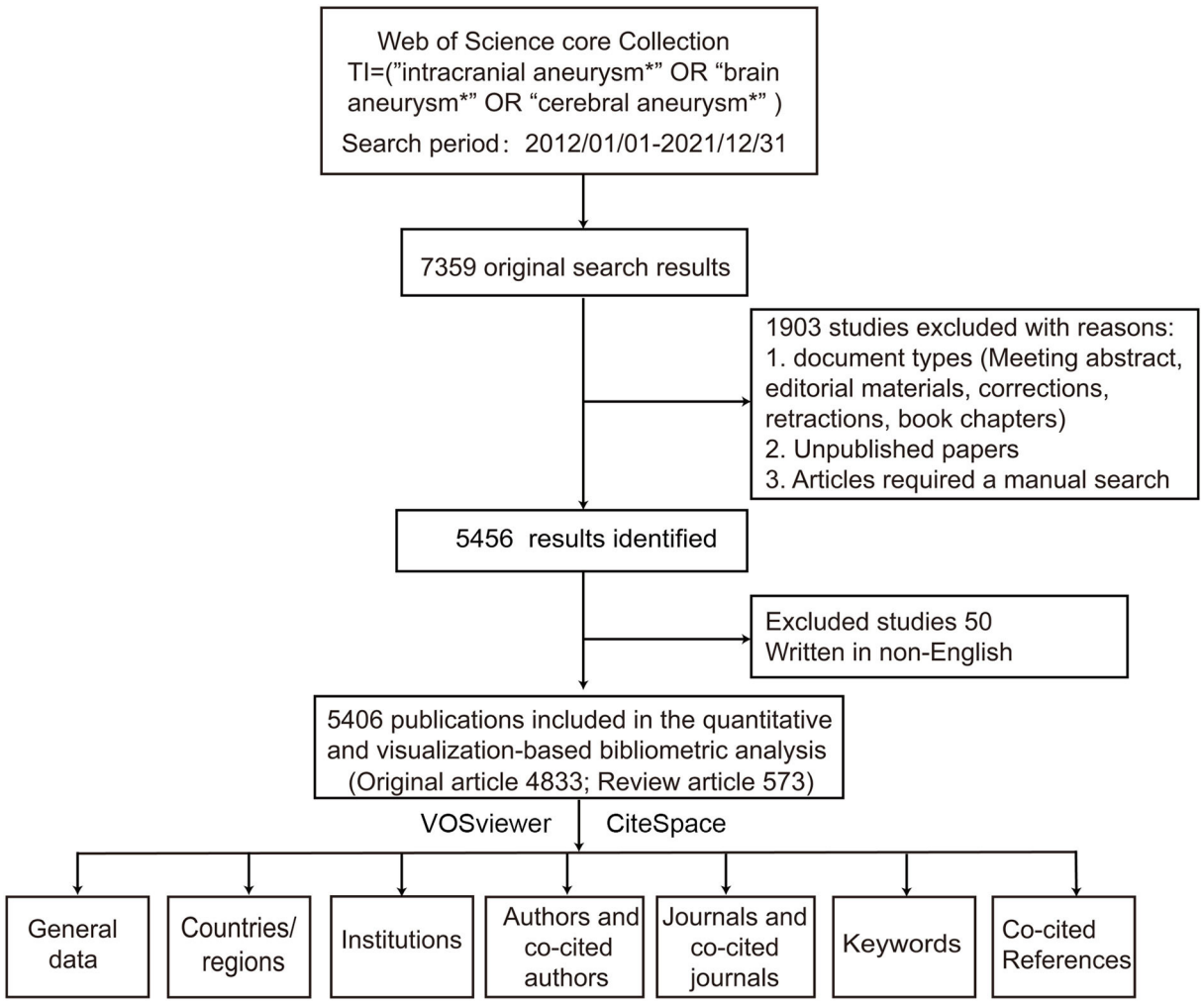


FIGURE 1
A flowchart of data screening and bibliometric analysis.

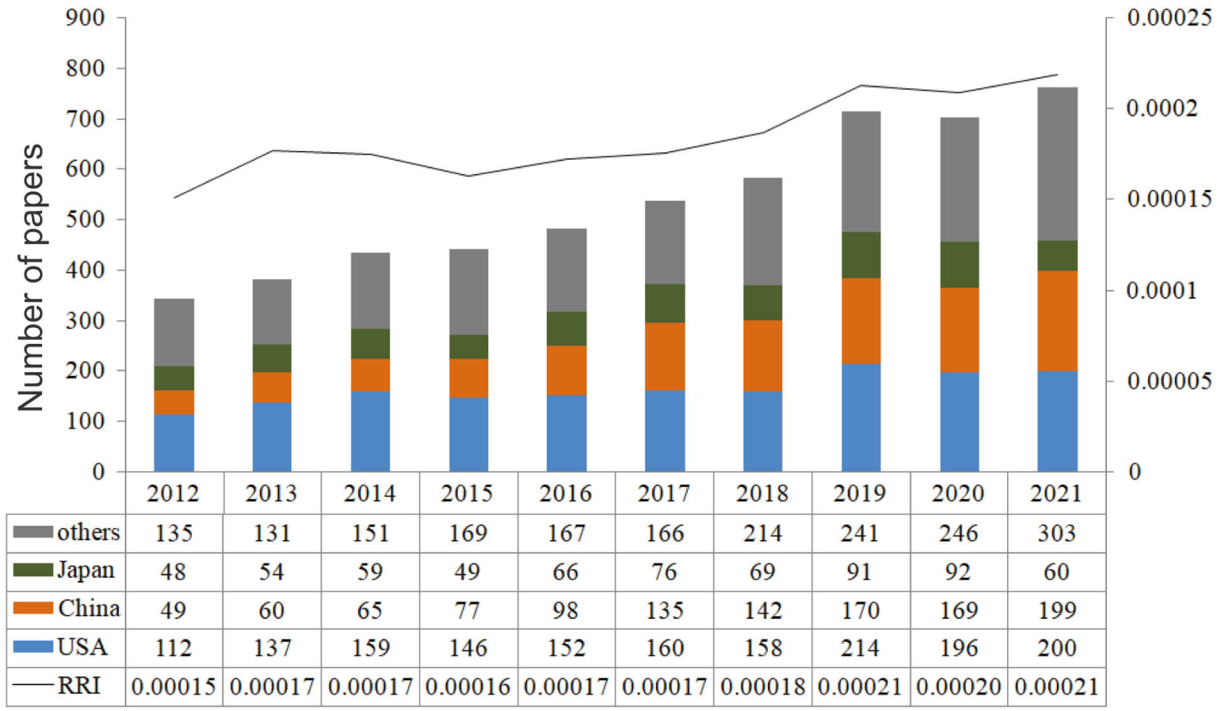
cooperation with total link strength (TLS = 629). China (TLS = 98), Canada (TLS = 76), and Japan (TLS = 72) were the top three countries that had closer academic cooperation with the USA.

Institutions

Figure 4A shows the top 10 institutions, five of which were located in the USA. Capital Medical University ranked the first in the number of publications (China, n = 211), followed by Mayo Clinic (the USA, n = 164) and the University of California, San Francisco (the USA, n = 89). In terms of total citations and citations per publication, Mayo Clinic (n = 4,005; 24.4) ranked the first, followed by the University of Helsinki (n = 2,932; 37.6), and the University of Iowa (n = 2,833; 36.3). Figure 4B presents the VOSviewer results that visualized the cooperation between institutions, which show that 51 institutions with more than 30 published papers were selected for analysis, whose cooperation was distinctly geographically distributed. Mayo Clinic performed the strongest cooperation with 186 TLS, followed by Capital Medical University (TLS = 170) and the University of Iowa (TLS = 161).

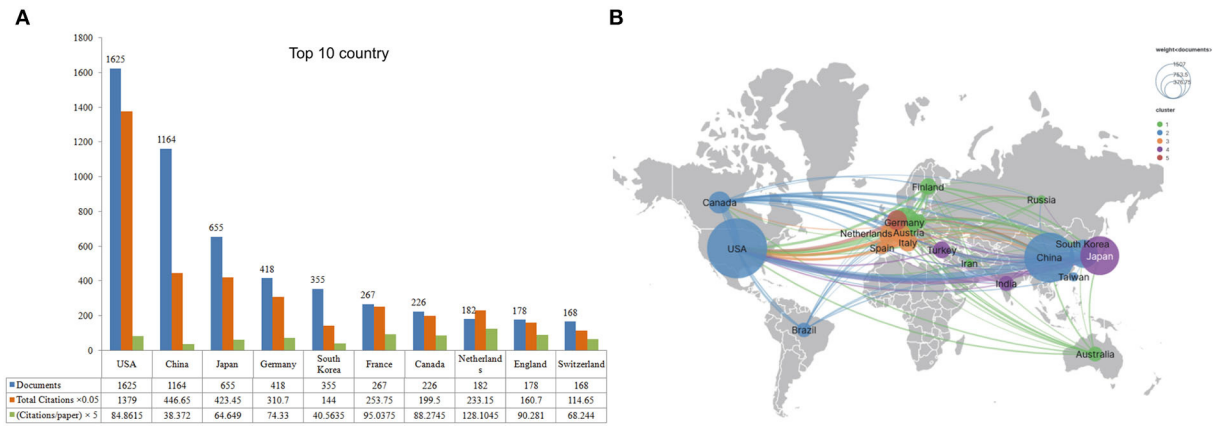
Journals and co-cited journals

The VOSviewer was used to perform a co-cited journal analysis to determine the most active and influential journals in the field of IA. A co-cited journal refers to a journal that has been cited by other journals in the same field. Table 1 describes the top 10 productive journals and co-cited journals, the former of which was led by World Neurosurgery with 606 publications (11.2%), Journal of Neurointerventional Surgery with 336 articles (6.2%), and American Journal of Neuroradiology with



	2012	2013	2014	2015	2016	2017	2018	2019	2020	2021
others	135	131	151	169	167	166	214	241	246	303
Japan	48	54	59	49	66	76	69	91	92	60
China	49	60	65	77	98	135	142	170	169	199
USA	112	137	159	146	152	160	158	214	196	200
RRI	0.00015	0.00017	0.00017	0.00016	0.00017	0.00017	0.00018	0.00021	0.00020	0.00021

FIGURE 2
The number of publications of the top three prolific countries across time, and the time course of relative research interest of IA.



	USA	China	Japan	Germany	South Korea	France	Canada	Netherlands	England	Switzerland
Documents	1625	1164	655	418	355	267	226	182	178	168
Total Citations ×0.05	1379	446.65	423.45	310.7	144	253.75	199.5	233.15	160.7	114.65
(Citations/paper) × 5	84.8615	38.372	64.649	74.33	40.5635	95.0375	88.2745	128.1045	90.281	68.244

FIGURE 3
The top 10 prolific countries/regions and inter-national collaboration network of IA research from 2012 to 2021. **(A)** The number of publications, citations (×0.05), and citations per paper (×5). **(B)** The collaborative map of countries for IA. Node size indicates the number of articles produced. The width of links indicates the cooperation strength.

255 articles (4.7%), while the latter by Stroke (16,447 co-citations), Neurosurgery (14,226 co-citations), and American Journal of Neuroradiology (14,069 co-citations).

Authors and co-authors

Table 2 lists the top 10 most productive authors and most co-cited authors (influential research teams and potential research partners), most of whom are from the USA. Siddiqui AH ($n = 67$ publications) from Suny Buffalo Department of Neurosurgery (USA) and Yang Xinjian ($n = 61$ publications) from Capital Medical university (China) and Gabriel Rinkel JE ($n = 59$ publications) from University Department of Neurology Utrecht (Netherlands), were the top three prolific authors between 2012 and 2021. A co-cited author was defined as an author who was co-cited in publications, and co-citation directly reflects the extent of an author's contribution. Wiebers D, Chalouhi

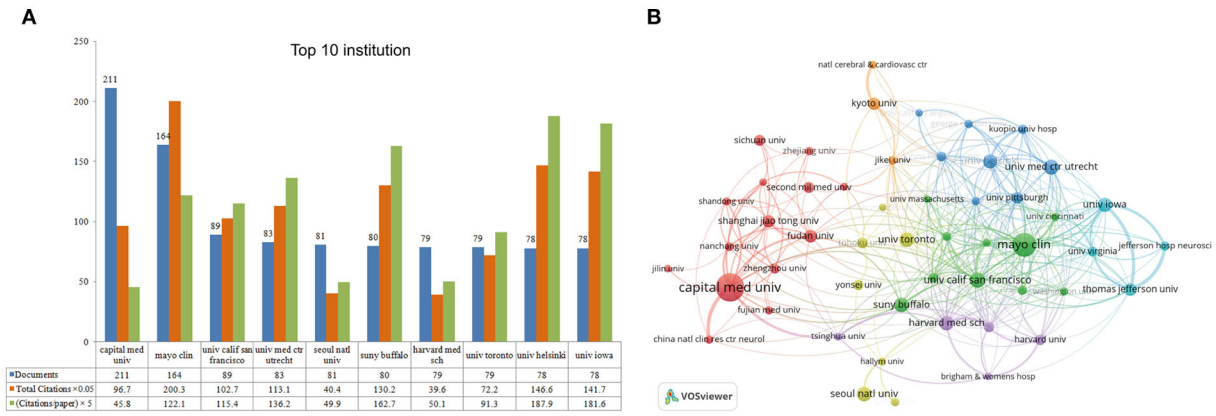


FIGURE 4
The top 10 most productive institutions and inter-institutional cooperation of IA research from 2012 to 2021. **(A)** The number of publications, citations (×0.05), and citations per paper (×5). **(B)** The cooperative map of institutions for IA visualized by VOSviewer. Node size indicates the number of articles produced. The width of links is positively associated with the cooperation strength.

TABLE 1 The top 10 prolific journals and co-cited journals on IA research between 2012 and 2021.

Rank	Journal	Publications	Citations	Citations/paper	IF*	Co-cited journal	Co-citations	IF*
1	World Neurosurg	606	4,289	7.0776	2.104	Stroke	16,447	7.914
2	J Neurointerv Surg	336	5,291	15.747	5.836	Am J Neuroradiol	14,266	3.825
3	Am J Neuroradiol	255	7,423	29.1098	3.825	Neurosurgery	14,069	4.654
4	J Neurosurg	216	3,748	17.3519	5.115	J Neurosurg	13,245	5.115
5	Neurosurgery	196	4,368	22.2857	4.654	J Neurointerv Surg	5,261	5.836
6	Interv Neuroradiol	180	1,030	5.7222	1.61	World Neurosurg	3,911	2.104
7	Stroke	142	6,430	45.2817	7.914	Acta Neurochir	3,045	2.216
8	Acta Neurochir	127	1,093	8.6063	2.216	Neuroradiology	3,033	2.804
9	J Clin Neuroscience	119	1,041	8.7479	1.961	Lancet	2,913	79.324
10	Neuroradiology	96	1,801	18.7604	2.804	Radiology	2,364	11.104

IF*:impact factor (2020).

N, and Laurent P were the three most co-cited authors in this field. Figure 5A depicts the author cooperative map obtained from VOSviewer, where Hernesniemi J and Chalouhi N were colored dark blue (the average year of publication in 2014–2016), indicating that they were active in the early phase, while Xinjian Yang, Jianmin Liu, Aihua Liu, and Shuo Wang were colored yellow-green or yellow (the average year of publication in 2017–2018), suggesting their active role in the late phase in the past 10 years. Figure 5B displays the top co-cited authors who received more than 300 co-citations.

Keywords

The keyword co-occurrence network was adopted to describe the knowledge map and frontier topics in a field. Similar keywords were merged using a thesaurus (Supplementary Table S1), for example, brain aneurysm and cerebral aneurysm were replaced by IA. In total, 55 keywords appearing at least 40 times were collected and grouped into the following clusters, which were named based on their respective characteristics. As seen in Figure 6A, cluster# 1 (red and green) represented the research on the clinical treatment of IA, with "endovascular treatment, clipping, coiling, stent, and flow diverter" serving as the most frequent keywords; cluster# 2 (blue) indicated research on the mechanisms of IA, with the most frequent keywords including "hemodynamics, computational fluid dynamics, inflammation, and rupture;" cluster# 3 (yellow) represented research on complications of IA, with most frequent keywords including "subarachnoid hemorrhage (SAH), delayed cerebral ischemia, and cerebral vasospasm"; cluster# 4 (purple) indicated imaging research in IA, whose most frequent keywords covered "magnetic resonance angiography, CTA, and DSA." In addition, CiteSpace was employed to visualize the distribution of keywords in different periods (Figure 6B), which showed that the topics

TABLE 2 Top 10 prolific authors and co-cited authors on IA research from 2012–2021.

Rank	Author	Publications	Citations	Citations/ paper	Country	Co-cited author	Co-citations	Country
1	Siddiqui, Adnan H.	67	1,335	19.9	USA	Wiebers, D	1,210	USA
2	Yang, Xinjian	61	7,93	13.0	China	Chalouhi, N	1,201	USA
3	Rinkel, Gabriel J. E.	59	1,339	22.7	The Netherlands	Pierot, L	1145	France
4	Jabbour, Pascal	55	1,774	32.3	USA	Cebral, Jr	1,028	USA
5	Chalouhi, Nohra	54	2,513	46.5	USA	Brinjikji, W	929	USA
6	Lanzino, Giuseppe	53	1,353	25.5	USA	Aoki, T	850	Japan
7	Starke, Robert M.	52	1,768	34.0	USA	Juvela, S	850	Finland
8	Li, Youxiang	47	661	14.1	China	Molyneux, Aj	735	England
9	Meng, Hui	46	961	20.9	USA	Vlak, Mhm	682	The Netherlands
10	Ogilvy, Christopher S.	41	876	21.4	USA	Raymond, J	644	Canada

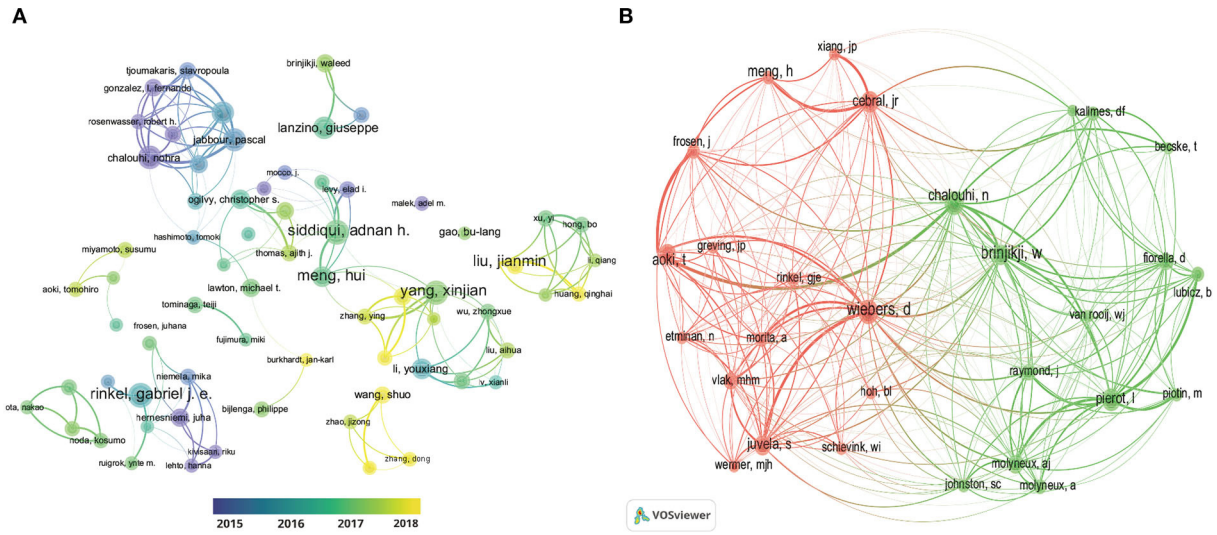


FIGURE 5
Author cooperation network and co-cited author network on IA studies from 2012 to 2021. **(A)** Collaborative map of prolific authors for IA studies from 2012 to 2021. **(B)** Co-cited authors of IA studies. Node size indicates the number of articles produced. The distance between any two nodes positively associates with the cooperation strength.

related to "neuroform stent, detachable coil, and reconstruction" were focused on the early stage of the recent decade, while themes like "flow diversion, prediction, delayed cerebral ischemia, age, growth, predictor, safety, and unruptured cerebral aneurysm" acquired more attention between 2018 and 2021.

Top cited articles and co-cited references

Table 3 lists the top 10 cited articles, involving six clinical research, two guidelines, and two reviews regarding the pathology and biology of IA. Morita et al. (12) published the most cited article in 2012 in the New England Journal of Medicine with 765 total citations, entitled *The Natural Course of Unruptured Cerebral Aneurysms in a Japanese Cohort*. This study conducted 11,660 aneurysm-years of follow-up on 5,720 patients with newly identified unruptured IA in Japan. It also found that the annual rupture rate was 0.95% in unruptured IA, and the rupture rate of unruptured IA is positively related to aneurysm size, daughter sac, and posterior circulation. Co-cited references were references co-cited by other literature studies (13). We identified 55,431 co-cited references from 5,406 publications, among which 65 references co-cited over 100 times were utilized to form a co-citation network. According to Figure 7A, the most-cited article (n = 826 co-citations) was entitled *Unruptured*

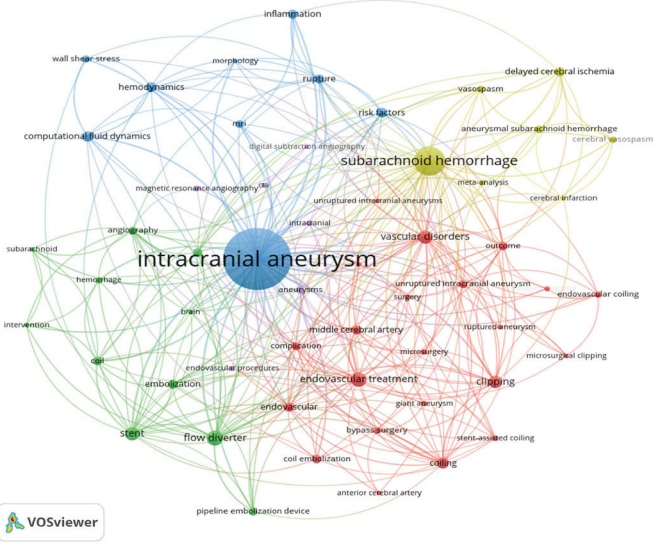


FIGURE 6
Analysis of keywords related to IA studies from 2012 to 2021. **(A)** The keyword co-occurrence network of IA studies in the recent 10 years. The keywords clustered into five groups according to their color. Large nodes represent keywords with high frequency; **(B)** The top 25 keywords with the strongest citation bursts on IA studies from 2012 to 2021 were displayed by CiteSpace. The red segment on the blue line denotes the burst duration.

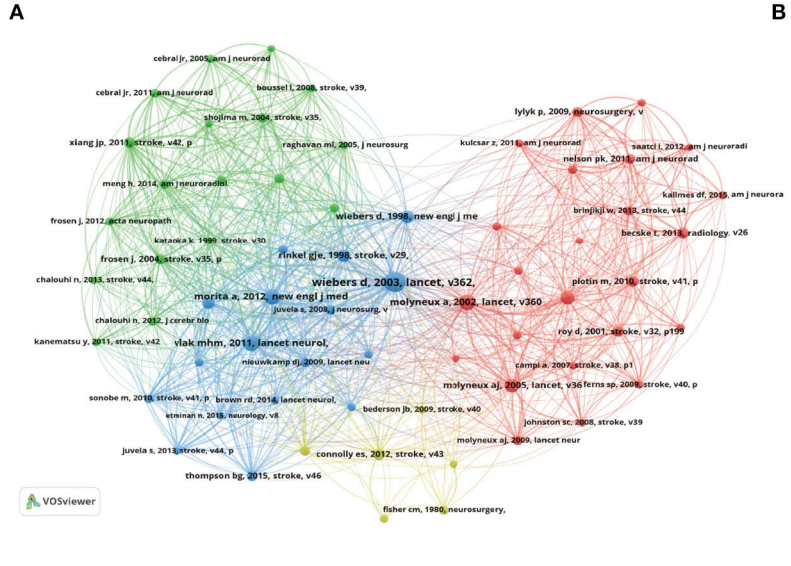


FIGURE 7
(A) The co-citation references network on IA studies from 2012 to 2021. **(B)** The top 24 references with the strongest citation bursts on IA studies from 2012 to 2021 were displayed by CiteSpace. The blue line represents the time from its first appearance to 2021, and the red line represents the burst time.

TABLE 3 The top 10 most cited publications on intracranial aneurysm research from 2012 to 2021.

Title	Author	Journal	Year	Total citations
The Natural Course of Unruptured Cerebral Aneurysms in a Japanese Cohort	Morita, A.	New England Journal Of Medicine	2012	762
European Stroke Organization Guidelines for the Management of Intracranial Aneurysms and Subarachnoid Haemorrhage	Steiner, T.	Cerebrovascular Diseases	2013	529
Development of the PHASES score for prediction of risk of rupture of intracranial aneurysms: a pooled analysis of six prospective cohort studies	Greving, JP.	Lancet Neurology	2014	524
Endovascular Treatment of Intracranial Aneurysms With Flow Diverters A Meta-Analysis	Brinjikji, W.	Stroke	2013	505
High WSS or Low WSS? Complex Interactions of Hemodynamics with Intracranial Aneurysm Initiation, Growth, and Rupture: Toward a Unifying Hypothesis	Meng, Hui.	American Journal of Neuroradiology	2014	377
Guidelines for the Management of Patients With Unruptured Intracranial Aneurysms A Guideline for Healthcare Professionals From the American Heart Association/American Stroke Association	Thompson, B.G	Stroke	2015	371
Treatment of Intracranial Aneurysms Using the Pipeline Flow-Diverter Embolization Device: A Single-Center Experience with Long-Term Follow-Up Results	Saatci, I.	American Journal of Neuroradiology	2012	302
Biology of intracranial aneurysms: role of inflammation	Chalouhi, N	Journal of Cerebral Blood Flow And Metabolism	2012	288
The durability of endovascular coiling vs. neurosurgical clipping of ruptured cerebral aneurysms: 18 year follow-up of the UK cohort of the International Subarachnoid Aneurysm Trial (ISAT)	Molyneux, A.J.	Lancet	2015	281
Pipeline embolization device (PED) for neurovascular reconstruction: initial experience in the treatment of 101 intracranial aneurysms and dissections	Fischer, S.	Neuroradiology	2012	280

Intracranial Aneurysms: Natural History, Clinical Outcome, and Risks of Surgical and Endovascular Treatment and was published by Wiebers et al. (1) in Lancet. Given that the reference burst in CiteSpace reflected researchers' interest in a certain article during a specific time period (10), we identified 24 references that had the strongest citation bursts, with the burst duration preset to be 5 years (Figure 7B). Of which, Molyneux AJ, 2009, LANCET NEUROL, V8, P427 (14) had the highest burst strength (n = 16.67 citation bursts), and articles with citation bursts ending in 2021 were as follows: Spetzler RF, 2015, J NEUROSURG, V123, P609 (15), Kallmes DF, 2015, AM J NEURORADIOL, V36, P108 (16), Frosen J, 2014, TRANSL STROKE RES, V5, P347 (17), Li MH, 2013, ANN INTERN MED, V159, P514 (2); and Pierot L, 2013, STROKE, V44, P2046 (18).

Discussion

This study employed WoSCC to search for IA-related articles over the recent decade and revealed an upward trend in article quantity between 2012 and 2021. However, the slight decrease in 2020 is noticeable. This is because the COVID-19 pandemic occurred in 2019, which lowered patients' visits to medical facilities due to lockdown and social isolation, and paused clinical and basic research.

The top three countries with high annual production in 2012 are the USA, Japan, and China (19). The growing annual production of China nearly equaled that of the USA in 2021 (199 and 200), which comes down to the following reasons. First, there is a high possibility that more patients are suffering from IA in China because of its largest and most aging population, as well as the high incidence of unruptured IA among Chinese adults aged 35–75 (7%) (2). Second, the number of neurologists and neurosurgeons in China increased sharply in recent years. Data from the World Federation of Neurosurgical Societies (WFNS) showed that China was the largest group of neurosurgeons (n = 11,000) in the world since 2016 (20), indicating that more researchers are devoted to the IA field. Third, more government funding and public attention to IA in China were found with the continuous growth in medicine and life quality. The increasing number of papers in China, however, does not necessarily stand for highly influential papers, researchers, and institutions. For example, only one Chinese

institution is listed in the top 10 most productive institutions, and two Chinese researchers occupy the top 10 most productive authors. Instead, from a macroscopic viewpoint, China's rank has been raised from the 8th (1991–2012) (19) to the 2nd (2012–2021) in total citations, which indicates significant progress in the last decade.

Unsurprisingly, the USA dominated the field, regardless of publications, total citations, prolific researchers, and institutions. As the world's largest economic entity, the USA is equipped with advanced scientific equipment, professional researchers, and the essential federal funds for scientific research; those factors contributed to its dominant role in the field of IA. The same is true for other fields, such as lumbar spinal stenosis (21) and adolescent idiopathic scoliosis (22). With regards to cooperation between countries, extensive collaborative relationships between the USA, China, Canada, Japan, and some European countries were observed, which validated their significant contributions and probability of producing influential IA-related works in the future.

Leading authors, institutions, and journals provided essential information about a certain field. Table 2 demonstrates the top 10 prolific authors and co-cited authors from 2012 to 2021, who are influential persons leading IA research and accelerating the progress in this field. In addition, the cooperative network of the authors visualized by VOSviewer (Figure 5A) provided information about the productivity and active period of the authors. Several Chinese researchers (e.g., Xinjian, Yang, Jianmin, Liu, Aihua, and Liu) played an active role in the late phase of the recent decade. Such dynamic change in researchers indirectly reflected China's growing position in the field of IA. In terms of journals, eight journals were found in both the top 10 list and the co-cited list, which deserves more attention among researchers due to the influential leading articles that may be published in them. With regard to institutions, Capital Medical University produced the highest number of publications, Mayo Clinic held the top spot in total citations over the recent decade, and other institutions included in the top 10 were engaged in the study of IA and served as potential partners.

A quick overview of a certain field can be realized through keyword analysis and highly cited articles (23). The major topics obtained from VOSviewer author keyword co-occurrence revealed the structure of the IA research knowledge base. Specifically, the three largest clusters almost represented the major topics in this field.

Cluster# 1 (red and green in Figure 6A): *research on the clinical treatment in IA*. Over the past decade, there has been much effort made to identify the best treatment for ruptured and unruptured IA, such as clipping or endovascular treatment (EVT), coiling, or stenting. Technological innovations and advancements in the neuroendovascular space shifted the standard for treating IA from open surgical approaches to endovascular therapies (24). EVT was mentioned in four articles in the top 10 most-cited articles and three co-cited references with the highest citation bursts (ending in 2021). For example, Pierot et al. (18) comprehensively reviewed the status of EVT for IA in 2013. Spetzler et al. (15) reported the 6-year results of the barrow ruptured aneurysm trial (BRAT), proving EVT of coil embolization's superiority to surgery and the higher retreatment rate in the coiling embolization group. Kallmes et al. (16) analyzed the neurological complication rate after pipeline embolization device placement and validated the higher rate of procedure-related morbidity and mortality in posterior circulation IA and giant IA. More importantly, the references with the highest citation bursts over the recent decade also described the detailed outcomes of endovascular coiling vs. clipping, supporting the higher risk of recurrent bleeding and a significantly lower 5-year death rate in the coiling group than in the clipping group (14). Specifically, the green cluster focused mainly on the flow diverter, and the keyword bursts in CiteSpace also showed that flow diversion ended in 2021, suggesting that the flow diverter received huge attention from IA researchers in recent years. In addition, three in five co-cited references published in 2021 discussed the application of flow diverter in IA (25–27). The widespread clinical use of flow diverters also brought more attention to their complications and limitations, such as delayed rupture (28, 29), thromboembolic complications, the need for prolonged antiplatelet therapy (30), and in-stent stenosis (31, 32). Therefore, the application of flow diverter in different types of IA should be expanded in future research (e.g., fusiform aneurysm and dissecting aneurysm), reducing the risk of complications.

Cluster# 2 (purple in Figure 6A): *mechanism research in IA*. The etiopathogenetic features of IA have also attracted much interest, such as inflammation and hemodynamics. Clinically, it is almost unpredictable whether and when rupture will happen as the majority of IAs are silent (3). Furthermore, the progression and rupture of IA were highly correlated with hemodynamic stress and inflammation (33). Therefore, studies of gene expression, hemodynamic characterization, and diagnostic biomarkers were active in recent years. Despite the absence of basic research among the most cited articles, several highly cited reviews should be noted. For instance, Meng et al. (34) reported that different hemodynamics, such as low wall shear stress or high wall shear stress, can crosstalk with different types of inflammable cells or vascular mural cells, mediating the initiation, growth, and rupture of IA. Chalouhi et al. (35) comprehensively discussed the role of inflammation in the biology of IA. Frösen et al. (17) highlighted the crucial role of smooth muscle cells (SMCs) in the formation, degeneration, and rupture of IA. Besides, the authors pointed out that more functioning SMCs or neointimal cells in the wall of the IA can compensate for the constant injury caused by hemodynamic stress and protease activity induced by inflammable cells. Although there is still a long way to go before these findings can be used in clinics,

we also hope for more breakthroughs in basic research in the future.

Cluster# 3 (purple in Figure 6A): *complications in IA* (e.g., aneurysmal subarachnoid hemorrhage (aSAH), delayed cerebral ischemia (DCI), and vasospasm) also received considerable attention. Cerebral vasospasm is common and leads to DCI. Hansen-Schwartz et al. reported that DCI should be most blamed for poor outcomes of patients who survive the initial strike of a ruptured IA (36). Thus, extensive studies investigating the biomarkers for DCI in recent 10 years, such as Al-Mufti et al. (37), reported that white cell counts over 12.11×0^9/L were the strongest predictor of DCI. Suzuki et al. (38) reported that higher pH in cerebrospinal fluid (CSF) and lower partial pressure of carbon dioxide (PCO_2) in CSF acted as a new potential contributor to the development of DCI. Other studies also summarized the role of genetic polymorphisms (39), imaging markers (40), clinical features (41), and serum biomarkers (42–44) in predicting DCI. Such results, however, were primarily obtained by single-center studies, failing to consider two essential attributes of a clinical biomarker, i.e., practicality and robustness. As a result, future prospective studies with multiple centers and larger cohorts should be conducted to validate these clinical biomarkers.

There are several limitations to this study.

The first is the inevitable omittance of publications concerning aSAH or several IA subtypes (e.g., carotid aneurysm, middle cerebral artery aneurysm, basilar aneurysm, anterior communicating aneurysm, etc.) because of the search term "intracranial aneurysm or cerebral aneurysm or brain aneurysm" in the title used to sort relevant articles. The second limitation is the failure to include other widely-accepted databases, such as PubMed, Scopus, and Google Scholar. This is because WoSCC provides the most comprehensive information regarding authors, institutions, and, especially, cited references, which best fit the data format of VOSviewer and CiteSpace. Third, the number of citations and H-index are influenced by time and remain controversial as a comprehensive indicator of the quality of one paper or the author (45). Fourth, the exclusion of articles written in languages other than English resulted in a language bias. Finally, the records update in WoSCC may result in retrieving discrepancies. However, the impact of these new publications was thought to be insignificant on the findings because of their low citations and our huge amount (thousands) of data. It is hypothesized that the bibliometric analysis will provide valuable insights into key points of IA research and future trends for researchers who are already engaged in the field or about to begin.

Conclusion

In summary, the current research provides a comprehensive analysis of the publications of IA from 2012 to 2021. The main topic of IA research is the choice of EVT or surgical clipping, particularly the application of flow diverter and its complications. More attention should be paid to research on the etiopathogenesis of IA from the perspective of inflammation-related Genes and hemodynamics.

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

QZ: conceptualization, methodology, funding acquisition, data curation, writing original draft, study findings, and read and approved the final version before submission. LW: data curation, writing review and editing, study findings, and read and approved the final version before submission. JL: conceptualization, methodology, supervision, critical review of the manuscript, study findings, and read and approved the final version before submission. 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.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2022.953285/full#supplementary-material

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Retreatment with a flow diverter for recurrent blood blister-like aneurysms after embolization: A single-center case series

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Background and purpose: Treatment of blood blister-like aneurysms (BBAs) has been a significant challenge mainly due to their high recurrence rate even after stent-assisted coiling (SAC) embolization. This study aims to evaluate the safety and efficacy of treating recurrent BBAs after SAC with a flow diverter (FD).

Methods: A retrospective series of patients with recurrent BBAs who underwent the retreatment with the FD from June 2018 to December 2021 was included to analyze perioperative safety and immediate postoperative and follow-up outcomes.

Results: The study enrolled 13 patients with recurrent BBAs previously treated with SAC. Within previous stents, an FD was deployed for retreatment, including eight Tubridge FDs and five PEDs. The time interval between initial treatment and FD implantation was 14–90 days. A total of 11 cases were treated with a single FD alone; two cases were treated with further endovascular coiling embolization, followed by FD implantation. The angiographic follow-up (6–12 months) was available in 12 patients, and all 12 recurrent BBAs were completely occluded. No perioperative complication was detected, and no rebleeding was found during the clinical follow-up (6–36 months).

Conclusion: The use of the FD to manage recurrent BBAs after SAC is technically feasible, safe, and effective. The key to the success of the procedure is to ensure that the FD stent is fully open and has good apposition with the previously implanted stent.

KEYWORDS

intracranial aneurysm, recurrent blood blister-like aneurysms, endovascular treatment, flow diverter, stent-assisted coiling

Introduction

Blood blister-like aneurysms (BBAs) normally refer to small, bleb-like and unidentifiable neck lesions without the internal elastic lamina, vascular intima, and media. Sometimes appearing as only a fragile fibrous layer usually at the anterior or anteromedial wall of the supraclinoid segment of the intracranial carotid artery (ICA),

BBA makes up 0.3–1.7% of all intracranial aneurysms and 0.5–2% of ruptured aneurysms (1). Due to its fragile state and difficult morphology, treatments including surgical clipping and endovascular treatment of such lesions have proven to be intractable (2). The overlapped stent-assisted coiling (SAC) technique for the treatment of BBAs may reduce the recurrence rate to an extent, but recurrence rates still range from 5.6 to 22.9% (3, 4). The optimal treatment of recurrent BBAs, including the timing, antiplatelet drugs, and treatment strategies (SAC, flow diverter, etc.), has not yet been determined.

A flow diverter (FD) is used in the treatment of BBAs and is associated with more favorable angiographic outcomes but also with complications and clinical outcomes, compared with SAC (5). However, for previously stented aneurysms, FD treatment had been reported to be less effective and prone to complications (6). Whether the effectiveness of FD implantation for recurrent BBAs after SAC is truly as poor as that of saccular aneurysms needs further research. Hence, we would like to report our initial experience in the retreatment of recurrent BBAs with FDs.

Materials and methods

Study design and patients

We have reviewed all patients with recurrent BBAs who were previously treated with SAC and received the retreatment with FDs at our institution between June 2018 and December 2021. A total of 13 patients with 13 recurrent BBAs were identified. All of these patients were initially treated at other hospitals. The first angiographic follow-up was performed within 2 weeks to 1 month after the initial treatment. The patients with major recurrence were referred to our hospital for further treatment. In total, two neurointerventionists assessed the surgical notes, medical charts, and radiologic images of the patients. Moreover, the patients' demographics, aneurysm characteristics, complications, and follow-up data were evaluated.

Procedure and perioperative medication

All procedures were conducted under general anesthesia *via* a transfemoral approach using biplane angiographic equipment. Heparin (4,000–5,000 U) was intravenously infused after the femoral sheath was placed, with the goal of maintaining the activated clotting time at 2.0–2.5 times as baseline during the procedure. A 6-F guiding catheter was introduced into the distal ICA. On the basis of the images generated from the reconstruction, the working projections were chosen for the procedure. Over a J-shaped tip microwire, a T-track microcatheter (0.029-inch diameter, MicroPort, Shanghai, China) or Marksman microcatheter (Medtronic, Irvine, CA) was passed through the previous stents to the M2 segment of the middle cerebral artery. Then, different position projections or VasoCT/XperCT were performed to ensure that the microcatheter was positioned completely within the previous stents. According to the measured data and the size of previous stents, an appropriate FD stent was selected. The FD was navigated and deployed across the dissecting segment using a standard push-and-pull technique in all cases. After deployment, angiography was used to document the correct expansion of the device. All patients underwent postoperative CT straight to detect any possible intracranial hemorrhage.

Dual antiplatelet drugs (100 mg/day aspirin plus 75 mg/day clopidogrel or 90 mg two times/day ticagrelor) were administered for at least 3 days before the procedure. All patients were administered aspirin (100 mg/day) and clopidogrel (75 mg/day) postoperatively. Postoperative DSA evaluation was performed at 2 weeks to 1 month, and the antiplatelet protocol was adjusted according to the angiographic results. For patients with aneurysm occlusion, they were administered with aspirin (100 mg/day) and clopidogrel (75 mg/day) for 6 weeks, followed by aspirin alone (100 mg/day) indefinitely.

Angiographic assessment and angiographic and clinical follow-up

The immediate angiographic results of BBAs after initial SAC were assessed using the Raymond scale (7): Raymond 1 shows complete occlusion, Raymond 2 residual neck, and Raymond 3 residual aneurysm. The immediate angiographic results of recurrent BBAs after the retreatment with the FD and follow-up outcomes were classified into five categories according to the Kamran–Byrne scale (8): Grade 0, which denotes no change; grade 1 (residual contrast filling >50% of the pretreatment aneurysm volume), grade 2 (residual contrast filling <50% of the pretreatment aneurysm volume), grade 3 (residual filling confined to the neck region), and grade 4 (complete obliteration). Recurrence was defined as increased contrast material filling the aneurysm sac compared with the immediate degree of embolization. The angiographic follow-up was generally performed at 1, 3, and 6 month post-treatment using DSA, and then yearly thereafter with DSA/CTA. The clinical outcome was assessed using the modified Rankin Scale (mRS) at the latest follow-up.

Results

Baseline characteristics

A total of 13 patients (all female) with 13 BBAs were identified. These patients had a mean age of 48.9 (ranging from 42 to 55) years. All patients had a prior history of

subarachnoid hemorrhage (Hunt–Hess grade from 1 to 3). All 13 BBAs were located at the supraclinoid segment (eight located at the C6 segment and five at the C7 segment) of the ICA, with 11 at the right ICA, while other two at the left. Overall, four patients were treated with a single LVIS stent (MicroVention Terumo, California, USA) or Enterprise stent (Codman&Shurtleff, Massachusetts, USA), four patients were treated with overlapped LVIS stents, four patients were treated with overlapped LVIS combined with Enterprise stents, and one patient with overlapped LVIS and LEO Plus stents (Balt, Montmorency, France). Immediate angiographic results after initial SAC showed Raymond 1 in three aneurysms, Raymond 2 in six aneurysms, and Raymond 3 in four aneurysms. After the initial treatment, no patient suffered from rebleeding. All recurrent BBAs were confirmed by DSA and referred to our hospital for further treatment, and the time interval between initial treatment and the first angiography follow-up was 14–90 days. The data are summarized in Table 1.

TABLE 1 Clinical data of all the patients.

Variable	Values*
Age (years)	48.9 (42–55)
Initial H-H Grade	
1	2
2	6
3	5
4	–
5	–
Location	
Right ICA	11 (84.6%)
Lift ICA	2 (15.4%)
Initial treatment strategy	
Single LVIS or Enterprise+Coils	4
Overlapped LVIS+Coils	4
LVIS+Enterprise+Coils	4
LVS+LEO plus+Coils	1
Initial Raymond grade	
1	3
2	6
3	4
Initial angiographic FU (days)	49.3 (14–90)
FD model	
Tubridge	8
Pipeline embolization devices	5
Postoperative K-B scale	
0	7
1	3
2	1
3	2
Angiographic follow-up (months)	7.6 (1–12)
Angiographic follow-up K-B scale	
0	13
1	–
2	–
3	–

H-H Grade, Hunt-Hess grade; ICA, intracranial carotid artery; FU, follow up; FD, flow diverter; K-B scale, Kamran-Byrne scale.
*Values are mean (minimum-maximum value) or number of patients (percentage).

Technical success and immediate results

The FD deployment was successful among all 13 patients, including eight Tubridge FDs (MicroPort Medical Company, Shanghai, China) and five pipeline embolization devices (PEDs; Medtronic, Irvine, CA). In all, 11 recurrent BBAs were treated by a single Tubridge FD or PED alone. Due to the obvious recurrence of the BBAs and the large size of the aneurysms, the remaining two aneurysms were first treated with further intrasaccular coiling, followed by Tubridge FD deployment. Based on the size of recurrent BBA, four and three coils were deployed during the procedure, respectively. All 13 FD stents were documented as being good wall appositions. In four patients, the FD was completely located inside the previous LVIS stent (not beyond the distal and proximal ends), and for the other nine patients, the FD stents were deployed to span the entire length of the LVIS or Enterprise stent. According to the Kamran–Byrne scale, immediate postoperative angiograms showed grade 0 in seven aneurysms, grade 1 in three aneurysms, grade 2 in one aneurysms, and Grade 3 in two aneurysms, following the retreatment, and the parent arteries and the covered branches by FD stents were all patent (Table 1).

Angiographic and clinical follow-up

Of all 13 patients, the angiographic follow-up (1–12 months) was available for 12 patients. It has showed that aneurysms of 10 patients completely occluded 1 month after the retreatment (Figure 1), whereas two aneurysms remained stable at the 1-month follow-up check. Dual antiplatelet therapies have therefore been changed to aspirin alone, and these aneurysms were completely occluded 2 months later. CTA showed that the two aneurysms had no sign of recurrence 1 year after the procedure. The parent arteries were all patent without any in-stent stenosis. The clinical follow-up at 6–36 months among all patients showed neither hemorrhagic nor thromboembolic events. The mRS score was 0 in all patients at the latest follow-up (Table 1).

Discussion

BBAs are rare vascular lesions and therapeutic challenges. Although several surgical strategies or endovascular treatments,

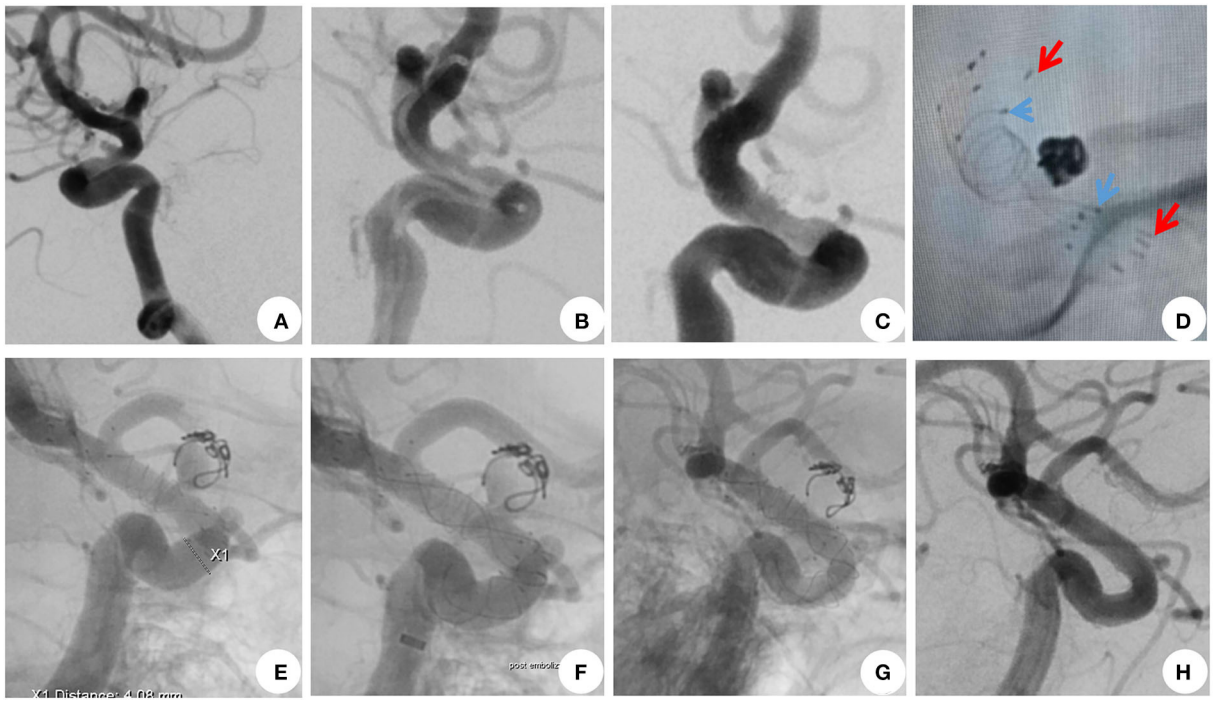

FIGURE 1
A 44-year-old woman with recurrent blood blister-like aneurysms (BBAs). **(A,B)** DSA showed a BBA located at the left supraclinoid segment of the intracranial carotid artery. **(C,D)** BBA was treated with overlapped LVIS and Enterprise stent-assisted coiling. The immediate postoperative angiogram showed the complete occlusion of the BBA. **(E)** At 1 month after the initial treatment, DSA showed that the BBA had recurred, and the coils were obviously compressed and dispositioned. **(F)** Recurrent BBAs were treated with a 4.0 × 25-mm Tubridge, which covered the aneurysm neck, and the stent opened well. **(G,H)** A 1-month follow-up angiography revealed complete occlusion of BBA and patency of the left intracranial carotid artery. The arrowheads are the ends of the LVIS and Enterprise stents.

including SAC or FD, have been proposed, there is no consensus on the optimal treatment for BBAs (9, 10). With fragile walls and an indistinct neck, surgeons are more likely to opt for a conservative strategy to prevent intraoperative rupture and result in low coil packing density. Therefore, SAC for the treatment of BBAs still has a high level of aneurysm rupture, recurrence, and rebleeding risk. A previous study has shown that complete occlusion rates associated with single, 2, and ≥3 stents were 42.9, 78.4, and 88.2%, respectively (3). Since the application of an FD in refractory aneurysms has achieved satisfactory results, it has also been tried in BBAs, which was first reported by Çinar et al. (11) in 2013. Of all seven BBAs, two were managed initially by other endovascular treatment options. Since then, more and more studies have reported the results of FDs in BBAs treatment. A meta-analysis confirmed that compared with other vascular reconstruction strategies, FD treatment has a higher rate of long-term complete occlusion and a lower rate of aneurysm recanalization but similar complications and clinical outcomes (5). Therefore, an FD can be used as an important treatment modality, even in the acute stage of ruptured BBAs. Because FD stents are not always available in some hospitals, SAC is still the main method, despite of its potential risk of recurrence.

Previously stented aneurysms with the retreatment with FDs turned out to be less effective and led to more complications. The occlusion rate reached 40.9–75% for aneurysms, while the complication rate could be as high as 16.7% (12–14). These unfavorable results might be related to the technique of deploying FDs within the previously deployed stent (15). First, the FD device may not be fully positioned within the previously implanted stent because the microwire may cross the previous stent through the cells in an "in–out–in" manner, and as the result, the FD was caught on the prior stent struts. However, in this study, of all 13 recurrent BBAs, 12 were treated with LVIS stents which had a relatively small cell size. When a microwire was advanced through the previous stent, rotating and pushing a J-shaped-tip microwire has proven to be an effective technique, which could prevent the microwire from going through the cells of previous stents. Second, the previous coil mass might interrupt the visibility of the FD. Fortunately, previously treated BBAs tended to have less impact on the visibility of FD stents because of their smaller size and less coil packing. When the wall position of the FD could not be determined due to the

surrounding coil mass, balloon angioplasty was performed. Moreover, all 13 BBAs located at the supraclinoid segment of the ICA without the influence of the bony structures of the cranial base, and full openings of all the FDs were able to be detected.

Indeed, one of the important factors affecting the aneurysm occlusion rate was the wall apposition of the FD device (16). Poor vessel wall apposition of the FD would lead to not only acute thrombosis but also an endoleak between the FD and the vessel wall, which might be the reason for persistent aneurysm filling and become an obstacle to neointima formation (17). Adequate opening and good wall apposition of FDs were critical for therapeutic efficiency, especially in the lesions previously treated with stents. It may be a good strategy to place the proximal and distal ends of the FD device beyond the previous stent, at the normal parent artery. This would allow the potentially unidentifiable gap between the parent artery and the previous stent to become a semi-enclosed space, which may gradually disappear. However, if the previously deployed stents were detected to have good wall apposition, in order to reduce the impact of FDs on normal branches and the difficulty of FD opening in vessels with tortuous curves or stenosis, selecting a shorter FD to cover only the distal and proximal ends of BBA neck could also achieve an ideal result. In addition, an intracranial covered stent, which could immediately isolate aneurysms from parent arteries, has also been used in the treatment of BBAs. Qi et al. (18) reported eight BBAs, including five recurrent BBAs treated with Willis covered stent. Follow-up results showed that all patients were in good condition without recurrence, while one patient developed delayed bleeding. However, because of the properties of this stent, its operation was relatively complex, and navigating the covered stent into the paraclinoid ICA was technically challenging and sometimes dangerous. Also, its impact on covered side branches could not be ignored. Further evaluation of the safety and efficiency of the covered stents is needed.

In conclusion, the treatment of BBAs remains technically challenging, with a high recurrence rate even after SAC embolization. In selected patients, the application of FDs for the retreatment of recurrent BBAs seems to be safe and effective. The key to the success of the procedure was to ensure that the FD stent had a full opening and had good apposition with the previously implanted stent. This study also has some major limitations, including the small sample size, the short angiographic follow-up period, single-center nature, retrospective design, and lack of comparison with a control group of patients—for instance, patients who were treated with SAC but did not require retreatment, which allowed higher durability of treatment.

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.

Ethics statement

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

Author contributions

YY and QH: conception and design. YY, SZ, and HY: data collection and statistical analysis. YY, SZ, HY, YW, and ZL: data analysis, interpretation, and drafting of the manuscript. YF and KZ: editing. QH: review and approval of the final version on behalf of all authors. YY: administrative, technical, and material support. 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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A multicenter retrospective controlled study of the Pipeline™ and Tubridge™ Flow Diverter devices for intracranial wide-necked aneurysms

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Purpose: To compare the safety and efficacy of Pipeline™ and Tubridge™ Flow Diverter devices (FDs) in the treatment of intracranial wide-necked aneurysms.

Methods: We retrospectively analyzed the clinical data of 92 patients with intracranial wide-necked aneurysms who were treated with those two flow-diverter devices (FDs) at four participating centers between July 2012 and December 2020.

Results: This study included 92 patients who underwent endovascular therapy using either Pipeline™ ($n = 39$) or Tubridge™ ($n = 53$) for treating intracranial wide-necked aneurysms. The periprocedural complication developed in 2.56% (1/39) patients of Pipeline group and 3.77% (2/53) patients of the Tubridge™ group. During perioperative period, one patient in Pipeline™ group showed subarachnoid hemorrhage (2.56%, 1/39) and two ischemic complications in the Tubridge™ group (3.77%, 2/53). Follow-up assessments were conducted on 31 patients (79.49%) in the Pipeline™ group (the mean follow-up period was 9.7 ± 3.3 months). The rate of complete aneurysm occlusion at the final angiographic follow-up was 77.42%. Patients with a modified Rankin scale (mRS) score of 0.44 ± 0.31. Follow-up assessments were conducted on 42 patients (79.25%) in the Tubridge™ group (the mean follow-up period was 9.1 ± 4.4 months). The rate of complete aneurysm occlusion at the final angiographic follow-up was 85.71%. Patients with mRS score of 0.52 ± 0.28. Three patients showed parent artery stenosis, and one showed parent artery occlusion.

Conclusion: Both the Pipeline™ and Tubridge™ are safe and effective for the treatment of intracranial wide-necked aneurysms, with no significant difference in the rate of complete aneurysm occlusion and perioperative complications between the two FDs.

KEYWORDS

intracranial wide-necked aneurysm, flow diverter devices, coil, endovascular therapy, perioperative complications

Introduction

The results of the International Subarachnoid Aneurysm Trial published in 2005 identified endovascular therapy as one of the primary treatments for intracranial aneurysms (1, 2). However, the rate of complete occlusion in endovascular treatment of wide-necked aneurysms remains suboptimal, and the risk of long-term recurrence remains high (3, 4).

Over the past decade, flow-diverter devices (FDs) have emerged as first-line endovascular treatment devices for intracranial aneurysms, particularly large and giant aneurysms (5, 6). The pipeline embolization device (PED) (Pipeline^{TM}; Medtronic Inc, Dublin, Ireland) was the first FD approved for clinical use and is currently the most reliable FD with respect to clinical and laboratory evidence (7–10). The Tubridge^{TM} vascular reconstruction device (TB) (Tubridge^{TM}; MicroPort Medical Company, Shanghai, China) was the first FD developed in China (11). We conducted a multicenter retrospective study comparing the clinical efficacy of the PED and TB for the treatment of intracranial wide-necked aneurysms and evaluated the prognosis of patients during the follow-up period. This study provides a theoretical basis for individualized selection of FDs on the basis of the characteristics of the patient's aneurysm.

Materials and methods

Participants

The clinical data of patients with unruptured intracranial wide-necked aneurysms confirmed by computed tomography angiography (CTA)/magnetic resonance angiography (MRA)/digital subtraction angiography (DSA) and treated with FDs at four medical centers (27 cases at the former General Hospital of Northern Theater Command, Shenyang, China; 27 at Shengjing Hospital of China Medical University, Shenyang, China; 10 at Liaohe Oilfield General Hospital, Panjin, China; and 28 at First Affiliated Hospital of Dalian Medical University, Dalian, China) between January 2012 and December 2020 were retrospectively analyzed. Patients were divided into two groups based on the FD implanted: The PED group included patients treated with the PED ($n = 39$, preoperative baseline modified Rankin scale [mRS] score of 1.15 ± 0.34), while the TB treatment group included patients treated with the TB ($n = 53$, preoperative baseline mRS score of 1.20 ± 0.29). An intracranial wide-necked aneurysm was defined as an aneurysm with a neck width of $\geq$4 mm (absolute wide-necked aneurysm) and/or dome-to-neck ratio $\leq$2 (relative wide-necked aneurysm).

The study cohort included 38 male and 54 female patients (range, 43–76 years; mean age, 59.7 $\pm$ 8.9 years). Forty-nine cases (53%) showed concomitant primary hypertension, and 44 (48%) showed concomitant type II diabetes mellitus. Clinical symptoms included headache ($n = 38$), focal neurological deficits included oculomotor paralysis, blurred vision et al. ($n = 29$), TIA:transient ischemic attack (TIA) ($n = 6$), and epilepsy ($n = 1$); 18 cases showed no clinical symptoms. The location of aneurysm included the ophthalmic segment of the internal carotid artery (ICA) in 20 cases, the cavernous segment of the ICA in 28, the paraclinoid segment of the ICA in 20, the posterior communicating segment of the ICA in 17, the petrous segment of the ICA in five, and the vertebrobasilar artery in two. All aneurysms in the group were saccular aneurysms, with a mean diameter of 6–30 mm (14.6 ± 4.5 mm); 14 cases involved aneurysms with a diameter of $\geq$ 25 mm, and 47 involved aneurysms with a diameter of $<$10 mm. The baseline characteristics of analyzed patients were showed in Table 1.

Perioperative treatment strategy

The preoperative antiplatelet therapy strategy was selected as described in the literature. All patients were given either oral clopidogrel 75 mg + aspirin 100 mg ($\geq$3 d) or

TABLE 1 Baseline characteristics of analyzed patients.

	Pipeline	Tubridge	*P*
Number of cases	39	53	
Age(mean ± SD years)	58.8 ± 7.7	60.1 ± 9.1	0.2831
Baseline mRS score (mean ± SD)	1.15 ± 0.34	1.20 ± 0.29	0.2845
Gender			0.8304
male	17	21	
female	22	32	
Hypertension	19	30	0.528
Diabetes	18	26	0.8347
Clinical presentation			0.439
Headache	18	20	
Neurological deficit	14	15	
TIA	1	5	
Epilepsy	0	1	
Asymptomatic	6	12	
Aneurysm location			
ICA ophthalmic	8	12	
ICA cavernous	13	15	
ICA paraclinoid	8	12	
ICA communicating	7	10	
ICA petrous	2	3	
vertebrobasilar artery	1	1	
Aneurysm size (mm)			0.7753
<10 mm	19	28	
10 mm−25 mm	14	17	
≥25 mm	6	8	

TIA, transient ischemic attack; ICA, internal carotid artery.

clopidogrel 75 mg + aspirin 300 mg (≥1 d) continuously before surgery. Postoperatively, dexamethasone 10 mg was administered intravenously for 3 d, followed by oral clopidogrel 75 mg + aspirin 100 mg q.d. (≥3 months), which was then changed to a single oral antiplatelet drug. Routine head CT re-examination was performed on postoperative day 2. Antiplatelet drugs were immediately discontinued if the patient developed subarachnoid hemorrhage in the perioperative period.

Treatment method

All procedures were performed under general anesthesia. The femoral artery was punctured using a modified Seldinger technique. Bilateral femoral artery access was used in 87 patients, and unilateral femoral artery access was used in five.

First, complete cerebral angiography and three-dimensional (3D) vascular reconstruction were performed to elucidate the relationship of the aneurysm location, size, and neck width with the artery containing the aneurysm. Neck compression angiography was used to elucidate the status of vascular compensation in anterior circulation aneurysms. The working angle was selected by 3D imaging; a 6F long sheath or 8F guiding catheter was used; and a 6F Navien guiding catheter (Medtronic, USA) was placed into the target artery under the guidance of a guidewire. A Synchro14 200 microwire was used to guide the SL-10 microcatheter across the neck of the aneurysm to the most distal normal vessel possible under a path diagram. The Synchro microwire was withdrawn and replaced with a Transend 300 microwire to the site, and the Marksman microcatheter/T-track microcatheter was replaced to the most distal part of the aneurysm. A 6F guiding catheter was placed in the sheath of the contralateral femoral artery to reach the aneurysm donor artery, and a microwire was used to guide the SL-10 microcatheter into the aneurysm. The appropriate FD was selected and delivered to the target location; the head end of the microcatheter was placed in the distal flat vessel; and the stent was released after confirming the fit such that it completely covered the aneurysm neck. Next, the stent was released, and angiography was performed again to determine whether the artery with the aneurysm and branching and perforating vessels were patent. The procedure was ended with natural neutralization of heparin by preplaced microcatheterization with coil filling and intra-aneurysmal contrast retardation. The indication for using of the coil in this study were considered that preventing the FD herniate into the aneurysm or three-dimensional rotational angiography showed that blood jet persistent inflow jet impingement to the aneurysm. FD implantation was immediate; microwire massage was not performed in 12 early cases, while subsequent microwire massage techniques were performed in the next 80 cases as follows: repeated passage through the FD using the microwire collaterals formation technique, combined with repeated passage of the microcatheter for microwire massage when necessary, which contributed to better opening and apposition of the FD. In some cases, balloons were applied to dilate the proximal end of the FD, and the incidence of ischemic complications was substantially reduced. During application, we also found less change in the canal diameter after PED release and a lower rate of shortening; the TB showed adaptability to different vessel diameters and a significantly higher rate of shortening. In all cases, angiography was performed after microwire massage, and proximal balloon dilation was required in 11 cases. This was performed as follows: if the opening was still unsatisfactory after FD release or if the proximal end of the stent was poorly apposed to the wall causing blood flow to still shoot proximal to the aneurysm, proximal balloon dilation was performed.

Imaging and clinical evaluation

Regular postoperative follow-up was conducted, and whole-brain DSA re-examination was performed 6–12 months after surgery and graded as complete occlusion, cervical residual near-complete occlusion, or incomplete occlusion. The prognosis of patients was evaluated using the mRS. Technical complications were defined as complications that occurred intraoperatively due to surgical operations. Perioperative clinical complications were defined as symptomatic complications that occurred during the perioperative period, excluding technical causes and including worsening of original symptoms, subarachnoid hemorrhage, cerebral infarction, and focal neurological deficits. All follow-up evaluations were performed using cerebral angiography re-examination to assess aneurysm healing and blood flow in the aneurysm-carrying artery, as well as using mRS scores (12) to evaluate patients' recovery of neurological function at the follow-up endpoint and to record deaths.

Statistics

SPSS 25.0 software was used for statistical analyses of data. Measurement data conforming to a normal distribution were expressed as means ± standard deviations, and the *t*-test was used for comparisons between groups. Measurement data not conforming to a normal distribution were expressed as medians and quartiles (M [P_{25}, P_{75}]), and the rank-sum test was used for comparisons between groups. Count data were expressed as the number of cases and percentage (cases [%]), and the χ^2 test or Fisher's exact probability method was used for comparisons between groups. Differences with $p < 0.05$ were considered statistically significant.

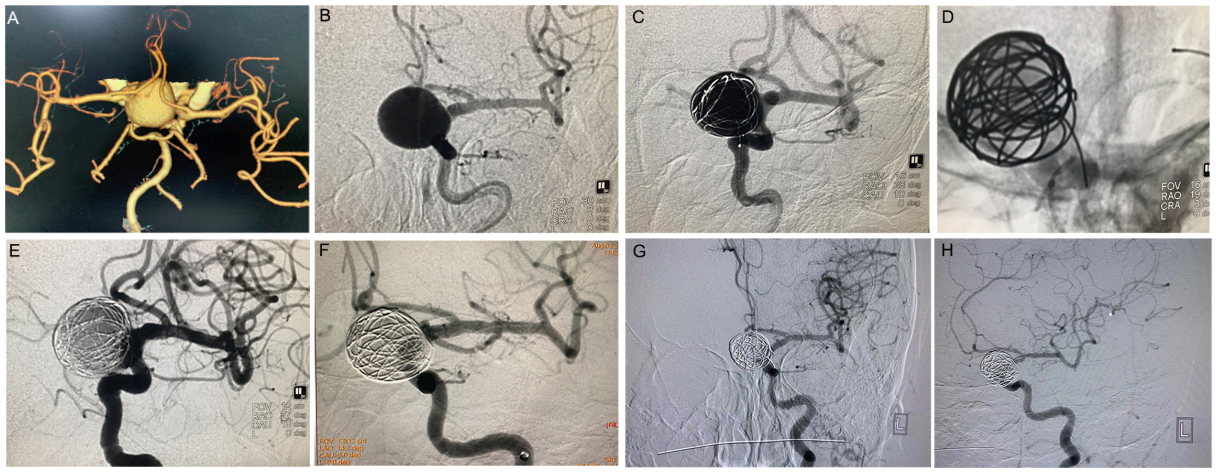

FIGURE 1
Pipeline™ treatment of giant wide-necked aneurysm in the clinoid segment of the internal carotid artery. **(A)** CTA results show a giant wide-necked aneurysm in the clinoid segment of the left internal carotid artery; **(B)** working angle measurement indicates an aneurysm size of approximately 19.2 mm × 22.7 mm and an aneurysm neck of 15 mm; **(C)** first, a microcatheter is used to release the coil, and the coil is formed into a basket to support Pipeline™ release; **(D)** release of the 4.0 × 25 Pipeline™; **(E)** the micro-guide wire is used to massage the stent to make the stent fit the wall completely; **(F)** 30 min later, the aneurysm is observed to be completely unremarkable on angiographic re-examination; and **(G,H)** 6 months after the procedure, DSA imaging re-examination shows complete healing of the aneurysm.

Results

Intraoperative status

Of the 92 patients, 39 were treated with the PED; a total of 42 stents were implanted, with 36 patients receiving one stent and three receiving two stents each (Figure 1). All patients in the PED group were treated with the FD combined with coils, and all PEDs were successfully implanted with a technical success rate of 100%. Five cases were not treated with guidewire massage, and 34 were treated with microwire massage to promote stent apposition, of which five were remedied with proximal balloon dilation of the stent. Fifty-three patients were treated with the TB, and a total of 58 stents were implanted; five patients had two stents implanted (Figure 2). Seven cases were not treated with guidewire massage, and 46 were treated with microwire massage to promote FD apposition, of which six were remedied with proximal balloon dilation of the FD. All TBs were successfully implanted with a technical success rate of 100%. In the TB group, five cases were treated with the FD alone and 48 were treated with the FD combined with coils. Imaging examination immediately after FD placement indicated a significant reduction in contrast filling into the aneurysm sac, and none of the cases in the PED group showed intraoperative displacement. Two patients in the TB group showed stent shortening, one showed satisfactory coverage of the aneurysm neck without additional treatment, and one received a replacement TB stent of the same diameter. Two patients in the TB group had intraoperative thrombosis, and they completely recovered after intra-arterial infusion of tirofiban and balloon angioplasty. Postoperative angiography indicated no stenosis in the artery with the aneurysm, and no occlusion of branching or penetrating arteries was observed.

Perioperative complications

One case in the PED group showed subarachnoid hemorrhage at 36 h after operation. The patient was unconscious, voluntarily discharged from the hospital, and died 5 days later. Four patients experienced a worsening headache that improved after symptomatic and hormonal treatment, and two reported decreased muscle strength after operation; no cases of infarction were observed on CT re-examination. The patients recovered within 48 h after volume expansion and rehydration therapy, continued oral dual antiplatelet therapy, intensive lipid-lowering therapy, and anti-vasospasm therapy. No bleeding complications were observed in the TB group. In the perioperative period, three patients showed worsening headache that which improved after treatment, three showed transient loss of muscle strength, and two showed speech disorders manifesting as dysarthria. Three cases resolved completely with medication. Only one case showed mild residual hemiparesis, and MRI showed brain stem infarction in this patient. Another case showed acute hemiparesis occurring 3 d after discharge; emergency cerebral angiography re-examination indicated unimpeded flow in the artery with the aneurysm, and the patient was treated with medication. Mild residual hemiparesis

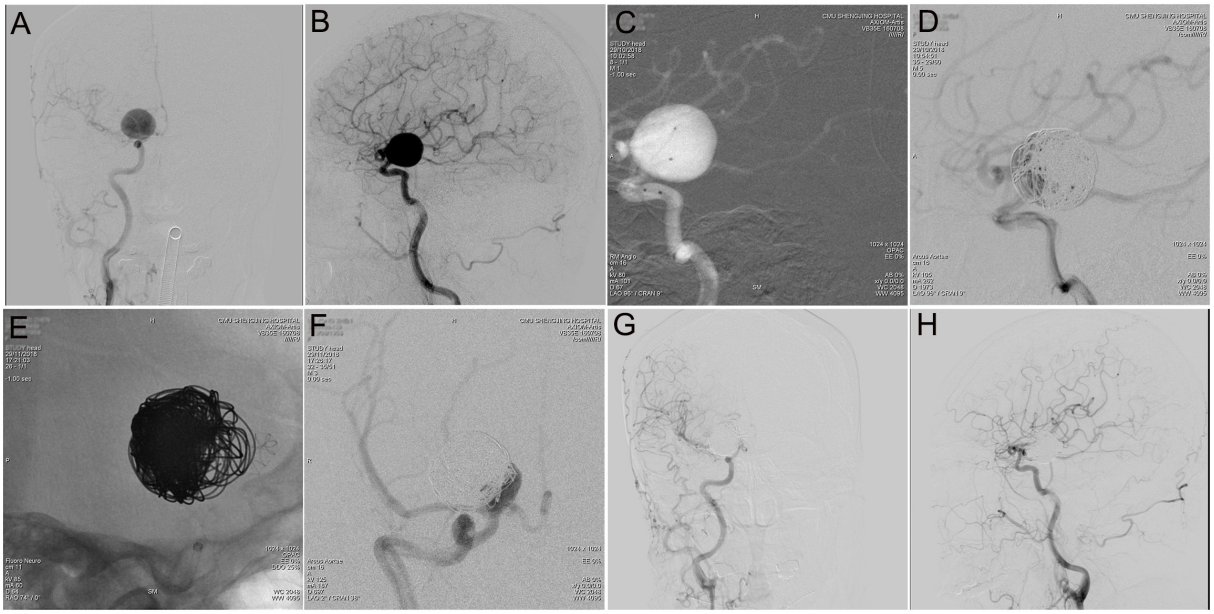

FIGURE 2
Tubridge^{TM} treatment of a giant wide-necked aneurysm in the clinoid segment of the internal carotid artery. **(A)** DSA results shows a giant wide-necked aneurysm in the clinoid segment of the right internal carotid artery; **(B)** working angle measurement indicates an aneurysm size of approximately 21.4 mm × 20.5 mm and an aneurysm neck of 13 mm; **(C)** application of the double-microcatheter technique with spring ring embolization of the aneurysm to support the second-stage Tubridge^{TM} release; **(D)** immediate postoperative imaging to complete most of the aneurysm embolization; **(E)** after 1 month, the second stage of Tubridge^{TM} release is 3.0 × 25, and the stent is massaged by the microcatheter to make the stent fit the wall completely; **(F)** immediate DSA imaging shows a small amount of residual aneurysm neck; and **(G,H)** 2 years after surgery, DSA re-examination shows complete healing of the aneurysm.

was observed, and infarction of the posterior limb of the internal capsule was found on MRI.

Postoperative follow-up

Outpatient or telephone follow-up was conducted for all patients (Table 2). During the follow-up period, two patients died, one from colon cancer and one from a car accident. In the PED group, one patient showed acute ipsilateral internal carotid artery occlusion 6 months after surgery; the patient underwent stent thrombectomy and had mild residual functional impairment. In the TB group, two patients experienced transient ischemic attacks, and the symptoms resolved after intensive lipid-lowering therapy. In the PED group, 31 patients underwent angiography re-examination; the follow-up period was 9.7 ± 3.3 months. Of these, 24 patients (77.42%) exhibited complete aneurysm occlusion, and the mRS score at the follow-up endpoint was 0.44 ± 0.31. One case showed stenosis of the parent artery. In the TB group, 42 patients underwent angiography re-examination, the follow-up period was 9.1 ± 4.4 months, with 36 patients (85.71%) exhibiting complete aneurysm occlusion, and the mRS score at the follow-up endpoint was 0.52 ± 0.28. Three cases showed stenosis, and one showed occlusion of parent artery, although the patient did not exhibit any neurological deficits.

Discussion

Treatment of intracranial aneurysms using FDs is a landmark advancement that has made some previously difficult and risky cases easier and safer to treat and has effectively improved long-term patient outcomes and significantly reduced the recurrence rate of aneurysms in comparison with traditional coil or stent-assisted embolization (13). The mechanism of FD treatment of intracranial aneurysms involves changing the direction of blood flow using densely distributed mesh filaments, which can decrease blood flow and induce thrombus formation in the aneurysm by significantly slowing or stagnating the blood flow in the lumen of the aneurysm. In addition, an FD provides a scaffold for endothelial growth, promoting endothelialization of the aneurysm neck and restoring arterial wall integrity (14, 15). Currently, most of the clinical evidence evaluating FDs for intracranial aneurysms has been obtained from single-arm retrospective studies or randomized trials comparing FDs with conventional therapies (4, 8, 16, 17). Comparative studies evaluating different FDs, which are important considering the increasing variety of commercially available FDs, are lacking.

TABLE 2 Outcome of the patients with intracranial wide-necked aneurysms who were treated with FDs.

	Pipeline	Tubridge	*P*
Follow-up (months) (median ± SD)	9.7 ± 3.3	9.1 ± 4.4	0.4759
Treatment strategy			
FD alone	0	5	
FD concomitant coiling	39	48	
Number of FD were implanted			
1	36	48	
≧2	3	5	
Remediation strategy			
① Microwire massage	34	46	
② Proximal balloon dilation	5	6	
Safety			
Technical complications	0	0	
Clinical complications			0.9037
① SAH	1	0	
② symptoms of cerebral ischemia	0	2	
Follow-up			
Follow-up angiography	31	42	
Aneurysm occlusion			0.3683
① Complete occlusion	24	36	
② Occlusion but residual neck	6	4	
③ Residual aneurysm	1	2	
Parent artery			0.3909
① Stenosis	0	1	
② Occlusion	1	3	
Functional at the endpoint of follow-up			
mRS score at the endpoint of follow-up	0.44 ± 0.31	0.52 ± 0.28	0.199
Mortality at the endpoint of follow up	1	1	

The PED was the first FD to be used in clinical practice and is currently the most commonly used FD. The TB, which was approved for the market in 2018, is the first Chinese-made FD. Zhou et al. (18) conducted a single-center cohort study of 28 patients with intracranial aneurysm treated with TB. Over a mean follow-up period of 9.9 months, the rate of complete aneurysm occlusion was 72%, and there were no cases of death or disability. The recent PARAT prospective multicenter trial, also conducted in China, evaluated the TB and stent-assisted coils for large/massive aneurysms with a follow-up period of 6 months and found a complete aneurysm occlusion rate of 75%, which was much higher than that in the stent-assisted coil embolization group (25%) (11).

In this study, we compared and analyzed cases of intracranial wide-necked aneurysms treated with the PED and TB in four medical centers. The rate of complete aneurysm occlusion at the end of the follow-up period was 77.42% (24/31) in the PED group and 85.71% (36/42) in the TB group; the difference was not significant ($p > 0.05$). The difference in the results of the analysis of clinical outcomes was also not significant ($p > 0.05$). These results indicate that the efficacy of the two types of FDs in the treatment of intracranial wide-necked aneurysms did not differ significantly.

FD performance was evaluated in terms of porosity, metal coverage, and mesh density. The PED's lumen is uniform in size, with a mesh size of 0.02–0.05 mm^2 and 30–35% metal coverage within the aneurysm artery per specifications (19). The TB has a self-expanding mesh duct with an abducted end. TB's metal coverage is 35%, and the mesh size is 0.04 mm^2 (18). When the distal and proximal diameters of the aneurysm-carrying artery are different, a larger-diameter TB can be used to ensure metal coverage and mesh density. If the PED diameter is smaller than that of the aneurysmal artery, it may be possible to increase the mesh size and to decrease the metal coverage due to the increased size (20). The transition-zone effects due to diameter differences between the aneurysmal artery and FD can be addressed by using multiple PEDs of different sizes (21).

In this study, we reviewed cases from four centers. During the perioperative period, one case of subarachnoid hemorrhage occurred in the PED group (2.56%, 1/39), and it was possibly associated with a previous history of hypertension. In contrast, two patients in the TB group developed acute ischemic stroke complications during the perioperative period (3.77%, 2/53), and MRI re-examination indicated acute brainstem infarction and internal capsule infarction. A retrospective analysis suggested that this may be related to antiplatelet drug resistance in both patients. Overall, there was no significant difference in the incidence of perioperative complications between the two groups ($p > 0.05$), indicating no difference in the safety of the two FDs in the treatment of intracranial wide-necked aneurysms.

Radial support

Another key index of an FD is the radial support force. In comparison with conventional intracranial stents, an FD has a lower radial support force, resulting in a softer FD with better throughput, but possibly at the cost of incomplete apposition, which is detrimental to endothelialization formation, and thromboembolic complications may also occur due to insufficient radial support in the use of an FD (15, 22). In this study, the PED was found to have weak radial support and was slightly difficult to open, especially in the curved part of the vessel, necessitating repeated pushing, pulling, and jiggling to ensure complete opening; although the TB showed slightly higher relative radial support and was easier to release, no statistically significant difference was found between these two different FD radial forces in terms of their effect on passage and apposition performance. In the early cases in this group, immediate imaging results were satisfactory with pushing,

pulling, and jiggling alone, although acute thrombosis within the FD or stenosis of the aneurysmal artery were observed a few min later, and the combination of microguide-forming collaterals with a microcatheter push massage and balloon dilation to the proximal end of the FD was required to reduce thromboembolic complications in some cases. Smaller changes in canal diameter after PED release along with a lower shortening rate were found in our cases; TB use also resulted in a significantly higher shortening rate due to slightly higher vascular adaptation. Therefore, with regard to device selection, both the PED and TB may be more suitable for cases with more uniform vessel diameters, while the TB with a slightly larger diameter may be more advantageous for aneurysmal arteries with large distal and proximal lumen disparities. During treatment, it is advisable to choose a slightly longer length for the TB than for the PED for the same cases.

Use of the coil

In addition to reducing blood flow into the aneurysm leading to its thrombosis, an FD provides a framework for de novo endothelial coverage of the aneurysm neck, which completely excludes the aneurysm from circulation. Indeed, complete occlusion of the aneurysm may be largely dependent on adequate endothelialization of the FD. Using a rabbit saccular aneurysm model, Kadirvel et al. (23) demonstrated the mechanism of *de novo* endothelial coverage in the PED, with extensive endothelialization of the FD by day 7. In completely occluded aneurysms, endothelialization manifested as a thin translucent layer at 4 weeks that became thicker; by 8 weeks, 66.5 and 70% of the samples had shown complete aneurysm occlusion at 30 and 60 d, respectively. Importantly, if endothelialization did not occur, there was no aneurysmal thrombosis in any case, and when the mesh was not occluded by the overlying tissue, it was always not occluded. In this study, 94.57% (87/92) of the cases were treated with a combination of coils and an FD in the hope that the coils would slow blood flow, promote thrombosis, and facilitate aneurysm healing. Interestingly, an 80% occlusion rate was also obtained (4/5) in the limited number of cases treated with an FD alone. Therefore, for FD treatment of large intracranial wide-necked aneurysms, the selection of an appropriate stent and appropriate release technique to optimize metal coverage and mesh density may be more important.

Limitations of the study

The main limitation of this study was the selection bias associated with different centers and physicians. The study duration was long, and the study was conducted at four centers; thus, the clinicians lacked sufficient clinical experience in most of the early cases; the strategies and techniques used in the procedures changed over time; and some of the complications may have been due to physician inexperience rather the instrumentation. Moreover, the imaging follow-up modality and time points were selected at the discretion of the patient and the assessment of outcomes was not blinded, which may have resulted in partial investigator bias. In addition, data collection and analysis were performed retrospectively, because of which the possibility of incomplete data cannot be ruled out.

Conclusion

Both the PED and TB are safe and effective in the treatment of large intracranial wide-carotid aneurysms, with no significant difference in the rate of complete aneurysm occlusion on angiography (77.42 vs. 85.71%, $p > 0.05$) or rate of perioperative complications (2.56 vs. 3.77%, $p > 0.05$) between the two. The TB shows advantages related to vascular lumen adaptability and release but is associated with has a higher incidence of shortening, while the PED shows the most reliable evidence at present and is still being upgraded. The technical characteristics of the two FDs may confer specific advantages in various indications, although large, prospective, controlled trials are needed to compare them and to determine the best indications for both.

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 the Institutional Review Board of Shengjing Hospital of China Medical University. The patients/participants provided their written informed consent to participate in this study.

Author contributions

ZL, FY, YG, and YX contributed to the study design. HC, FY, YG, YX, MW, and ZL performed the clinical follow-up. HC, JL, YL, KF, CL, and ZL performed the literature search, data collection, and drafted the manuscript. ZL, FY, YG, and YX contributed to data analysis and interpretation. HC and ZL contributed to editing and revision of the manuscript. 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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Neuroform atlas stent-assisted coiling of tiny wide-necked intracranial aneurysms

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Objective: To investigate the safety and efficacy of Neuroform Atlas stent-assisted coiling for the treatment of tiny wide-necked intracranial aneurysms and evaluate risk factors associated with procedure-related complications.

Methods: We retrospectively examined 46 patients with 46 tiny wide-necked aneurysms who were treated using Atlas stent-assisted coiling at our institution from August 2020 to May 2022. Patient and aneurysm characteristics, procedural details, procedure-related complications, and angiographic and clinical outcomes were analyzed.

Results: A total of 10 patients presented with aneurysmal rupture. Atlas stent placement was successful in all patients. Angiography immediately after the procedure showed complete occlusion in 38 patients (82.6%), neck remnant in 7 (15.2%), and partial occlusion in 1 (2.2%). The mean angiographic follow-up was 8.4 months (range, 6–16). At the last follow-up, angiography showed complete occlusion in 41 patients (89.1%) and neck remnant in 5 (10.9%). No aneurysm recurrence or in-stent stenosis occurred. Incidence of procedure-related complications was 10.8% (intraprocedural aneurysm rupture, two cases; acute thrombosis, two cases; and coil migration, one case); only one patient (2.2%) experienced procedural neurological morbidity. The mean clinical follow-up was 9.7 months. A favorable outcome was achieved in 45 patients (97.8%). In univariate logistic regression analysis, aneurysm size (odds ratio, 4.538; $P = 0.045$) was significantly associated with procedure-related complications. However, multivariate analysis found no independent risk factors.

Conclusion: Atlas stent-assisted coiling of tiny wide-necked intracranial aneurysms is feasible and effective. Outcomes and occlusion rates are favorable and morbidity is low. The complication rate may be higher in larger tiny aneurysms.

KEYWORDS

Neuroform atlas stent, tiny intracranial aneurysms, wide-necked, stent-assisted coiling, endovascular treatment

Introduction

Aneurysms with a maximum diameter of ≤3 mm are defined as tiny (1–3). A greater number of tiny aneurysms are being diagnosed owing to recent advances in neuroradiological techniques and improvements in imaging resolution (4). Treatment of these aneurysms is particularly challenging because they are characterized by thin fragile walls. When surgically clipping a tiny aneurysm, partial clipping of the parent artery is frequently required to prevent the clip from falling off (5). When performing endovascular embolization, coil stabilization within the sac is difficult, particularly in wide-necked aneurysms; in addition, subarachnoid hemorrhage (SAH) may result from a catheter or coil piercing the fragile aneurysm wall (6).

Management of tiny wide-necked intracranial aneurysms is controversial. Reported rupture rates are low, ranging from 0 to 0.4% (7). However, tiny aneurysms account for 15% of all ruptured aneurysms, which suggests that rupture of tiny aneurysms is not uncommon and that they should be treated (8).

In May 2020, the Neuroform Atlas stent (Stryker Neurovascular, Fremont, CA, USA) was introduced in China. Since then, it has been widely used to treat wide-necked aneurysms. The Atlas stent is a self-expanding laser-cut nitinol stent that is delivered using a low-profile microcatheter (size, 0.0165–0.017 inch). Its novel mixed open-cell/closed-cell design enhances stability within the vessel, provides high flexibility, and promotes proper apposition to the vessel wall (9). These design innovations, along with the development of smaller coils, may result in fewer complications and better efficacy when treating tiny aneurysms. Although previous studies have confirmed Atlas stent safety and efficacy (10–12), they included few patients with tiny wide-necked aneurysms. This study aimed to report our preliminary experience with Atlas stent-assisted coiling of tiny wide-necked aneurysms. We also examined safety and efficacy and evaluated risk factors for procedure-related complications.

Materials and methods

Patient population and data collection

We performed a retrospective analysis of consecutive adult patients who underwent Atlas stent-assisted coiling of tiny wide-necked intracranial aneurysms between August 2020 and May 2022 in our institution. All aneurysms were diagnosed using digital subtraction angiography (DSA). Tiny was defined as a maximum diameter of ≤3 mm. Wide-necked was defined as a dome-to-neck ratio <2. Patients with ruptured and unruptured saccular aneurysms were included. Those with blood blister-like aneurysms, which have a broad base, lack an identifiable neck, and originate from a nonbranching portion of an artery (13), were excluded. We also excluded patients who did not have postoperative imaging follow-up. The study was approved by the institutional review board of Beijing Tiantan Hospital. All patients provided written informed consent.

The following baseline clinical data were recorded: age, sex, cigarette smoking, alcohol intake, hypertension, diabetes mellitus, and clinical presentation. Imaging data were analyzed to record aneurysm size, shape, location, rupture status, and

TABLE 1 Patient and aneurysm characteristics.

Characteristics	No. (%)
Total number of patients	46
Age (years) (mean ± SD)	56.1 ± 9.2
Female	32 (69.6)
Comorbidities	
Hypertension	36 (78.3)
Diabetes mellitus	6 (13.0)
Hyperlipidemia	4 (8.7)
Coronary heart disease	5 (10.9)
Smoking	12 (26.1)
Alcohol use	7 (15.2)
Presentation	
Incidental	25 (54.3)
Chronic Headache/dizziness	11 (24.0)
Acute SAH	10 (21.7)
Total number of aneurysms	46
Aneurysm size (mm) (mean ± SD)	2.5 ± 0.3
Aneurysm neck width (mm) (mean ± SD)	2.2 ± 0.4
Dome/neck ratio (mean ± SD)	1.0 ± 0.4
Parent artery diameter proximal (mm) (mean ± SD)	2.6 ± 0.8
Parent artery diameter distal (mm) (mean ± SD)	2.2 ± 0.8
Aneurysm location	
Anterior circulation	37 (80.5)
ICA	7 (15.2)
MCA	6 (13.0)
ACA	6 (13.0)
Anterior choroidal artery	3 (6.5)
AComA	11 (24.0)
PComA	4 (8.8)
Posterior circulation	9 (19.5)
BA	5 (10.8)
PCA	1 (2.2)
PICA	3 (6.5)
Ruptured aneurysm	10 (21.7)
Bifurcation aneurysm	37 (80.4)
Procedure duration (minutes) (mean ± SD)	110.3 ± 31.7

SD, standard deviation; SAH, subarachnoid hemorrhage; ICA, internal carotid artery; MCA, middle cerebral artery; ACA, anterior cerebral artery; AComA, anterior communicating artery; PComA, posterior communicating artery; BA, basilar artery; PCA, posterior cerebral artery; PICA, posterior inferior cerebellar artery.

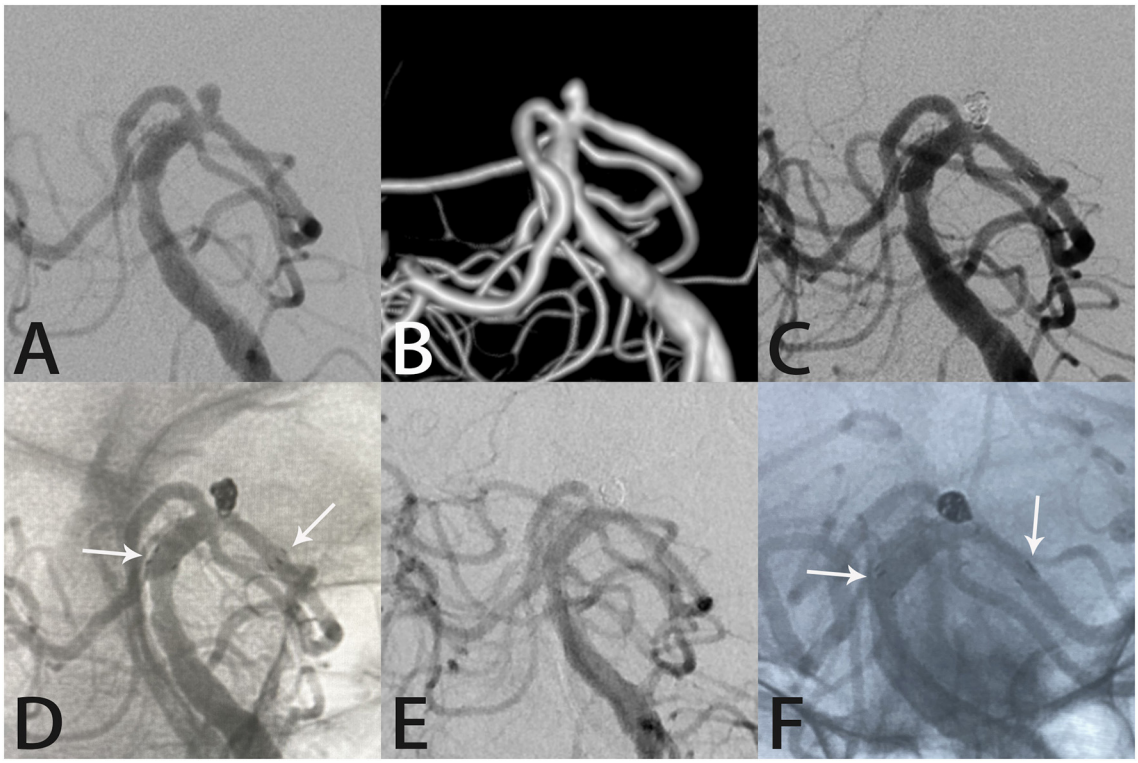

FIGURE 1
Images from a 66-year-old woman with a tiny left posterior cerebral artery aneurysm. Digital subtraction angiography with three-dimensional reconstruction images demonstrated a left posterior cerebral artery aneurysm **(A,B)**. Angiography immediately after Atlas stent-assisted coiling showed complete aneurysm occlusion **(C)**. An unsubtracted image shows the three radiopaque markers (white arrows) at the proximal and distal ends of the Atlas stent (4.0 × 15 mm) and the coils within the aneurysm sac **(D)**. Follow-up angiography 6 months later showed complete aneurysm occlusion, parent artery patency, stability of the Atlas stent (white arrows indicate the ends of the stent), and the coils densely packed within the aneurysm sac **(E,F)**.

dome-to-neck ratio. Hunt and Hess's grade was recorded in patients who presented with aneurysmal rupture.

Endovascular treatment and antiplatelet regimen

Patients with unruptured aneurysms were premedicated with aspirin 100 mg and clopidogrel 75 mg daily for at least 5 days. Patients with ruptured aneurysms received 300 mg loading doses of both aspirin and clopidogrel 4 h before the procedure. All procedures were performed *via* the femoral approach under general anesthesia and full anticoagulation with heparin (targeted activated clotting time was two to three times above the patient's baseline value). A triaxial guide-catheter system using a 6-Fr Cook (Cook Medical, Bloomington, IN, USA) or 6-Fr Neuron MAX (Penumbra, Alameda, California, USA) long sheath, 5-Fr or 6-Fr Navien (Covidien, Irvine, California, USA) intermediate support catheter, and Excelsior SL-10 or XT-17 microcatheter (Stryker Neurovascular) was used to deploy the stent. Aneurysm morphology and parent arterial structure were assessed using a three-dimensional rotational angiography and the proper working projection was selected. An Echelon-10 microcatheter (Medtronic, Dublin, Ireland) was then placed into the aneurysm lumen. An Excelsior SL-10 or XT-17 microcatheter was placed into the parent artery under microguidewire guidance. Aneurysm coiling was performed using the jailing technique; if this failed, the trans-cell technique (through the struts) was performed. All endovascular procedures were performed by neurointerventionalists with more than 10 years of experience. Aspirin 100 mg and clopidogrel 75 mg daily were continued for at least 3 months after the procedure, and then aspirin alone for 6 months or life.

Postoperative evaluation and follow-up

Procedure-related complications were categorized as hemorrhagic, ischemic, or other. Hemorrhagic complications were defined as visualization of contrast leakage from the aneurysm or ruptured vessel during the procedure or visualization of intracranial hemorrhage on an imaging study

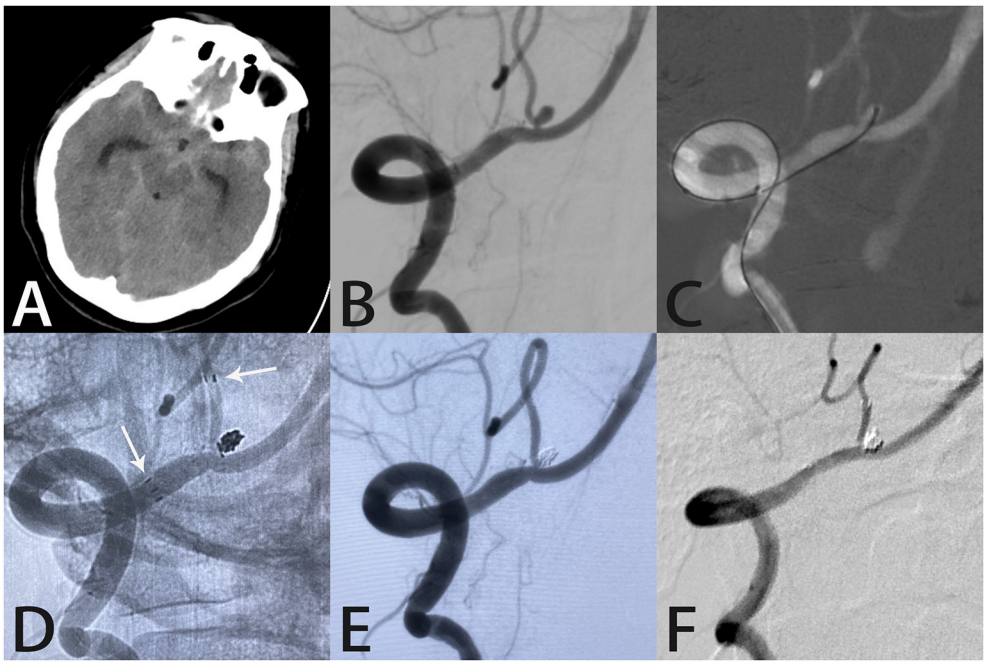

FIGURE 2
Images from a 45-year-old woman with a tiny ruptured right posterior inferior cerebellar artery aneurysm. Computed tomography showed subarachnoid hemorrhage in the lateral fissure and basal cisterns **(A)**. Angiography demonstrated a right posterior inferior cerebellar artery aneurysm **(B)**. A microcatheter was delivered into the aneurysm sac **(C)**. An unsubtracted image showed the distal end of the Atlas stent (3.0 × 15 mm) was placed in the right posterior inferior cerebellar artery with the proximal end in the right vertebral artery (white arrows indicate the ends of the stent) **(D)**. Angiography immediately after the procedure showed complete aneurysm occlusion and unobstructed blood flow in the posterior inferior cerebellar artery **(E)**. Follow-up angiography 7 months later showed complete aneurysm occlusion with the coils densely packed within the aneurysm sac **(F)**.

performed after the procedure. Ischemic complications were defined as thromboembolic events associated with re-treatment, namely persistent focal neurological deficit, transient ischemic attack, or cerebral infarction.

Clinical outcome was evaluated immediately after the procedure and 3, 6, 12, and 24 months after the procedure *via* outpatient clinic visits or phone calls using the modified Rankin Scale (mRS). Clinical outcome was classified as favorable (mRS score 0–2) or poor (mRS score 3–6). Morbidity was defined as any procedure-related neurological deterioration that caused an increase in the mRS score. Imaging follow-up (DSA or computed tomography angiography) was performed 6, 12, and 24 months after the procedure and was evaluated using the Raymond–Roy (RR) occlusion classification system: grade I, complete occlusion; grade II, residual neck; and grade III, residual aneurysm (14).

Statistical analysis

Statistical analyses were performed using SPSS software version 24.0 (IBM Corp., Armonk, NY, USA). Continuous variables with a normal distribution are expressed as means with standard deviation (SD); those with a skewed distribution are expressed as medians with an interquartile range. Categorical variables are expressed as numbers with percentages. Continuous variables were compared using the Student's *t*-test or Wilcoxon rank-sum test, as appropriate. Categorical variables were compared using the chi-square or Fisher's exact test as appropriate. Variables with $P < 0.1$ in univariate logistic regression analyses were included in the multivariate analysis to determine independent risk factors for procedure-related complications. $P < 0.05$ was considered significant.

Results

Patient and aneurysm characteristics

A total of 46 tiny wide-necked intracranial aneurysms in 46 patients (32 women, 14 men) were included for analysis. The mean patient age was 56.1 years (range, 39–74). A total of 10 patients presented with a ruptured aneurysm. The Hunt-Hess grade was I in five patients, II in three, and III in two. All patients with an unruptured aneurysm had an mRS score <2 on admission. Of the 46 aneurysms, the location was anterior

TABLE 2 Postprocedural and follow-up angiographic and clinical outcomes.

Characteristics	No. (%)
Successful stent placement	46 (100)
Number of stents	
Single Atlas	43 (93.5)
Double Atlas	3 (6.5)
Post-procedural immediate aneurysm occlusion, RROC	
I	38 (82.6)
II	7 (15.2)
III	1 (2.2)
Procedure-related complications	
Intraprocedural aneurysm rupture	2 (4.3)
Acute thrombosis	2 (4.3)
Coil migration	1 (2.2)
Angiographic follow-up available	46 (100)
Aneurysm occlusion at follow-up, RROC ($n = 46$)	
I	41 (89.1)
II	5 (10.9)
Follow-up time (months) (mean±SD)	8.4 ± 2.1
Clinical follow-up available	46 (100)
Follow-up mRS scores	
0	259 (70.6)
1	86 (23.4)
2	12 (3.3)
3	1 (2.2)
Follow-up time (months) (mean±SD)	9.7 ± 1.6

RROC, Raymond–Roy occlusion classification; SD, standard deviation; mRS, modified Rankin scale.

circulation in 37 (80.4%) and posterior circulation in 9 (19.6%). The mean aneurysm size was 2.5 ± 0.3 mm (range, 1.9–3.0). Mean dome-to-neck ratio was 1.0 ± 0.4 (range, 0.4–2.0). Patient and aneurysm characteristics are shown in Table 1.

Postprocedural angiographic and clinical outcomes

Atlas stent deployment was successful in all patients (100% technical success rate). A single stent was placed in 43 cases (93.5%) and two stents were placed in 3 (6.5%). Immediate postprocedural angiography showed complete occlusion (RR grade I) in 38 patients (82.6%), neck remnant (RR grade II) in 7 (15.2%), and partial occlusion (RR grade III) in 1 (2.2%). Complete occlusion was achieved in all 10 patients with a ruptured aneurysm. Figures 1, 2 show representative cases. Postprocedural angiographic and clinical outcomes are shown in Table 2.

Procedure-related complications occurred in five patients (10.8%), including two intraprocedural aneurysm ruptures, two acute thromboses, and one case of coil migration. No procedure-related death occurred. Both cases of intraprocedural rupture occurred in anterior communicating artery aneurysms. In one, aneurysm perforation occurred during coil placement. Although the rapid deployment of additional coils successfully controlled the hemorrhage, the redundant coils protruded into the parent artery and slowed blood flow in the A2 segment of the right anterior cerebral artery. Therefore, we placed another Atlas stent such that the two stents formed a "Y-shape." Angiography immediately after the procedure showed complete aneurysm occlusion and unobstructed A2 segment blood flow. The patient experienced transient headaches following the procedure and computed tomography showed only a small amount of SAH (Figure 3). On the other, the patient developed hemiparesis from an intracranial hematoma caused by intraprocedural re-rupture of a ruptured aneurysm; the mRS score was 4 at discharge, which improved to 3 at the last follow-up. Two patients developed in-stent thrombosis during the procedure and were immediately treated with intra-arterial thrombolysis using tirofiban. Recanalization was achieved in both without any clinical sequelae. Coil migration occurred in one patient during coiling, which was treated using Atlas stent deployment to prevent coil protrusion into the parent artery. This patient remained neurologically intact throughout the follow-up. Procedural morbidity and mortality rates were 2.2% and 0, respectively.

Follow-up angiographic and clinical outcomes

The mean angiographic follow-up was 8.4 ± 2.1 months (range, 6–16). Complete occlusion (RR grade I) was achieved in 41 patients (89.1%) and a neck remnant (RR grade II) was present in 5 (10.9%). No aneurysms recurred and no in-stent stenosis developed during follow-up, even in the three patients treated with the Y-stenting technique.

The mean clinical follow-up was 9.7 ± 1.6 months (range, 8–18). Clinical outcome was favorable in 45 patients (97.8%) and poor in 1 (2.2%). The mRS score was 3 in the single patient with poor clinical outcomes. Follow-up angiographic and clinical outcomes are shown in Table 2.

Risk factors for procedure-related complications

Univariate logistic regression showed that aneurysm size (odds ratio [OR] 4.538; 95% confidence interval [CI],

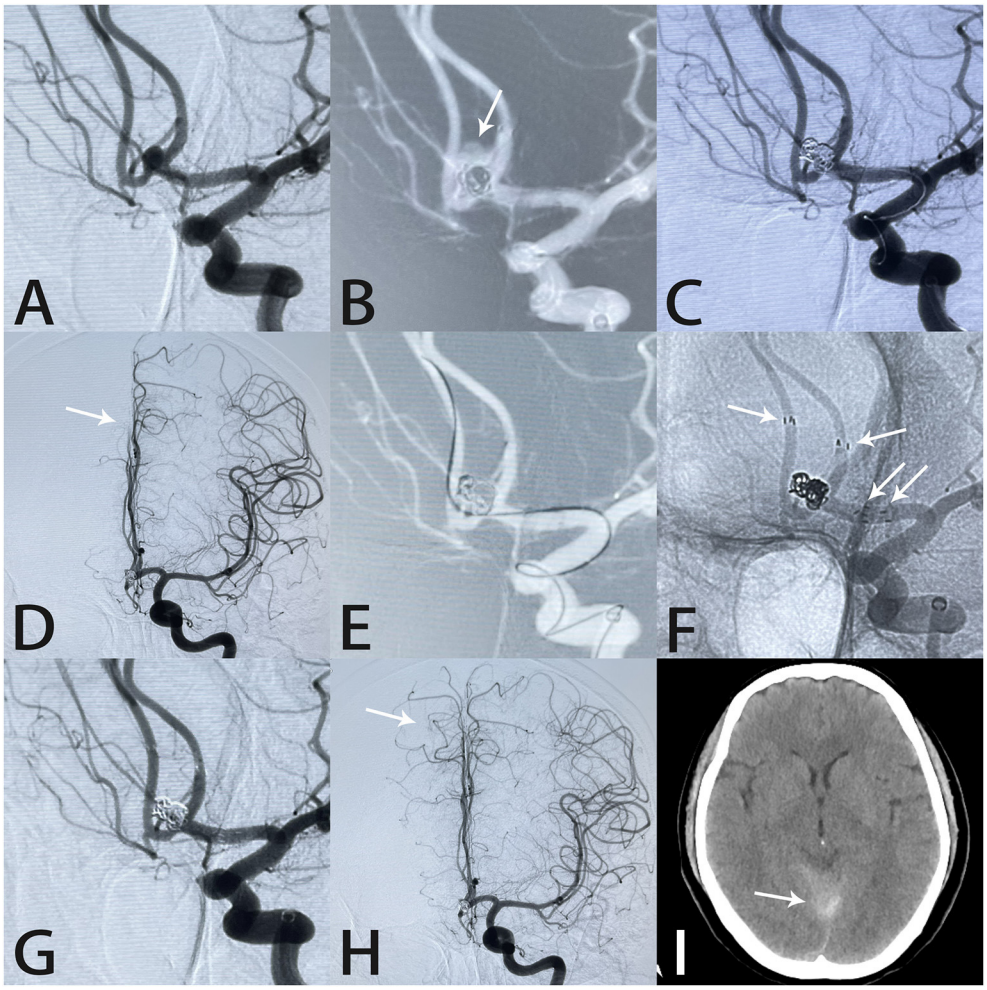

FIGURE 3
Images from a 56-year-old woman with a tiny anterior communicating artery aneurysm. Angiography demonstrated an anterior communicating artery aneurysm **(A)**. The aneurysm (white arrow) ruptured during coil placement **(B)**. Rapid deployment of additional coils controlled the hemorrhage **(C)**. Intraprocedural angiography showed slow blood flow in the A2 segment of the right anterior cerebral artery (white arrow) **(D)**. An Echelon-10 microcatheter was navigated into the right anterior cerebral artery in preparation for Atlas stent deployment **(E)**. Two Atlas stents formed a "Y-shape" (white arrows) **(F)**. Angiography immediately after the procedure showed complete aneurysm occlusion and unobstructed blood flow in the A2 segment (white arrow) **(G,H)**. Postprocedural computed tomography showed subarachnoid hemorrhage in the tentorium cerebelli **(I)**.

1.068–13.489; $P = 0.045$) was significantly associated with procedure-related complications. However, none of the variables examined was an independent risk factor for procedure-related complications in multivariate analysis (Table 3).

Discussion

Although guidelines for the treatment of tiny intracranial aneurysms are lacking, commonly applied strategies include surgical clipping and endovascular embolization. Clipping is not ideal for treating tiny aneurysms because it usually causes parent artery narrowing and is associated with a high incidence of complications (15). In a series of 32 tiny aneurysms (≤3 mm) that were surgically clipped, Rahmanian et al. reported a 30.8% intraoperative aneurysm rupture rate and 11.5% mortality (16). Considering the high rates of morbidity and mortality associated with neurosurgical clipping, safer and more effective treatment methods are needed for tiny aneurysms, especially those that have a wide neck. Endovascular embolization can achieve permanent occlusion in up to 85% of intracranial aneurysms and has a lower procedure-related hemorrhage rate (17, 18). Since the publication of the International Subarachnoid Aneurysm Trial, the treatment paradigm for intracranial aneurysms has shifted from surgical clipping to endovascular embolization (19). Moreover, recent technological advances,

TABLE 3 Univariate and multivariate analyses of risk factors for procedure-related complications.

Parameters	Procedure-related complications		Univariate analysis		Multivariate analysis	
	Yes ($n = 5$)	No ($n = 41$)	OR (95% CI)	*P*-value	OR (95% CI)	*P*-value
Age (years)	53.4 ± 10.7	56.4 ± 9.1	0.963 (0.868–1.070)	0.487		
Female, yes	4 (80.0)	28 (68.3)	0.538 (0.055–5.306)	0.596		
Hypertension, yes	3 (60.0)	33 (80.5)	0.364 (0.052–2.553)	0.309		
Current smoker, yes	1 (20.0)	11 (26.8)	0.682 (0.069–6.784)	0.744		
Regular alcohol abuse, yes	1 (20.0)	6 (14.6)	1.458 (0.138–15.387)	0.754		
Ruptured aneurysm, yes	1 (20.0)	9 (22.0)	0.889 (0.088–8.979)	0.920		
Aneurysm size (mm)	2.9 ± 0.1	2.5 ± 0.3	4.538 (1.068–13.489)	0.045	3.868 (0.411–25.781)	0.094
Aneurysm neck width (mm)	2.5 ± 0.3	2.2 ± 0.4	5.672 (0.738–30.518)	0.093	4.436 (0.142–37.723)	0.187
Dome/neck ratio	0.9 ± 0.4	1.0 ± 0.4	0.348 (0.019–6.467)	0.479		
Parent artery diameter proximal (mm)	2.4 ± 0.4	2.7 ± 0.8	0.512 (0.111–2.369)	0.392		
Parent artery diameter distal (mm)	2.0 ± 0.2	2.3 ± 0.8	0.522 (0.127–2.147)	0.368		
Anterior circulation, yes	4 (80.0)	32 (78.0)	1.125 (0.111–11.365)	0.920		
Ruptured aneurysm, yes	1 (20.0)	9 (22.0)	0.889 (0.088–8.979)	0.892		
Procedure duration (minutes)	126.1 ± 20.6	108.4 ± 32.5	1.014 (0.990–.039)	0.250		

OR, odds ratio; CI, confidence interval.

TABLE 4 Summary of studies examining stent-assisted coil embolization of tiny aneurysms (≤3 mm).

References	Stent type	No. of aneurysms	Rupture/ Unrupture	Mean aneurysm size (mm)	Immediate complete occlusion (%)	Complete occlusion at the last follow-up (%)	Complications (%)
Zheng et al. (24)	Enterprise/Neuroform/ Solitaire	52	10/42	2.6	86.5	93	4 (8)
Wu et al. (22)	LVIS	32	32/0	2.28	40.6	82.1	1 (3.6)
Li et al. (2)	Enterprise/Solitaire	16	16/0	1.7	56.3	93.8	2 (12.6)
Zhou et al. (20)	LVIS	42	8/34	2.4	76.2	90.5	2 (4.8)
Zhao et al. (25)	Enterprise/Neuroform/ LEO	17	17/0	2.3	58.8	NA	1 (5.9)
Zhang et al. (26)	Solitaire	9	9/0	NA	66.7	77.8	1 (11.1)
Total (mean)		168 (28)	15/13	2.3	64.2	87.4	11 (6.5)

such as smaller coils and smoother microcatheters, and accumulated operator experience have improved the safety and efficacy of endovascular treatment of tiny aneurysms (20). In a meta-analysis that included 1,105 tiny aneurysms (844 ruptured and 261 unruptured), immediate and long-term complete occlusion rates were 85 and 91%, respectively, and rates of intraprocedural rupture and thromboembolism were 7 and 4%, respectively (3).

Since the introduction of the initial Neuroform stent (Stryker Neurovascular) in 2002, various commercially available intracranial stents have followed. The Atlas stent is the successor to the Neuroform stent and has a structure that is compatible with a 0.0165-inch microcatheter, which enables safer and easier treatment of tiny aneurysms on small vessels. Several studies have demonstrated the safety and effectiveness of the Atlas stent for treating both unruptured and ruptured intracranial aneurysms (10, 11). Compared with the LVIS Jr stent (MicroVention, Inc., Aliso Viejo, CA, USA), the Atlas stent is associated with a higher occlusion rate and lower in-stent stenosis rate (21). However, safety and efficacy data regarding Atlas stent-assisted coiling for treating tiny aneurysms is lacking.

Stent assistance during coiling assists with coil placement improves coverage of the aneurysm neck and increases coil packing density. In addition, the presence of stent wires across the aneurysm neck may provide a structural basis for endothelialization and improve hemodynamic conditions. In our series, Atlas stent deployment was successful in all patients, similar to the results of two other studies (22, 23). Table 4

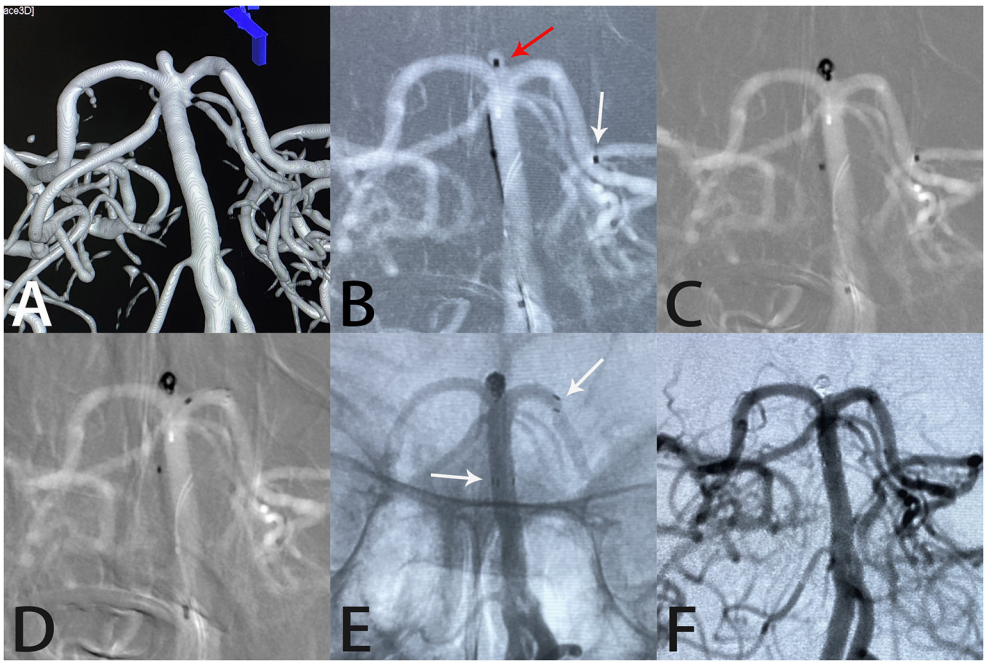

FIGURE 4
Images from a 65-year-old woman with a tiny basilar artery aneurysm. Three-dimensional digital reconstruction angiography demonstrated a basilar artery aneurysm **(A)**. An Echelon-10 microcatheter was first navigated into the left posterior cerebral artery in preparation for deployment of the Atlas stent (white arrow); then, another Echelon-10 microcatheter was placed into the aneurysm sac (red arrow) for coil placement **(B, C)**. An Atlas stent (3.0 × 15 mm) was deployed through another microcatheter to cover the aneurysm neck **(D)**. An unsubtracted image showed that the coils were packed densely within the sac and the Atlas stent was fitted well against the vessel wall (white arrows indicate the ends of the stent) **(E)**. Angiography immediately after the procedure showed complete aneurysm occlusion and unobstructed blood flow in the left posterior cerebral artery **(F)**.

summarizes the results of six studies that examined stent-assisted coil embolization of tiny aneurysms published within the past 10 years. Collectively, the complete occlusion rates immediately after the procedure and at the last follow-up were 64.2 and 87.4%, respectively. In our study, the corresponding rates were 82.6 and 89.1%, respectively. Corresponding rates for the LVIS stent (MicroVention, Inc.) were 40.6 and 82.1%, respectively, while those for conventional stents were 37.8 and 80%, respectively (22, 27). A meta-analysis of small intracranial aneurysms (≤3 mm) treated using endovascular techniques reported postoperative and follow-up complete occlusion rates of 85% and 91%, respectively (3).

The Atlas stent may be associated with a higher rate of complete occlusion than other stents because its design allows for a lower profile delivery, improved trackability, and higher conformability to the vessel wall. Available diameters range from 3.0 to 4.5 mm and lengths range between 15 and 30 mm; therefore, the Atlas stent can be used to treat tiny aneurysms located on small distal vessels. Furthermore, dense coil packing was performed in all aneurysms in our study, regardless of rupture status, and the jailing technique was used in most cases. This technique, in which the coil delivery catheter is placed into the aneurysm before stent deployment (Figure 4), may be safer than the trans-cell coiling technique for treating tiny wide-necked aneurysms. With the trans-cell technique, the stent is deployed first and then the coil delivery catheter is delivered into the aneurysm through the stent interstices; however, catheter navigation can be difficult and any unexpected movement may pierce the aneurysm wall and cause hemorrhage.

Intraprocedural rupture during endovascular aneurysm treatment usually leads to poor clinical outcomes. Several studies have shown that the risk of intraprocedural aneurysm rupture appears to be higher for aneurysms <3 mm in diameter (28, 29). In addition, a 2016 meta-analysis of aneurysms <3 mm in diameter reported a 7% intraprocedural rupture rate (3), which is higher than the 4.3% rate in our series. However, we excluded patients with blood blister-like aneurysms, which have a higher risk of intraprocedural rupture.

Intraprocedural rupture prevention is critical for success when treating tiny aneurysms. We prefer to use coils that are ultra-soft and slightly smaller than the maximum diameter of the aneurysm, which enables a high packing density. In addition, we place the microwire tip near the neck of the aneurysm rather than inside it to avoid piercing the aneurysm. Furthermore, to achieve adequate maneuverability, the shape of the tip should be adjusted based on the angle between the parent artery and

the aneurysm. Delicate maneuvering contributes to lowering the risk of intraprocedural rupture. Li et al. (2) developed the stent-assisted coil-jailing technique, which staples the redundant coil tail between the stent and the parent artery wall, which lowers the risk of intraprocedural rupture and coil displacement.

The Atlas stent may be associated with an increased risk of intraprocedural thrombosis. Intraprocedural thrombosis is mainly associated with poor stent–vessel wall apposition, inadequate antiplatelet therapy, longer procedure time, and thrombogenicity of endovascular embolization materials (30, 31). In our study, in-stent thrombosis occurred in two patients (4.3%), which is slightly higher than the rate reported by Ioanniaid et al. (3.1%) (32). Fortunately, the tirofiban administration resulted in recanalization in both.

Our overall complication rate of 10.8% was higher than the collective rate compiled from our literature review (6.5%). Although aneurysm size was associated with procedure-related complications in our univariate analysis, the multivariate analysis did not identify any independent risk factors.

Most neurointerventionalists are reluctant to place stents in patients with a ruptured aneurysm because they are in a hypercoagulable state and at risk for in-stent thrombosis and associated ischemic complications. In addition, the administration of antiplatelet drugs may cause intracranial hemorrhage again. However, we found no significant difference in procedure-related complications between ruptured and unruptured aneurysms.

Limitations

Our study has several limitations. First, it was retrospective in design and was conducted in a single center. Therefore, selection bias may have been introduced. Second, the mean angiographic follow-up was only 8.4 months, which is too short to determine the true final complete occlusion rate. Third, we did not compare the results of stent-assisted coiling and coiling alone. This comparison would better demonstrate the effect of stenting on outcomes in endovascular treatment of tiny aneurysms.

Conclusion

Atlas stent-assisted coiling of tiny wide-necked intracranial aneurysms is safe and effective. Outcomes and occlusion rates are favorable and morbidity is low; however, the complication rate may be higher in larger tiny aneurysms. Prospective multicenter studies with long-term follow-ups are warranted.

Data availability statement

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

Ethics statement

This study was reviewed and approved by the Ethics Committee of Beijing Tiantan Hospital. Written informed consent to participate in this study was provided by the patients or their legal guardian/next of kin.

Author contributions

LD and XC collected the clinical data, performed the statistical analysis, and wrote the manuscript. LZ, ZZ, and QP helped to collect the clinical data. PL and ML helped revise the manuscript, designed the research, and handled funding and supervision. ML approved the final version on behalf of all authors. 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.

Publisher's note

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Clinical outcomes of pipeline embolization devices with shield technology for treating intracranial aneurysms

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Introduction: As a common endovascular treatment for intracranial aneurysms, the pipeline embolization device (PED) is considered a standard treatment option, especially for large, giant, wide-necked, or dissecting aneurysms. A layer of phosphorylcholine biocompatible polymer added to the surface of the PED can substantially improve this technology. This PED with shield technology (pipeline shield) is relatively novel; its early technical success and safety have been reported. We conducted a systematic literature review with the aim of evaluating the efficacy and safety of the pipeline shield.

Methods: We searched the PubMed, Embase, and Cochrane databases, following the preferred reporting items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines.

Results: We selected five prospective and two retrospective studies for review. A total of 572 aneurysms were included; of these, 506 (88.5%) were unruptured. The antiplatelet regimens were heterogeneous. The rate of perioperative and postoperative complications was 11.1% [95% confidence interval (CI): 6.5–18.9%]. The adequate occlusion rate at 6 months was 73.9% (95% CI: 69.1–78.7%). The adequate occlusion rate of more than 12 months was 80.9% (95% CI: 75.1–86.1%). The mortality rate was 0.7% (95% CI: 0.2–1.5%). Subgroup analyses showed that aneurysm rupture status had no effect on aneurysm occlusion rate, patient morbidity, or mortality.

Conclusion: This review demonstrates the safety and efficacy of the pipeline shield for treating intracranial aneurysms. However, direct comparisons of the pipeline shield with other flow diverters are needed to better understand the relative safety and effectiveness of different devices.

KEYWORDS

flow diverters, pipeline embolization device with shield technology, pipeline shield, intracranial aneurysm, endovascular therapy

Introduction

Flow diverters (FDs) enable the application of endovascular therapy for intracranial aneurysms in an increased number of indications. The utilization of FDs has become the preferred treatment option for various types of aneurysms (1–3). Despite their relatively recent development, numerous FDs have been introduced for clinical use. Currently available coating FDs include the pipeline embolization device (PED) with shield technology (referred to as the pipeline shield), derivo embolization device (DED), and p64/p48 MW HPC (Table 1). The pipeline shield incorporates a phosphorylcholine surface coating (4), which is a third-generation PED. It has been shown to reduce intimal hyperplasia (5) and increase early neointimal growth in preclinical studies (6). In *ex vivo* (4) and *in vitro* studies (7, 8), the pipeline shield significantly reduced thrombogenicity in comparison with other FDs. As a new therapeutic technique for intracranial aneurysms, the efficacy of complications associated with the pipeline shield remains unclear, and there is currently no relevant literature that summarizes existing findings. Therefore, this meta-analysis aimed to explore the efficacy and safety of the pipeline shield in treating intracranial aneurysms.

Methods

Search strategy

We searched the PubMed, Embase, and Cochrane databases to identify studies using the pipeline shield for treating intracranial aneurysms. We used the following search terms: "flow diverter," "pipeline embolization device," "PED," "shield technology," "surface modification," and "aneurysm." We followed the applicable Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (9). We reviewed literature published between device inception and March 2022 and carefully screened the search results to select studies that were particularly relevant to pipeline shield devices in the neurointerventional field.

Selection criteria

For this review, we included all English-language articles on the use of the pipeline shield for treating intracranial aneurysms. Case reports were excluded. Animal, *in vitro*, and cadaveric studies were excluded. We also excluded non-primitive research and conference abstracts. We assessed the center and time frame of included studies with the aim of excluding articles with overlapping cohorts and identifying the most recent and complete studies. We included studies on pipeline shield devices for treating intracranial aneurysms and pooled data on aneurysm occlusion rates, procedural complications, and mortality. The initial search results and screening process are shown in a PRISMA-based (9) flowchart (Figure 1).

Data selection

We extracted the following data from the included studies: the number of patients, sex ratio, mean age, total number of aneurysms, proportion of ruptured aneurysms at presentation, sizes and neck width of aneurysms, shapes of aneurysms (i.e., blister, fusiform, pseudoaneurysm, or dissecting), locations of aneurysms, devices per aneurysm, mortality rates, morbidity rates, adequate occlusion rate, antiplatelet regimens, and usage of detachable devices.

Statistical analysis

We used the R package "META" (https://cran.r-project.org) to analyze the acquired data. We calculated proportions across studies and performed meta-analyses using fixed- and random-effects (RE) models for the weighted estimation of the overall rates of each outcome of interest (i.e., periprocedural and postoperative complications, adequate occlusion, and mortality). We also estimated 95% confidence intervals (CIs) and event rates for each outcome. I^2 statistics were used to assess statistical heterogeneity between studies. For data with I^2 heterogeneity values >50%, RE models were used. Forest plots were generated based on the proportions and estimated overall rates (Figure 2). Subgroup analyses were conducted using Stata 14.0.

Results

The preliminary search results contained 67 articles, 30 of which were duplicates. Ultimately, seven articles were selected for further analysis.

Study characteristics

The characteristics of all included studies are presented in Table 2. Of the seven studies, two were retrospective (10, 17) and five were prospective (12–16). Adjunctive coiling was used in six studies, two of which also used adjunctive balloons. One study used the pipeline shield exclusively. A total of 524 patients with 572 intracranial aneurysms were included. A total of 11.5% of the aneurysms had ruptured before treatment. Most aneurysms were in the anterior rather than posterior circulation

TABLE 1 Comparison of pipeline shield and other surface-coated FDs.

	Pipeline shield	p64/p48 MW HPC	DED
Basic information	Medtronic, 2014	Phenox, 2017	Acandis, 2016
Description (implant section of each device)	A self-expanding mesh cylinder braided from Cobalt-Chromium alloy wires.	A tubular vascular implant that consists of 48 interwoven nitinol wires which are filled with a platinum core.	24 Nitinol wires with radiopaque platinum core looped at the end, with a 48-wire braid.
Coating description	3 nm thick covalently bound phosphorylcholine surface modification.	Glycan-based multilayer hydrophilic polymer coating.	50 nm thin oxide and oxynitride layer.
The mechanism of surface coating	Phosphorylcholine is a major component of the outer membrane of erythrocytes, thus reducing platelet adhesion and activation.	Inhibits initial platelet adhesion mediated by GPIIb/IIIa binding to surface-adsorbed fibrinogen.	Reduces friction during delivery and expansion, thus reducing thrombogenicity.

DED, Derivo Embolization Device; FDs, Flow Diverters; PHC, Hydrophilic Polymer Coating.

(92.1 vs. 7.9%). Aneurysm morphology was identified for all 572 aneurysms: 87.9% were saccular, with the remainder being fusiform, dissecting, blister, or pseudoaneurysms. Table 2 details aneurysm body diameter, neck dilation extent, and parent artery data.

Complications and mortality

The rate of perioperative and postoperative complications was 11.1% (95% CI: 6.5–18.9%). The overall mortality rate was 0.7% (95% CI: 0.2–1.5%).

Angiographic outcomes

The rate of adequate occlusion at 6-month follow-up was 73.9% (95% CI: 69.1–78.7%). The adequate occlusion rate of more than 12 months was 80.9% (95% CI: 75.1–86.1%). Moreover, the rate of adjunctive coiling use was 37.2% (95% CI: 20–69.1%).

Subgroup analysis

Subgroup analysis showed that, in the unruptured aneurysm group, the adequate occlusion rate was 80.6% (ES = 80.6%, 95% CI: 73.4–87.8%, $I^2 = 0\%$, $p = 0.652$; Figure 3A), the morbidity rate was 8.8% (ES = 80.6%, 95% CI: 3.8–13.8%, $I^2 = 0\%$, $p = 0.463$; Figure 3B), and the mortality rate was 0.4% (ES = 0.4%, 95% CI: 0.0–3.0%, $I^2 = 0\%$, $p = 0.001$; Figure 3C). The adequate occlusion rate, morbidity rate, and mortality rate in the ruptured aneurysm group were 50.0, 35.7, and 7.1%, respectively (Figure 3). Although the overall tendencies are noteworthy, the evidence is insufficient to draw any final conclusions.

Discussion

FDs are new important tools for treating intracranial aneurysms (18). Considering the novelty of these devices, the risk of thromboembolic events post-implant remains a concern. It is known that patients who have undergone flow shunt placement should be treated with prolonged dual antiplatelet therapy (DAPT) to prevent thrombosis. The pipeline shield is a surface-coated device that improves the hemocompatibility of PEDs and has been shown to reduce surface platelet and fibrin adhesion as well as thrombin generation (4, 7, 19). In our review, these benefits were indirectly verified. Compared to PEDs without shield technology (11), the pipeline shield was found to be associated with higher adequate occlusion and lower mortality rates (Table 3).

Few studies were controlled according to the rupture status of the aneurysms. In fact, the primary treatment for ruptured aneurysms, including antiplatelet and endovascular therapies, differs from that for unruptured aneurysms. For unruptured aneurysms, in addition to encouraging patients to quit smoking and control their blood pressure, clinical decisions are made using PHASES and unruptured intracranial aneurysm treatment scores (20). Unruptured aneurysms show that short-term growth should be treated rapidly (21). Ruptured aneurysms must be treated surgically. In these patients, in addition to basic supportive care, early aneurysm occlusion is critical (22, 23). The choice of treatment depends on the overall condition of the patient, the characteristics of the aneurysm, the presence of associated hematomas and mass effects, and the overall microsurgical and endovascular expertise of the treatment center.

The pipeline shield appears to have similar outcomes to those of other well-established and more widely used FDs. In a study evaluating Silk FDs, Florez et al. reported a mortality rate of 2.8%, total thromboembolic complication rate of 6.06%,

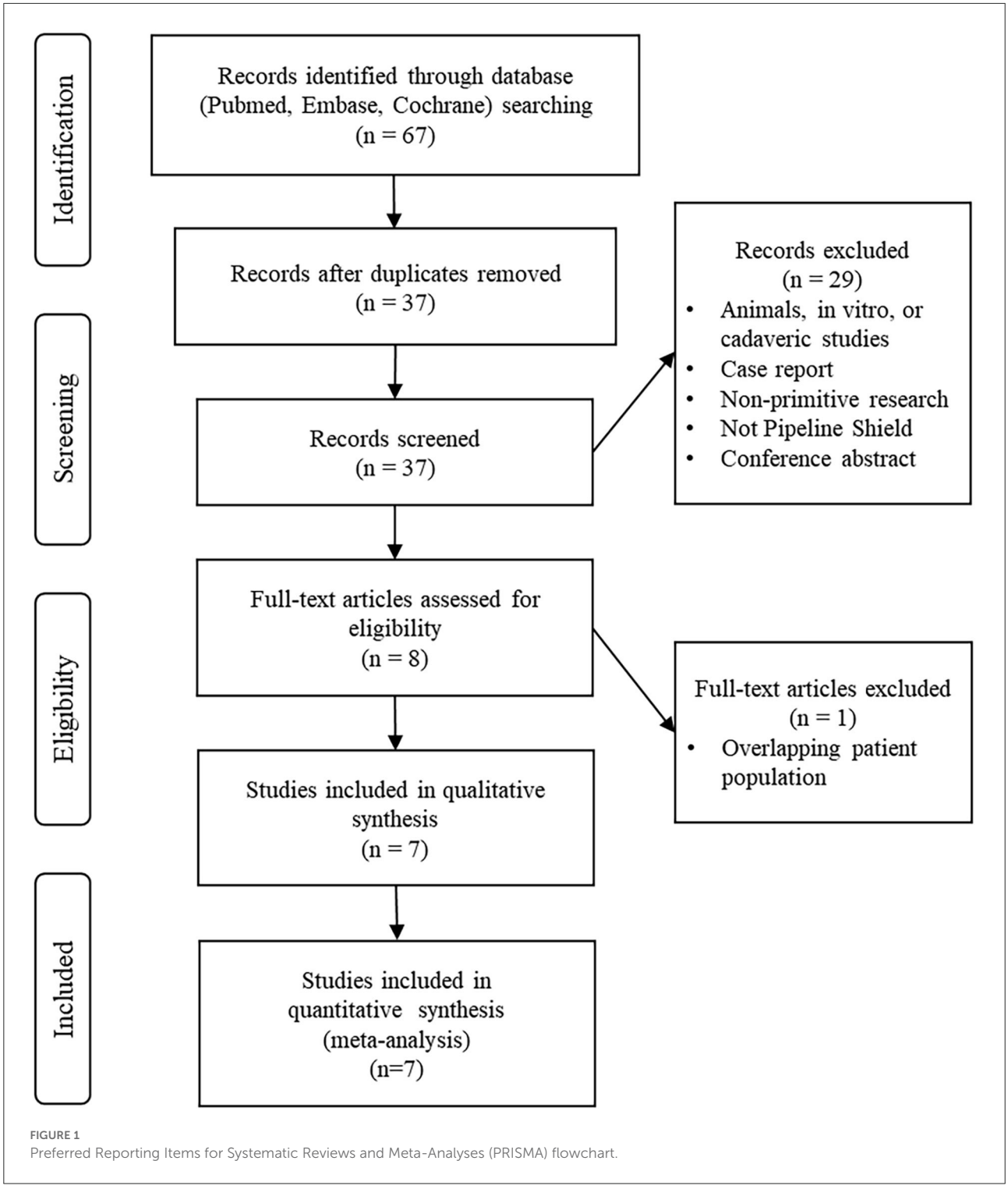

FIGURE 1
Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flowchart.

and complete aneurysm occlusion rate of 80.4% (24). In another systematic review, the rate of complete or near-total occlusion of small intracranial aneurysms treated with a Silk Vista Baby FD was 72.1% at early follow-up. The postoperative mortality rate was 2.5%, including neurological death in three cases (1.8%) (25). Asnafi et al. reported that the rate of midterm complete occlusion of the Woven EndoBridge device was 22% in an unruptured aneurysm group compared with 45%

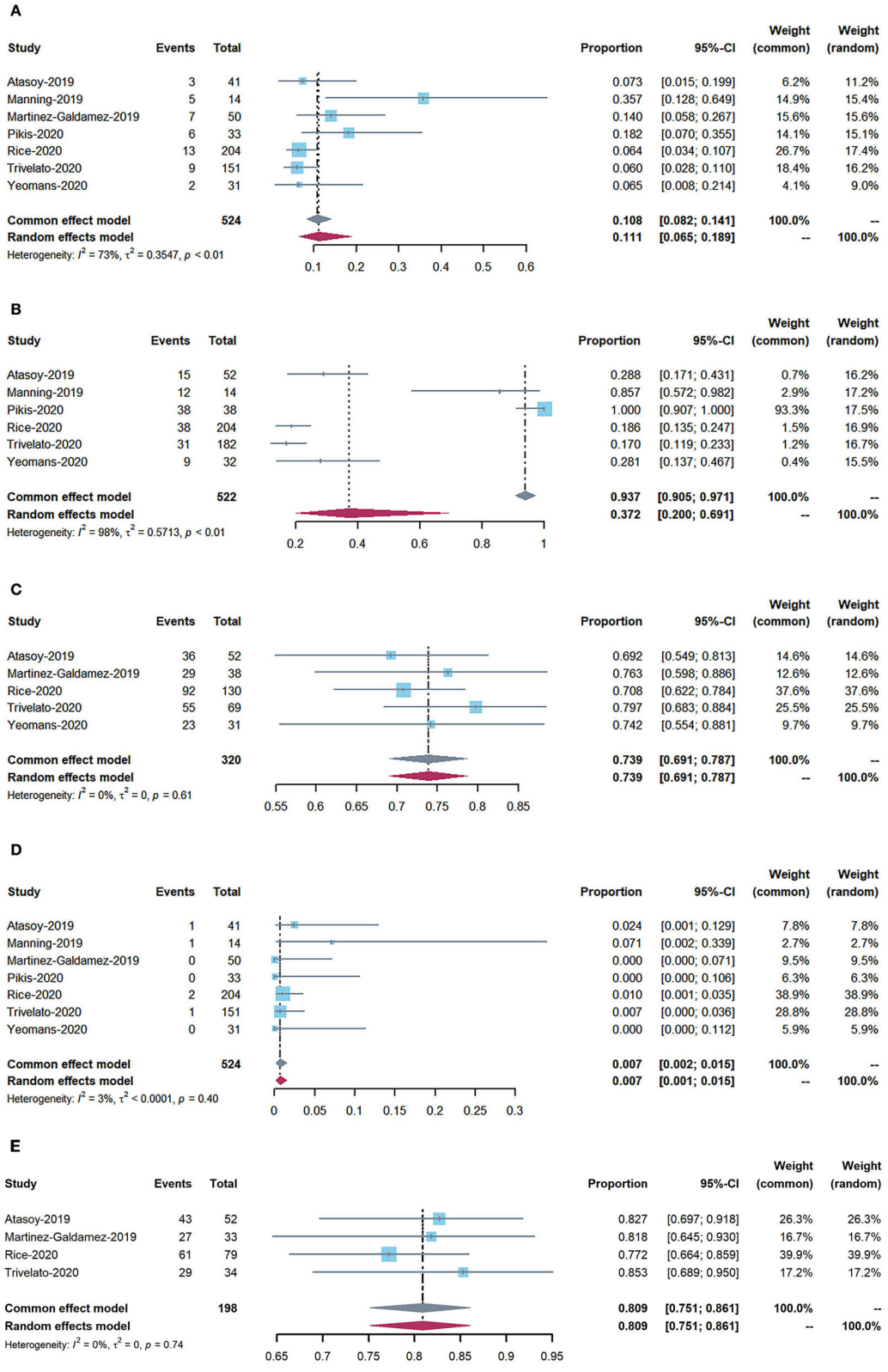

FIGURE 2
Forest plots: **(A)** periprocedural and postoperative complications; **(B)** use of adjunctive coiling; **(C)** adequate occlusion at 6-month follow-up (defined as Raymond–Roy class 1, O'Kelly–Marotta grade D, or Kamran grade 4); **(D)** mortality; and **(E)** adequate occlusion rate of more than 12 months follow-up.

TABLE 2 Characteristics of each study included in our review.

Study, year	No. of patients	Age (mean years), sex (% F)	Design	No. of aneurysms, status	Aneurysm sizes	Neck width	Fusiform, dissecting, pseudoaneurysm or blister (%)	Circulation (%)	Locations (%)	No. of the usage of the pipline shield device				Adjunctive devices (%)		Mortality rate (%)	Morbidity rate* (%)	Adequate occlusion rate (%)
										One device	Multiple devices	Unsuccessful	Devices per aneurysm	Coiling	Balloon			
Atasoy et al. (10)	41	56, 68.3%	Retrospective study	52 unruptured	60.8%<10 mm 34.6% 10–25 mm 3.8% ≥ 25 mm	5.0, 1.0–21.0 mm (Mean, Range)	5.80%	Anterior circulation:88.5% Posterior circulation:11.5%	3.8% ICA C4 55.7% ICA paraophthalmic segment 23.1% ICA C7 3.8% ICA terminal segment 1.9% MCA M1 5.8% BA 3.8% VA 1.9% PCA	1 device per aneurysm: 41	2 devices per aneurysm;2	One device	0.86	28.8%(15/52)	-	2.4% (1/41)	7.3% (3/41)	69.2% (36/52) at 6 months; 82.7% (43/52) at 18 months.
Manning et al. (11)	14	63, 85.7%	Retrospective study	14 ruptured	35.7%>10 mm 64.3% ≤ 10 mm	Unknown	50%	Anterior circulation:57.1% Posterior circulation:42.9%	21.4% MCA M1 14.3% ACA A1/A2 7.1% AChA 7.1% AcommA 7.1% ACA A2 21.4% VA 14.3% PICA 7.1% PcommA	Unknown	Unknown	-	1.2	85.7% (12/14)	-	7.1% (1/14)	35.7% (5/14)	50.0% (7/14) patients with immediate aneurysm occlusion
Martinez-Galdamez et al. (12)	50	53, 82%	Prospective study	50 unruptured	76% < 10 mm 22% 10–25 mm 2% ≥ 25 mm	Unknown	2.00%	Anterior circulation:94% Posterior circulation:6%	94% ICA 6% VA	Unknown	Unknown	Three devices	1.12	-	-	0	14% (7/50)	76.3%(29/38) at 6 months; 81.8%(27/33) at 12 months.
Pikis et al. (13)	33	54.4, 81.8%	Prospective study	31 unruptured 7 ruptured	68.4% < 10 mm 21.1% 10–25 mm 3% ≥ 25 mm	Unknown	7.90%	Anterior circulation:92.1% Posterior circulation:7.9%	92.1% ICA 7.9% BA	1 device per aneurysm: 35; 1 device for three aneurysms: 1	2 devices per aneurysm: 1	-	0.97	100%(38/38)	-	0	18.18% (6/33)	Not pursued.
Rice et al. (14)	204	54.8, 81.4%	Prospective study	166 unruptured 38 ruptured	50% < 7 mm 33.8% 7–13 mm 13.7% 13–25 mm 2.5% ≥ 25 mm	4.6 ± 2.39 mm(mean ± SD)	4.90%	Anterior circulation:93.6% Posterior circulation:6.4%	1.5% ACA A1 2.5% ACA A2 5.9% AcommA 1.0% MCA M1 0.5% MCA M2 6.4% MCA bifurcation 1.0% ICA C1 0.5% ICA C2 1.5% ICA C3 3.9% ICA C4 8.8% ICA C5 41.2% ICA C6 19.1% ICA C7 6.4% VA V4	1 device per aneurysm: 177	2 devices per aneurysm;23	Four devices	1.1	18.6% (38/204)	10.8% (22/204)	1.0% (2/204)	6.4% (13/204)	70.8% (92/130) at 6 months; 77.2% (61/79) at 12 months.
Trivelato et al. (15)	151	52.7, 79.5%	Prospective study	175 unruptured 7 ruptured	The mean aneurysm size was 7.0 mm; 27 (14.8%) aneurysms were large, and 7 (3.8%) were giant.	4.1 ± 2.1 mm(mean ± SD)	7.10%	Anterior circulation:93.4% Posterior circulation:6.6%	6.5% ACA 11.0% Cavernous 8.2% Communicating 10.4% MCA 53.8% Paraophthalmic 11.1% Other	1 device per aneurysm: 177	2 devices per aneurysm: 4; 3 devices per aneurysm: 1	-	1.03	17%(31/182)	11.5% (18/182)	0.66% (1/151)	6.0% (9/151)	79.7% (55/69) at 6 months; 85.3% (29/34) at 12 months.
Yeomans et al. (16)	31	58.8, 84.1%	Prospective study	32 unruptured	50% < 10 mm 41% 10–25 mm 9% ≥ 25 mm	5.9 ± 3.0 mm(mean ± SD)	100%	Anterior circulation:94% Posterior circulation:6%	3.1% ACA 15.6% ICA C4 6.3% HA 3.1% MCA bifurcation 18.8% ICA paraophthalmic 46.9% PcommA 3.1% Distal BA 3.1% Proximal BA	1 device per aneurysm: 29	2 devices per aneurysm: 3	-	1.09	28.1% (9/32)	-	0	6.5% (2/31)	74.2% (23/31) at 6 months.

ACA, anterior cerebral artery; AcommA, anterior communicating artery; AChA, anterior choroidal artery; A1/A2, first/second segment; BA, basilar artery; C1, cervical segment; C2, petrous segment; C3, lacerum segment; C4, cavernous segment; C5, clinoid segment; C6, ophthalmic segment; C7, communicating segment; F, female; HA, hypophyseal artery; ICA, internal carotid artery; MCA, middle cerebral artery; M1, pre-bifurcation segment; M2, post-bifurcation segment; No, number; PCA, posterior cerebral artery; PcommA, posterior communicating artery; PICA, posterior inferior cerebellar artery; SD, standard deviation; VA, vertebral artery; V4, intradural segment; *Perioperative and postoperative 1 year such as ischemic/hemorrhagic stroke and other complications.

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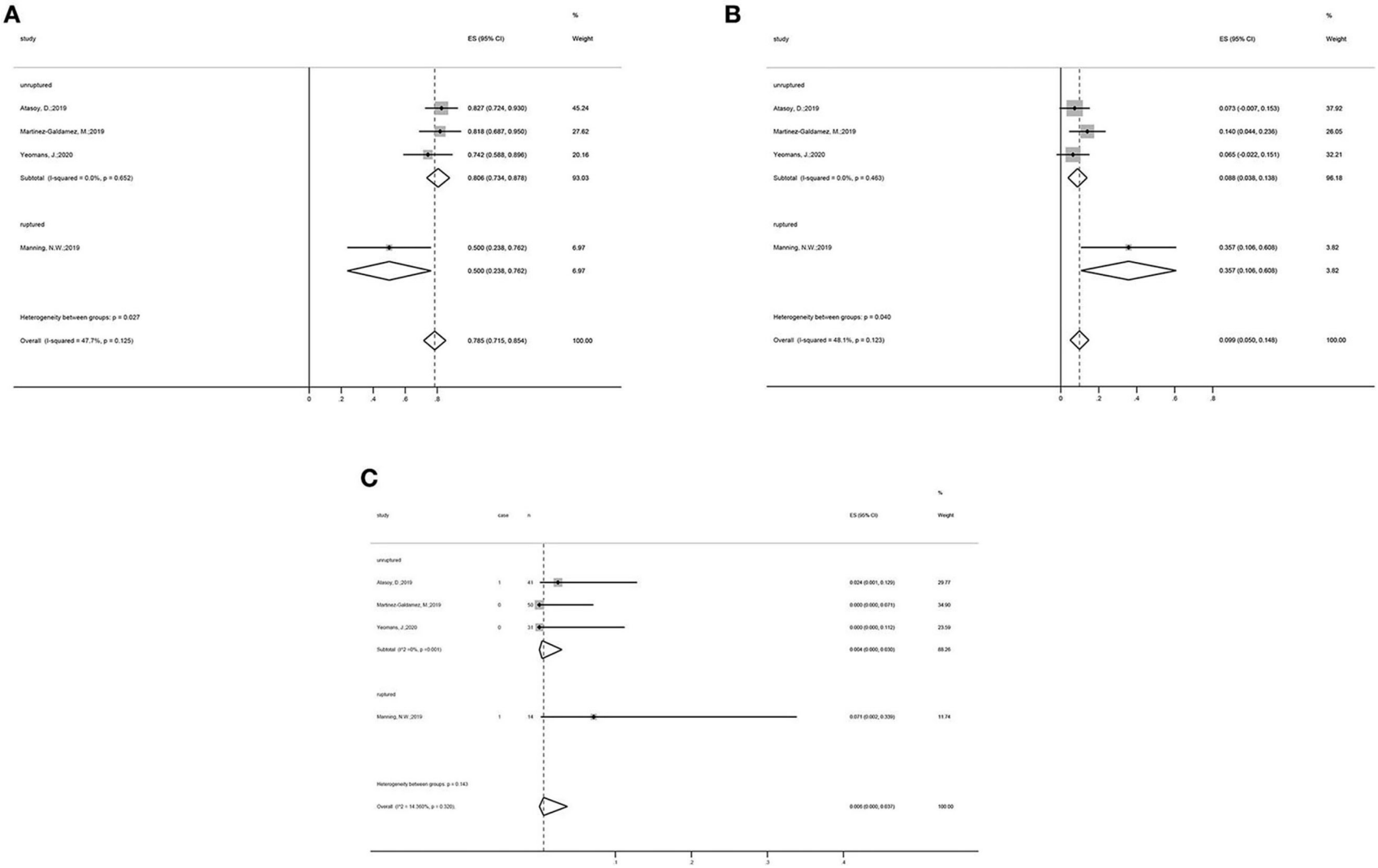

FIGURE 3
Subgroup analysis forest plots: Subgroup analysis on the **(A)** adequate occlusion rate, **(B)** morbidity rate, and **(C)** mortality rate, all categorized by the status of aneurysms (unruptured vs. ruptured group).

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TABLE 3 Comparison between PED with shield technology and the PED without shield technology.

	PED with shield technology	PED without shield technology (11)
Occlusion rate	80.9%	76.8%
Complication rate	11.1%	1.4%
Mortality rate	0.7%	0.7%

PED, pipeline embolization device.

in a ruptured group. Perioperative morbidity was 4%, and perioperative mortality was 1% (26). In a meta-regression analysis predicting aneurysm treatment outcomes with PEDs, the estimated aneurysm occlusion rate was 76%, and the estimated death and modified Rankin Scale $\leq$2 rates at unspecified follow-up times were 2 and 92%, respectively (27). Wakhloo et al. performed a study evaluating Surpass devices and found intraprocedural in-stent clot formation in 3.7% of patients. The overall morbidity rate was 6%, and the mortality rate was 2.7% (28). In another systematic review on the utilization of pipeline flex devices for treating unruptured intracranial aneurysms, a low periprocedural risk of death (0.8%) or major complications (1.8%) was reported. The risk of major complications occurring was significantly higher for large/giant aneurysms (4.4%) than for small aneurysms $<$10 mm (0.9%) (29). Bhatia et al. performed a systematic review on the utilization of flow redirection endoluminal devices for treating intracranial aneurysms and reported that the occlusion rate between 4 and 6 months was 73.8%, the overall reported morbidity rate was 3.9%, and procedure-related mortality was 1.4%. Complication rates fell into five categories: technical (3.6%), ischemic (3.8%), thrombotic or stenotic (6%), hemorrhagic (1.5%), and non-neurological (0.8%) (30). The DED is another surface-modified FD. In a meta-analysis of its utilization, the rate of periprocedural ischemic and hemorrhagic complications was 4.9%, the complete angiographic occlusion rate was 81.4%, and the mortality rate was 2.1% (31). Moreover, Li et al. performed a meta-analysis on the outcome of FDs with surface modifications and determined that the rate of aneurysm occlusion was 80.5% at 6 months and 85.6% at 12 months. The pooled estimate for the total ischemia rate was 6.7%, of which the severe ischemia rate was 1.8%. Morbidity and mortality rates were 6.0 and 0.7%, respectively (32).

When we collated the data, we found that some aneurysms were treated using adjunctive devices in addition to FDs, but details about the patients requiring adjunctive devices were not provided; thus, we could not analyze whether such devices were beneficial. However, in a study on pipeline-assisted coiling vs. pipeline in FDs for treating intracranial aneurysms, the authors reported that joint PED and coiling were safe with no increase in complications when compared with PED alone. Aneurysm occlusion rates and functional outcomes with PED and coiling remained comparable to those of treatment with PED alone (33). Atassoy et al. purported that putative occlusion rate differences were unlikely to be caused by a difference in adjunctive coiling (10). The rates of adjunctive coil use did not appear beneficial for aneurysm occlusion, and evidence for potential benefits is currently lacking (33). Interestingly, adjunctive coiling may be more helpful for preventing aneurysm rupture during thrombosis than for increasing the occlusion rate. Moreover, additional overlapping devices may increase coverage by increasing mesh density, thereby affecting occlusion rate. In endovascular treatments, the aneurysm sac diameter may influence the occlusion rate, especially in aneurysm coiling. As mentioned above, however, a meta-analysis on FDs revealed no relationship between the sac diameter of aneurysms and occlusion rates (34). Compared with the coils alone, combining other techniques can treat complex aneurysms and reduce the recurrence rates. In a study by Lin et al., coils in conjunction with a PED yielded higher aneurysm occlusion rates and reduced the need for retreatment (35). Because FDs cannot provide direct dome protection, large and giant aneurysms could take longer to completely occlude when treated with percutaneous endovascular embolization alone (36). Therefore, until total occlusion is achieved, these aneurysms remain at risk of rupture during the follow-up period (37, 38). In addition, studies have found intraoperative device prolapse and postoperative device displacement/shortening (39, 40), which may lead to rupture and the need for retreatment (40). Therefore, for aneurysms at risk of imminent rupture, the combined use of coils and PEDs may be more effective and provide additional mechanical support, thereby reducing the risk of device dislocation and need for retreatment.

In a meta-analysis evaluating the efficacy of FDs in posterior compared to anterior circulation aneurysms, posterior circulation aneurysms were found to be effectively treated using FDs, with comparable occlusion rates to those in anterior circulation aneurysms. However, the risk of periprocedural complications was not negligible (41). Early studies have reported higher complication rates associated with the use of FDs in the posterior circulation (42–45). This may be due to the presence of numerous perforating arteries supplying the brainstem (46). We could not compare the treatment effects between anterior and posterior circulation aneurysms because we were unable to obtain more detailed information.

Owing to the complexity of patients' conditions and disagreements on antiplatelet regimens for pipeline shield utilization, protocols for antiplatelet therapy among the trials included in our review were not uniform (Table 4). The FDs need DAPT to prevent thrombosis and ischemic complications. However, DAPT increases the risk of hemorrhagic complications (47). Studies have shown that the pipeline shield can reduce platelet adhesion to the surface

TABLE 4 Antiplatelet regimen in each study.

Study, year	Antiplatelet	Platelet-resistance testing
Atasoy et al. (10)	DAPT 7–10 days preprocedure, continued clopidogrel once daily for 6–9months and continued aspirin for life (all doses, 75mg daily).	No.
Manning et al. (17)	14/14(100%) patients received SAPT therapy. 2/14(14%) patients were preloaded, and 2/14(14%) patients were loaded immediately postoperatively. The remaining 10/14(71%) patients were loaded intraoperatively.	Not mentioned.
Martinez-Galdamez et al. (12)	Prior to the procedure, 46/50 (92%) patients received DAPT (aspirin +clopidogrel/prasugrel) and 4/50 (8%) patients received SAPT (clopidogrel). 50/50 (100%) patients were prescribed DAPT between ≥1 month and ≤1 year post-procedure.	Not mentioned.
Pikis et al. (13)	31/33(94%) patients received DAPT (aspirin 100 mg/day +clopidogrel 75 mg/day) 5 days preprocedure. 1/33(3%) patient received DAPT (aspirin 100 mg/day +prasugrel 10 mg/ day) 5 days preprocedure. 1/33(3%) patient received SAPT (prasugrel 10 mg/ day) 5 days preprocedure. All patients were instructed to continue with the preprocedural antiplatelet regimen until the 6 month angiographic and clinical follow-up.	No.
Rice et al. (14)	195/205 (95.6%) patients received antiplatelet therapy prior to study treatment. DAPT was administered pre- procedure (≥7 days) in 57/195 (29.2%) of subjects, on days 1–6 preprocedure in 104/195 (53.3%), on the day of the procedure in 182/195 (93.3%), and immediately prior to the procedure in 161/195 (82.6%). 193/195 (99%) subjects received DAPT post- procedure, and of these, 20% (39/195) interrupted DAPT within 3 months and continued with SAPT [either aspirin (19.5%) or clopidogrel (0.5%)]. 24/195(12.3%) subjects never interrupted DAPT during follow-up. SAPT was administered pre- procedure (≥7 days) in 4/195 (2.1%) of subjects, on days 1–6 pre- procedure in 9/195 (4.6%), on the day of the procedure in 8/195 (4.1%), and immediately pre- procedure in 13/195 (6.7%). Only 2/195 (1.0%) of subjects received SAPT post- procedure.	Not mentioned.
Trivelato et al. (15)	Patients were asked to take DAPT (aspirin 100 mg/day+ clopidogrel 75 mg/day or ticagrelor 90 mg twice a day) for 5 days prior to the intervention and for 6 months afterward. Aspirin was maintained for another 6 moonths. For ruptured aneurysms, all patients were premedicated with a loading dose of aspirin (300 mg) plus clopidogrel (600 mg) 3 h before the procedure. After treatment, these patients received the standard antiplatelet regimen.	No.
Yeomans et al. (16)	The elective cases received dual antiplatelet therapy post-procedure. The acute cases received single antiplatelet therapy post-procedure. Elective patients received single oral doses of aspirin 300 mg and clopidogrel 600 mg the night before the procedure. The VerifyNow P2Y12 assay (Werfen, Spain) was used to confirm an adequate response to dual antiplatelet therapy. All unruptured, elective aneurysm patients with a good P2Y12 antagonist response were placed on a post-procedure regimen of oral clopidogrel 75 mg once daily for 5 months and oral aspirin 75 mg once daily for 12 months. The procedure would have been abandoned in P2Y12 antagonist non-responders. Poor P2Y12 antagonist responders would have been given oral prasugrel 5–10 mg once daily for 5 months. Acute patients received a single intravenous dose of aspirin 500 mg immediately prior to the deployment of the Pipeline device during the procedure. All acute patients received a single antiplatelet therapy regimen post-procedure of oral aspirin 75 mg once daily for 12 months.	VerifyNow P2Y12 assay.

DAPT, dual antiplatelet therapy; SAPT, single antiplatelet therapy; IV, intravenous injection.

(19, 48, 49). *In vivo*, single antiplatelet therapy with pipeline shield had similar thrombogenicity to that of DAPT with PED-Flex (4). Therefore, pipeline shield devices may reduce the need for antiplatelet drugs, thereby reducing the risk of hemorrhage. The role of antiplatelet and anticoagulant medications in treating unruptured aneurysms has been controversial. Retrospective studies have reported that patients taking long-term aspirin exhibit a reduced risk of rupture, while those taking dipyridamole and new aspirin may be at risk of subarachnoid hemorrhage (50, 51). In another study, patients taking aspirin (28%) were found to have lower bleeding rates than those not taking aspirin (40%) (52). Aspirin was also not found to worsen outcomes after subarachnoid hemorrhage (51). In contrast, anticoagulants were associated with poor prognosis

after subarachnoid hemorrhage (53) but did not increase the risk of aneurysm rupture (54, 55).

Our study has the following limitations. As some articles included in our review reported retrospective results based on small samples, our results may be biased. Further, as antiplatelet therapy regimens vary between studies and institutions, no reliable conclusions could be drawn regarding antiplatelet therapy.

Conclusion

Technological improvements have greatly improved endovascular treatment options for aneurysms. As a novel surface-modified PED, the pipeline shield is increasingly used to treat intracranial aneurysms. From our review, we determined that this intervention results in low rates of mortality and a high rate of 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.

Author contributions

CL and LJin conceived the project and drafted the manuscript. EL, BL, and ZF searched the databases and analyzed data. JD, SY, PL, and LJia were responsible for the whole process of supervision. SZ and WH revised the manuscript. All authors read and approved the final version of the 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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Coiling followed by staged flow diversion for large and giant intracranial aneurysms

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Objective: Delayed aneurysm rupture is a fatal complication after flow diversion treatment for large and giant intracranial aneurysms. This study aimed to investigate the feasibility and safety of coiling first and followed by planned flow diversion to prevent delayed aneurysm rupture.

Methods: From January 2017 to December 2021 in two institutions, patients with unruptured intracranial aneurysms treated by coiling first and planned flow diversion were retrospectively collected. Data on demographic and aneurysmal characteristics, procedural details, and clinical and angiographic outcomes were reviewed.

Results: Thirty patients were included (7 Males and 23 Females; Median age 57 years). Aneurysmal size ranged from 11.8 to 26.8 mm, with a median value of 18.5 mm. All aneurysms were located within the intradural segment of internal carotid arteries. Coiling and planned flow diversion were successfully performed in all patients. The time interval between coiling and flow diversion was 3.9–6.7 weeks, with a median value of 5.2 weeks. No hemorrhagic or ischemic complications occurred during the procedures and follow-up. Complete or subtotal occlusion was achieved in 86.7% (26/30) at the last angiographic follow-up (median 6.7 months).

Conclusion: The preliminary data suggested that coiling unruptured intracranial aneurysms followed by planned flow diversion is both safe and effective. Further studies with larger cohorts are needed to verify the effect of this new strategy in preventing delayed rupture after flow diversion.

KEYWORDS

intracranial aneurysm, flow diverter, complication, delayed aneurysm rupture, endovascular treatment

Introduction

Flow diverter (FD) has been an optimal endovascular treatment technique for large and giant intracranial aneurysms (IAs), and its indication continues to be expanded (1). Despite the high occlusion rate, complications of FD treatment could not be ignored. Delayed aneurysm rupture is a rare but fatal complication after FD placement (2, 3). The mechanism of this complication has not been well established, but it is believed that the interaction between hemodynamic changes caused by FD and sequential thrombosis formation plays a crucial role. Some hemodynamic studies revealed that FD placement could result in dramatic and undesirable flow changes, which increased intra-aneurysmal pressure and wall tension (4).

Concomitant coiling with FD is suggested by some authors to prevent delayed aneurysm rupture by obstructing inject flow (fast and concentrated contrast agent flow shooting from aneurysm neck to aneurysm sac on 2D-DSA) and accelerating thrombosis formation (5). However, there is no reliable evidences that concomitant coiling could eliminate delayed rupture. As shown in the review of Rouchaud et al. (3), 20 % of aneurysms that experienced delayed rupture were coiled. This could be explained by that though concomitant coiling could accelerate the thrombosis process, there's still a time lag before stable aneurysm obliteration by thrombosis.

Based on the existing knowledge of the mechanism of delayed rupture, we hypothesize that coiling first to induce adequate intra-aneurysmal thrombosis formation and then implanting FD in a second stage would benefit to reduce the risk. Here, we reported a cohort of unruptured intracranial aneurysms that were treated with this preliminary modality to investigate its feasibility and safety.

Methods

The Institution Review Boards of Changhai Hospital and Ningbo City First Hospital approved this retrospective study. All the patients were informed of staged coiling followed by flow diversion treatment for their intracranial aneurysms.

Patients selection

Between January 2017 and December 2021 in the two institutions, 30 patients with unruptured intracranial aneurysms were treated with coiling followed by planned FD implantation. The demographic characteristics, clinical presentation, aneurysmal morphology, and location were collected for the 30 cases (Table 1).

Staged coiling followed by flow diversion treatment would be conducted when an aneurysm met the following characteristics: (1) maximum diameter > 10 mm (large, 10–25 mm; giant, >25 mm); (2) relatively narrow neck (dome to neck ratio ≥2.0); (3) inject flow sign; (4) located within the intradural segment of cerebral arteries.

TABLE 1 Characteristics of patients and aneurysms.

Characteristic	Value
Gender [*n* (%)]	
Male	7 (23.3)
Female	23 (76.7)
Age (years)	
Range	25–68
Median (IQR)	57 (48, 61)
Hypertension [*n* (%)]	7 (23.3)
Diabetes [*n* (%)]	5(16.7)
Smoking [*n* (%)]	8 (26.7)
Family history of aSAH [*n* (%)]	1 (3.3)
Clinical presentation [*n* (%)]	
Headache	10 (33.3)
Visual symptoms	7 (23.3)
Incidentally	7 (23.3)
Dizziness	5 (16.7)
Ischemic events	1 (3.3)
Aneurysm location [*n* (%)]	
Ophthalmic Segment	13 (43.3)
Supraclinoid Segment	13 (43.3)
Communicating Segment	4 (13.3)
Maximum diameter (mm)	
Range	11.8–26.8
Median (IQR)	18.5 (16.1, 20.9)
Neck diameter (mm)	
Range	2.9–9.0
Median (IQR)	5.9 (5.3, 6.5)
Dome to neck ratio	
Range	2.0–4.9
Median (IQR)	3.1 (2.9, 3.5)

Endovascular procedures and antiplatelet protocol

All endovascular procedures were performed under general anesthesia and systematic heparin. *Via* femoral artery approach, a femoral artery sheath and a guiding catheter were used to provide proximal support. In the first stage of coiling, microcatheters were pre-shaped and guided by microwires into aneurysm sacs to deliver coils. The staged FD was performed at least 4 weeks after coiling to allow adequate thrombosis formation within the aneurysm. During the interval period, phone call follow-up was conducted to confirm the safety of

patients. They were advised to accept staged FD within one month after the delay for thrombosis formation. After FD implant, 80 mg methylprednisolone was given intravenously to prevent the risk of rupture associated with thrombus-induced inflammation. FDs used in our institutions were Tubridge Flow Diverter (TFD, MicroPort, Shanghai, China) and Pipeline Embolization Device (PED, Medtronic, USA). Both TFDs and PEDs were developed through a dedicated microcatheter (for TFD: T-track, MicroPort; for PED: Marksman, Medtronic) using the push-pull technique. In cases that required further coiling, another microcatheter would be positioned in the aneurysm sac before the deployment of FDs.

Each patient received dual antiplatelet treatment (100 mg/day aspirin plus 75 mg/day clopidogrel) for at least 3 days before FD implantation. A postoperative antiplatelet regimen was administered as follows: <3 months: 100 mg aspirin+75 mg clopidogrel; ≥3 months: 100 mg aspirin indefinitely. For patients with clopidogrel resistance according to Thrombelastography (TEG) examination, ticagrelor 90 mg twice a day would be given.

TABLE 2 Treatment characteristics of the patients.

Characteristic	Value
Interval between Coiling and FD (weeks)	
Range	3.9–6.7
Median (IQR)	5.2 (4.3, 6.0)
FD Type [*n* (%)]	
Tubridge	21 (70.0)
Pipeline	9 (30.0)
Adjunctive Techniques with FD [*n* (%)]	
Balloon remodeling	2 (6.7)
Further coiling	3 (10.0)
Procedural-related complication [*n* (%)]	
Hemorrhagic complication	0 (0.0)
Ischemic complication	0 (0.0)
Duration of Follow-up after FD (months)	
Range	4.4–15.3
Median (IQR)	6.7 (5.8, 8.6)

FD, flow diverter.

Angiographic outcomes evaluation

All patients were advised to undergo angiographic follow-up 6 months after the treatment and annually thereafter. Two experienced neuroradiologists interpreted the angiography images together to avoid bias. Angiographic outcomes of coiling and FD treatment were classified into 3 categories to allow comparison between different treatment phases: (a) complete occlusion, no contrast filling of the aneurysm sac; (b) subtotal occlusion, minor residual sac filling or neck remnant; (c) incomplete occlusion, substantial residual sac filling.

Results

Patients and aneurysms

There were 23 (76.7%) women and 7 (23.3%) men, with a median age of 57 years (range 25–68 years). Aneurysms were detected for headache in 10 (33.3%) patients, visual symptoms in 7 (23.3%) patients, dizziness in 5 (16.7%) patients, transient ischemic stroke in 1 (3.3%) patient, and incidentally found in 7 (23.3%) patients.

Of the 30 aneurysms, 2 were Giant aneurysms (>25 mm) and the others were large aneurysms (10–25 mm). All the cases were saccular aneurysms. The maximum diameters of the intracranial aneurysms ranged from 11.8 to 26.8 mm, with a median size of 18.5 mm (IQR 16.1–20.9 mm). The aneurysm neck ranged from 2.9 to 9.0 mm, with a median value of 5.9 mm (IQR 5.3–6.5 mm). The dome-to-neck ratio (maximum diameter/neck width) of the aneurysms ranged from 2.0 to 4.9, with a median value of 3.1 (IQR 2.9–3.5). All aneurysms were located at intradural segments of internal carotid arteries, with 13 (43.3%) aneurysms at the ophthalmic segment, 13 (43.3%) at the supraclinoid segment, and 4 (13.3%) at the communicating segment.

Clinical outcomes

All procedures, coiling and staged FD implantation, were successfully performed. The treatment characteristics of all patients were listed in Table 2. TFDs were implanted in 21 aneurysms and PEDs in 9 aneurysms. Balloon remodeling was needed in 2 (6.7%) patients, in which the position of FD was not satisfied. Additional coiling was performed in 3 (10.0%) patients during the staged procedures. No procedure-related hemorrhagic or ischemic events occurred. Clinical follow-up ranged from 4.4 to 15.3 months, with a median interval of 6.7 months (IQR 5.8–8.6 months). No deterioration of the mRS score was observed during follow-up. Of the 7 patients with vision deficits, improvement of vision happened in 2 patients and the others were stable.

Angiographic outcomes

Angiographic outcomes in all treatment stages were shown in Table 3. The obliteration process of the aneurysm was illustrated in Figure 1. After first-stage coiling, the immediate results showed that complete occlusion was achieved in 1(3.3%)

TABLE 3 Radiologic outcomes.

Angiographic outcomes	No. of aneurysms (%)			
	Immediate after coiling	Pre-flow diverter	Immediate after flow diverter	Last follow-up
Complete occlusion	1 (3.3)	1 (3.3)	1 (3.3)	19 (63.3)
Subtotal occlusion	5 (16.7)	4 (13.3)	7 (23.3)	7 (23.3)
Incomplete occlusion	24 (80.0)	25 (83.3)	22 (73.3)	4 (13.3)

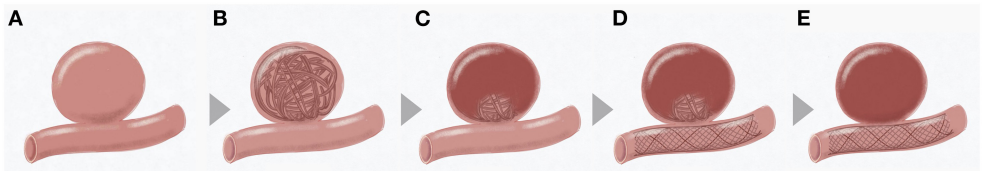

FIGURE 1
Flow chart of coiling followed by staged flow diversion for unruptured intracranial aneurysms. **(A)** Sketch of an intracranial aneurysm; **(B)** First-stage coiling; **(C)** Thrombosis formation induced by coiling; **(D)** Second-stage flow diversion; **(E)** Complete occlusion after flow diversion.

patient, subtotal occlusion in 5 (16.7%), and incomplete occlusion in 24 (80.0 %).

The median delay of staged FD implantation was 5.2 weeks (range 3.9–6.7 weeks; IQR 4.3–6.0 weeks). The angiography right before FD implantation showed complete occlusion in 1(3.3%) patient, subtotal occlusion in 4 (13.3%), and incomplete occlusion in 25 (83.3%). Compared to the immediate results of initial coiling, coil compression was observed in 9 (30.0%) aneurysms, improvement in 14 (46.7%), and unchanged in 7 (23.3%). Immediately after FD implantation, the degree of occlusion was improved in 10 aneurysms (3 from incomplete to subtotal occlusion; 7 remained incomplete but with a reduction of filling volume).

The duration of follow-up after FD treatment ranged from 4.4 to 15.3 months, with a median value of 6.7 months (IQR 5.8–8.6 months). At the last follow-up, complete occlusion was achieved in 19 (63.3%) patients, subtotal occlusion in 7 (23.3%) patients, and incomplete occlusion in 4 (13.3%) patients. No in-stent stenosis was observed during the follow-up. All covered branches (17 ophthalmic arteries, 8 anterior choroid arteries, and 5 posterior communicating arteries) were patent, except for 2 cases where the flow of covered ophthalmic arteries reduced without symptom. Figure 2 displayed the treatment procedures and 6-month follow-up outcome in an aneurysm located at the ophthalmic segment. The example cases for aneurysms located at the supraclinoid segment and the communicating segment were attached at Supplementary Figures S1, S2.

Discussion

Delayed aneurysm rupture is a serious complication after FD treatment with extremely high mortality (6). According to a current review, the overall incidence of delayed aneurysm rupture after FD treatment is 1.8% (2). In this study, we proposed a preliminary modality that coiling followed by staged FD for unruptured large and giant IAs. No procedure-related complication occurred and the angiographic outcomes were relatively satisfied, which might suggest the feasibility and safety of this staged strategy.

The concept of coiling followed by staged flow diversion has been introduced in acute ruptured intracranial aneurysms previously. Brinjikji et al. (7) reported 31 patients with complex ruptured intracranial aneurysms by acute coiling followed by staged flow diversion and concluded that the strategy is both safe and effective. Howard et al. (8) also reported a cohort of 22 patients with ruptured intracranial aneurysms treated with staged flow diversion and achieved a subtotal occlusion rate of 91% in follow-up. For unruptured large and giant aneurysms, this strategy could also be effective because thrombosis formation is equally important. The delayed ruptured cases resulted from sudden but undesirable flow changes, such as increasing intra-aneurysmal pressure and aneurysm wall tension (4, 9, 10).

Previously, various attempts have been made to prevent delayed aneurysm rupture by enhancing the flow diversion effect and accelerating thrombosis formation. Concomitant coiling with FD is suggested to help accelerate thrombosis formation (5, 11, 12). Park et al. (12) reported that concomitant coiling with FD resulted in a significantly lower retreat rate compared with FD alone. Similarly, Bender et al. (5) shared their experience of single-stage FD with coiling and concluded that coiling can expedite and improve occlusion outcomes without a significant increase in morbidity. Despite these desirable results, the effect of concomitant coiling on preventing delayed rupture is not clear. Indeed, according to a literature review by Rouchaud et al.

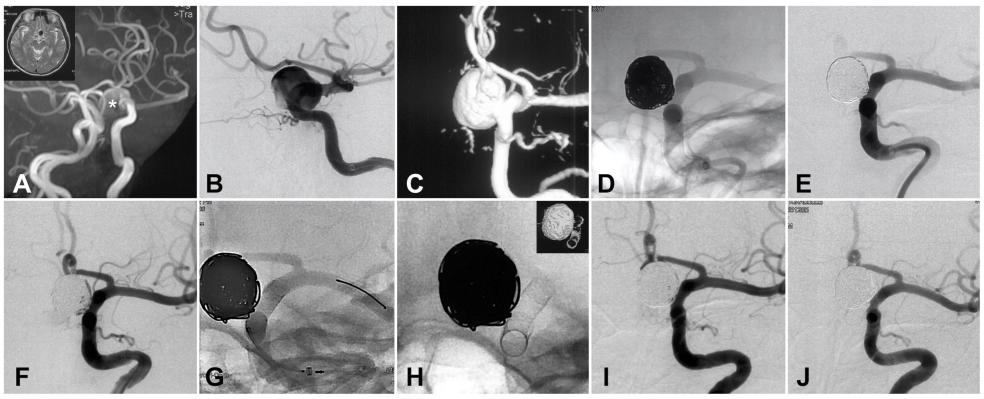

FIGURE 2
Illustration of coiling and staged flow diverter treatment for a large intracranial aneurysm. **(A)** CT and CT angiography identified the giant internal carotid aneurysm. **(B)** DSA confirmed the size and location of the aneurysm. **(C)** Three-dimension re-construction of the DSA. **(D)** First-stage coiling of the giant aneurysm. **(E)** Angiography after first-stage coiling. **(F)** DSA image right before the staged flow diverter (FD) treatment. **(G)** The procedure of FD implantation. **(H)** The shape and location of the implanted FD. **(I)** Angiography immediately after FD implantation. **(J)** Six-month follow-up DSA showed the complete occlusion of the giant aneurysm. *The position of aneurysm cavity.

(3), over 80% of aneurysms that ruptured after FD treatment were not previously coiled; but they also pointed out that coiling might not be a panacea as 20% of delayed rupture happens in aneurysms with concomitant coiling. Although coiling has shortened the process of thrombosis formation, there is still a time lag before adequate thrombosis is established.

Therefore, we hypothesized that coiling first, which can accelerate the process of stable thrombosis formation by occupied effect and constantly disturbing the blood flow perfused into the aneurysm sac, and then implanting FD in a second stage would help to reduce the rupture risk caused by those harmful flow changes. In theory, the thrombosis induced by first-stage coiling could provide more protection for the aneurysmal dome by resisting those dramatic and harmful flow changes caused by staged FD placement The intra-aneurysmal pressure increases would be milder so the possible rupture of an aneurysm might be reduced. In our series, no hemorrhagic complication occurred in all 30 cases, either in the interval between initial coiling and staged FD placement, or after FD placement, which might suggest the feasibility and safety of staged FD for selected lesions. Another priority is that the staged strategy could avoid the usage of anti-platelet medicine in the acute phase, which would favor thrombosis formation inside aneurysms. In addition, the staged FD treatment makes the technique much easier and safer than the single-stage contaminant coiling with FD. In particular, the staged modality would shorten the single procedural time and reduce technical complexity. After FD placement, 80 mg methylprednisolone would be continuously used for 3 days to prevent the possible rupture resulting from thrombus-induced inflammation.

Despite the possible benefit of staged-FD treatment, several concerns need to be noticed. Firstly, patient selection for staged FD is driven by various factors. The compliance with dual antiplatelet therapy and imaging follow-up is most important for selecting patients. The staged strategy should not be recommended to a potentially noncompliant patient. Secondly, second-stage FD placement should be applied timely to avoid significant recurrence after coiling. In the present series, the interval staged FD placement after coiling ranged from 3.9 to 6.7 weeks, with a median value of 5.2 weeks. During this interval, 9 aneurysms presented with acceptable coil compression before staged FD placement. Lastly, this treatment is more costly compared with stent-assisted coiling or FD placement alone. The average cost for coiling plus staged-FD is more than 40,000 USD. Therefore, the risk of rupture and benefit from the operation needs to be fully evaluated before the decision for staged-FD treatment.

Based on the experience of delayed rupture from literature and our clinical practice, we proposed several factors that might result in high delayed rupture risk and should consider coiling first and followed by staged FD.

(1) Intra-dural lesions. The coiling and staged FD technique might be more meaningful for aneurysms distal to the dural ring, which may cause fatal intracranial hemorrhage. (2) Large and giant aneurysms. Several studies have suggested a higher risk of rupture, especially delayed rupture, in large and giant aneurysms (3, 13–15). (3) Aneurysm geometry. Several geometry parameters, for example, aspect ratio (AR) and dome-to-neck ratio (DNR), rely on the width of the neck. Aneurysms with a larger DNR had been proven to correlate with increasing rupture risk (16, 17). In addition, a relatively narrow neck could provide stability for coils, making coiling easy and safe. (4) Flow pattern. Previous hemodynamic studies suggested that the impinging inflow is associated with increased tension of

the aneurysm wall and increased rupture risk (18). In a review of 13 cases of delayed rupture aneurysms by Kulcsar et al. (14), an inflow jet was observed in all cases on DSA images. Coiling and the consequent thrombosis could help to eliminate the direct impact of the inflow jet on the aneurysm wall, and this effect could be enhanced by the staged FD implantation.

This study has several limitations. Firstly, the retrospective design might add obvious bias to patient selection. Secondly, while no delayed aneurysm rupture occurred in this cohort, these data might not be generalizable considering the small sample size. Further studies, both clinical observations, and animal experiments are warranted to determine the mechanism, indication, appropriate interval, and other technical details. Also, no posterior circulation aneurysms were included in this cohort due to the small sample size. Thirdly, some patients enrolled in this study could otherwise be treated by other strategies such as surgical clipping and stent-assisted coiling. The comparison among different strategies was not made in this study. Lastly, the follow-up periods were short. There were incompletely occluded aneurysms at the last follow-up. Long-term follow-up is manipulated to investigate the efficacy and durability of this treatment. Lastly, the cost-effectiveness of this new strategy should also be further discussed.

Conclusion

Overall, our data suggested that coiling followed by planned flow diversion is both safe and effective for unruptured intracranial aneurysms with a potentially high risk of delayed rupture. Further studies with prospective design and increasing sample size are warranted to determine the effect of this staged modality on preventing delayed aneurysm rupture.

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 the Ethics Committee of Changhai Hospital. The patients/participants provided their written informed consent to participate in this study.

Author contributions

JL and ZL: conception or design of the work. YZh, ZL, and YZe: acquisition of data. QL, RZ, and YF: analysis of data. PY and QH: interpretation of data. NL and HM: drafting the work. BH, YX, and ZL: revising the work. JL: final approval of the version. 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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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2022.1024447/full#supplementary-material

SUPPLEMENTARY FIGURE S1
Illustration of coiling and staged flow diverter treatment for a large intracranial aneurysm located at supraclinoid segment. **(A)** The anteroposterior angiography identified size and location of the giant internal carotid aneurysm. **(B)** The lateral angiography confirmed morphology the aneurysm. **(C)** Three-dimension re-construction of the DSA. **(D)** First-stage coiling of the giant aneurysm. **(E)** Angiography after first-stage coiling. **(F)** DSA image right before the staged flow diverter (FD) treatment. **(G)** The shape and location of the implanted FD. **(H)** The parent artery was unaffected after the implanted FD. **(I)** Angiography immediately after FD implantation. **(J)** Six-month follow-up DSA showed the complete occlusion of the giant aneurysm.

SUPPLEMENTARY FIGURE S2
Illustration of coiling and staged flow diverter treatment for a large intracranial aneurysm located at communicating segment. **(A)** The anteroposterior angiography identified the giant internal carotid aneurysm. **(B)** The lateral angiography confirmed location and size of the aneurysm. **(C)** Three-dimension re-construction of the DSA. **(D)**

First-stage coiling of the giant aneurysm. **(E)** Angiography after first-stage coiling. **(F)** DSA image right before the staged flow diverter (FD) treatment. **(G)** The procedure of FD implantation. **(H)** The shape and location of the implanted FD. **(I)** Angiography immediately after FD implantation. **(J)** Six-month follow-up DSA showed the complete occlusion of the giant aneurysm.

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Tubridge flow diverter for the treatment of small and medium aneurysms

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Background: Tubridge flow diverter is a widely used device aimed at reconstructing parent arteries and occluding complex aneurysms in China. The experience of Tubridge in treating small and medium aneurysms is still limited. In this study, we aimed to evaluate the safety and efficacy of the Tubridge flow diverter for the treatment of the two types of aneurysms.

Methods: We reviewed the clinical records of aneurysms treated with a Tubridge flow diverter between 2018 and 2021 in a national cerebrovascular disease center. Cases were divided into small and medium aneurysms according to aneurysm size. The therapeutic process, occlusion rate, and clinical outcome were compared.

Results: In total, 57 patients and 77 aneurysms were identified. The patients were divided into two groups: small aneurysms (39 patients, 54 aneurysms) and medium aneurysms (18 patients, 23 aneurysms). There were 19 patients with tandem aneurysms (a total of 39 aneurysms) in the two groups, among which 15 patients (30 aneurysms) were in the small aneurysm group and four patients (nine aneurysms) were in the medium aneurysm group. The results show that the mean maximal diameter/neck in the small and medium aneurysms was 3.68/3.25 and 7.61/6.24 mm, respectively. In total, 57 Tubridge flow diverters were successfully implanted without unfolding failure, and there were six patients with new mild cerebral infarction in the small aneurysm group. The complete occlusion rate on the last angiographic follow-up was achieved in 88.46% of the small aneurysms group and 81.82% of the medium aneurysms group. The complete occlusion rate of patients with tandem aneurysms in the last angiographic follow-up was 86.67% (13/15) of the small aneurysms group and 50% (2/4) of the medium aneurysm group. Intracranial hemorrhage was nonencountered in the two groups.

Conclusion: Our preliminary experience suggests that the Tubridge flow diverter might be a safe and effective treatment for small and medium aneurysms along the internal carotid artery. Long stents may increase the risk of cerebral infarction. Adequate evidence is required to clarify the definite indications and complications in a multicenter randomized controlled trial with a long-term follow-up.

KEYWORDS

Tubridge, flow diverter, small aneurysm, medium aneurysm, tandem aneurysm

Introduction

Intracranial aneurysm is one of the most common cerebrovascular diseases. The main management methods include clipping, endovascular therapy, and close follow-up. At present, a blood flow diverter, a new effective means of endovascular therapy, is widely used in the treatment of large or giant aneurysms, but there

are few reports on the treatment of small aneurysms and medium aneurysms (1). These aneurysms are most commonly found along the internal carotid artery.

Tubridge is a new type of flow diverter device developed by MicroPort Medical Company (Shanghai, China) based on previous hemodynamic studies of intracranial aneurysms that aims at treating complex aneurysms that are difficult to access by clipping or conventional endovascular treatment, such as large or giant aneurysms, and providing more treatment options for neurointerventionalists and neurosurgeons (2). Numerous studies have since demonstrated its safety and efficacy in the treatment of aneurysms with varying morphologies and anatomic locations.

Currently, there is no study evaluating endovascular treatment of small and medium aneurysms with a Tubridge flow diverter. Therefore, we collected the clinical records, compared the outcomes following Tubridge deployment in patients in the two groups, reviewed the current literature, and discussed its future use.

Materials and methods

Patient selection

The institutional review board of the hospital approved this study and waived the requirement for patient-informed consent due to its retrospective design. We collected the cases of unruptured intracranial aneurysms treated with Tubridge flow diverter from 2018 to 2021 except large (>10 mm) and giant (≥ 25 mm) aneurysms. Patients were then divided into two groups: small aneurysm (≤5 mm) and medium aneurysm (≤10 mm).

Anticoagulation and antiplatelet management

Each patient received systemic heparin after the placement of the microcatheter. The activated clotting time was maintained at 2–3 times the baseline throughout the procedure. Each patient received dual antiplatelet drugs (100 mg/day aspirin plus 75 mg/day clopidogrel) for at least 3 days before the procedure. The intravenous loading dose of tirofiban was 5 μg/kg for 3–5 min and the maintenance dose of tirofiban was 0.1 μg/ (kg·min) for 24 h after Tubridge flow-diverter deployment. A postoperative antiplatelet regimen was administered as follows: ≤3 months, 100 mg/day aspirin + 75 mg/day clopidogrel; >3 months, 100 mg/day aspirin, and 1 year.

Tubridge flow diverter and implantation/coiling procedure

The Tubridge flow diverter is a braided, self-expanding stent device with flared ends. Current Tubridge flow diverters are available in various diameters (2.5–6.5 mm) and lengths (12–45 mm). The Tubridge is composed of nickel–titanium and two platinum–iridium microfilaments. All Tubridge flow diverters were designed with a pore size of 0.040–0.050 mm^2 to provide high metal coverage (∼30.0%−35.0%) at the aneurysm neck after full opening.

The Tubridge is mounted to a delivery wire and constrained within a removable sheath. The tip of the delivery wire is J-shaped, which is designed to help prevent vascular injury, facilitate microcatheter removal through previous devices, and deploy a second flow diverter.

A Tubridge flow-diverter device was introduced *via* the 0.029 inch diameter microcatheter into the target zone. The device began to expand in the artery and was deployed by pushing the delivery wire and simultaneously drawing the microcatheter. In general, the shortening rate after complete deployment is approximately <50.0%, depending on the size of the Tubridge and any discrepancies between the proximal and distal vessel diameters. The device can be retracted until released to the marker in the middle of Tubridge. Before the stent is completely released, coiling embolization is feasible. After the first flow diverter was deployed, a second diverter was considered if necessary.

Angiographic evaluation and clinical outcome

An angiographic evaluation was assessed with digital subtraction angiography based on protocols. The angiographic results obtained immediately after the procedures were based on retention or decreased filling of the contrast agent in the aneurysms. Aneurysm occlusion on follow-up angiography imaging was assessed by the treating interventionalist. The occlusion rate was categorized as complete occlusion (100%), near-complete occlusion (90%−100%), and partial occlusion (<90%). Clinical outcomes were assessed by using the modified Rankin Scale at the last follow-up.

Statistical analysis

Continuous variables, including demographics, aneurysm characteristics, and procedural characteristics, were represented as mean ± SD. Categorical data were presented as numbers and percentages. Continuous variables were compared using the unpaired Student's *t*-test or the Mann–Whitney test and categorical variables were compared using the Fisher's exact test or, if there were more than two possible categories, using the chi-squared test. Statistical significance was defined as $p < 0.05$.

Results

Patient characteristics

In total, 57 patients (38 women and 19 men) and 77 aneurysms with a mean age of 56 years (ranging from 33 to 81 years) and 40.35% of high BMI (≥24) were identified from 2018 to 2021. The case numbers were 39 and 18 in the small and medium aneurysm groups, respectively. The pretreatment mRS score of 41.03% of patients in the small aneurysm group and 44.44% of patients in the medium aneurysm group was 1. The proportion of BMI ≥24 in the medium aneurysm group was significantly higher than that in the small aneurysm group ($p < 0.05$). There was no significant difference in age, gender, or pretreatment mRS between the two groups (Table 1).

Abbreviations: BMI, body mass index; mRS, modified Rankin Scale.

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TABLE 1 Baseline characteristics of enrolled patients.

Parameters	Small aneurysm	Medium aneurysm	*p*-Value
Cases	39 (68.42%)	18 (31.58%)	
Age (years)	55 ± 9	56 ± 10	0.92
Gender (M/F)	12/27	7/11	0.55
BMI ≥24	12 (30.77%)	11 (61.11%)	<0.05*
No. of aneurysms	54	23	0.83
Side of aneurysms			
Right	29 (53.70%)	11 (47.83%)	0.64
Left	25 (46.30%)	12 (52.17%)	
Aneurysm locations			
Middle cerebral artery	1 (2.56%)	0 (0%)	0.49
Internal carotid artery	38 (97.44%)	18 (100%)	
Aneurysm shape			
Saccular	53 (98.15%)	23 (100%)	0.51
Fusiform	1 (1.85%)	0 (0%)	
Dissecting	0 (0%)	0 (0%)	
Aneurysm measurements			
Mean maximal diameter	3.68 ± 0.82	7.61 ± 1.64	<0.05*
Neck size	3.25 ± 0.96	6.24 ± 1.97	
Parent artery diameter			
Distal diameter	3.55 ± 0.45	3.56 ± 0.40	0.99
Proximal diameter	4.21 ± 0.49	4.47 ± 0.46	0.93

*Statistically significant.

Aneurysm characteristics

The aneurysm numbers were 54 and 23 in the small and medium aneurysm groups, respectively. There were 29 and 11 cases on the right side in the small and medium aneurysm groups, respectively ($p = 0.64$). Aneurysms were primarily saccular and located along the internal carotid artery in the two groups. The median maximal diameter of the aneurysm was 3.68 ± 0.82 mm in the small aneurysm group and 7.61 ± 1.64 mm in the medium aneurysm group. The neck diameter of the aneurysms was 3.25 ± 0.96 mm in the small aneurysm group and 6.24 ± 1.97 mm in the medium aneurysm group. The distal diameter of the parent artery was 3.55 ± 0.45 mm in the small aneurysm group and 3.56 ± 0.40 mm in the medium aneurysm group. The proximal diameter of the parent artery was 4.21 ± 0.49 mm in the small aneurysm group and 4.47 ± 0.46 mm in the medium aneurysm group (Table 1).

Implantation/coiling outcome

There was no significant difference in the number ($p = 1$), diameter ($p = 0.97$), or length ($p = 0.91$) of Tubridge in the two groups. Opening failure did not occur during the procedure. The proportion of coil embolization in the medium aneurysm group was higher than that in the small aneurysm group ($p = 0.08$). Branch coverage, such as the ophthalmic artery and posterior communicating artery in the parent artery, occurred in 38 and 18 patients in the small and medium aneurysm groups, respectively. Decreased filling or retention of contrast agents in the aneurysm lumen occurred in 25 (46.30%) and 18 (78.26%) aneurysms in the small and medium aneurysm groups ($p < 0.05$), respectively. There were six patients with new mild cerebral infarction in the small aneurysm group and 0 patients in the medium aneurysm group. No intracranial hemorrhage occurred (Table 2).

TABLE 2 Treatment of Tubridge flow diverter.

Parameters	Small aneurysm	Medium aneurysm	*p*-Value
No. of stents	39	18	1
Stent size			
Diameter	4.03 ± 0.44	4.14 ± 0.52	0.97
Length	29.74 ± 7.60	28.89 ± 5.91	0.91
Unfold failure	0	0	–
Coiling	1 (2.56%)	3 (16.67%)	0.08
Branch coverage	38 (97.44%)	18 (100%)	0.49
Stagnation/decreased contrast filling	25 (46.30%)	18 (78.26%)	<0.05*
Adverse event	6 (15.38%)	0 (0%)	0.08

*Statistically significant.

Follow-up outcome

The mean times of the last angiographic follow-up were 6.8 ± 1.70 and 8.6 ± 1.30 months in the small and medium aneurysm groups, respectively. A total of three cases were lost to follow-up, including two cases in the small group and one case in the medium group. There were six patients suffering from new mild cerebral infarction with no symptoms after Tubridge flow diversion implantation. The mRS score at the last follow-up was 0.16 ± 0.37 (small aneurysm group) and 0.17 ± 0.57 (medium aneurysm group). Mild stent stenosis occurred in one case of the small aneurysm group, but it did not result in any ischemia symptoms. At the last angiographic follow-up, complete occlusion was achieved in 88.46% of patients in the small aneurysm group and 81.82% of patients in the medium aneurysm group. The mRS at the last follow-up improved in 43.75% (7/16) and 50.00% (4/8) of the two groups, and none worsened in the small and medium aneurysm groups, respectively. There was no morbidity or mortality in any group (Table 3).

The clinical and radiologic outcome of Tubridge flow diversion for tandem aneurysms

There were 19 cases with 39 tandem aneurysms embolized by Tubridge flow diversion, including 18 patients with two tandem aneurysms and one patient with three tandem aneurysms. Decreased filling or retention of contrast agents in the aneurysm lumen occurred

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TABLE 3 Outcome measures of follow-up.

Parameters	Small aneurysm	Medium aneurysm	*p*-Value
Cases/aneurysms	37/52	17/22	
Last angiography	6.80 ± 1.70	8.60 ± 1.30	0.65
mRS score	0.16 ± 0.37	0.17 ± 0.57	1
Stent stenosis	1 (2.56%)	0 (0%)	0.49
Occlusion rate			
Complete	46 (88.46%)	18 (81.82%)	0.44
Near-complete	6 (11.54%)	4 (18.18%)	
Partial	0 (0%)	0 (0%)	

in 23 (58.97%) aneurysms of the tandem aneurysms. A total of three patients suffered from new mild cerebral infarction with no symptoms, and no aneurysm ruptured during the operation. The complete occlusion rate of patients with tandem aneurysms on the last angiographic follow-up was 89.75% (35/39; Table 4). The mRS at the last follow-up improved in 50.00% of the cases of the tandem aneurysms group.

Discussion

In this article, we report a preliminary experience with Tubridge placement for the treatment of small and medium aneurysms in the anterior circulation. Our results show that the usage of Tubridge for the treatment of small and medium intracranial aneurysms could achieve a high occlusion rate with low morbidity and mortality. In addition, there was no obvious difference in the aneurysm occlusion rate, clinical outcome, or complications between the small and medium groups. These findings mirrored a higher aneurysm occlusion rate and low complication in the two types of aneurysms.

Flow diversion device for the treatment of small and medium aneurysms

Coiling and stent-assisted coiling are traditional and validated methods for the embolization of small/medium intracranial aneurysms. However, there is still a risk of aneurysm rupture during the insertion of microcatheters and coils into the aneurysm, especially for small aneurysms. Flow diversion devices have rapidly emerged as an essential option for the treatment of intracranial aneurysms, especially for large, giant, and complex aneurysms, due to their high embolization and low complications, which simplifies the procedure by not requiring aneurysmal catheterization (1, 2). However, the use of flow diversion devices in small aneurysms remains to be determined.

Recently, many studies have examined the efficacy and safety of flow diverters for small/medium intracranial aneurysms and indicated high occlusion rates with low morbidity and mortality. The PREMIER study is the first prospective multicenter study to evaluate the use of flow diverters in small/medium, unruptured

TABLE 4 Baseline characteristics, treatment and follow-up of tandem aneurysms.

Parameters	Result
Baseline characteristics	
Patients	
Age (years)	60
Gender (M/F)	7/12
BMI ≥ 24	4 (21.05%)
Aneurysms	
No. (small/medium size)	34 (87.18%)/5 (12.82%)
No. of patients with × aneurysms	
2	18 (94.74%)
3	1 (5.26%)
Side of aneurysms	
Right	22 (56.41%)
Left	17 (43.59%)
Aneurysm locations	
CAVE	5
OPHT	19
p-COMM	2
Aneurysm shape	
Saccular	39
Fusiform	0
Dissecting	0
Aneurysm size (larger/smaller)	
Mean maximal diameter	4.41 ± 1.78/3.07 ± 1.70
Neck size	3.53 ± 1.11/2.57 ± 1.10
Parent artery	
Distal diameter	3.75 ± 0.39
Proximal diameter	4.38 ± 0.45
Length of affected segment	12.24 ± 3.65
Treatment	
No. of stents	19
Stent size	
Diameter	4.13 ± 0.45
Length	31.84 ± 7.65
Unfold failure	0
Coiling	1 (5.26%)
Branch coverage	
OPHT-A	18 (94.74%)
p-COMM-A	1 (5.26%)
Stagnation/decreased contrast filling	23 (58.97%)
Adverse event	3 (15.79%)
Latest follow-up	
Last angiography	7.4 ± 1.89

(Continued)

TABLE 4 (Continued)

Parameters	Result
Stent stenosis	0
Occlusion rate	
Complete	35 (89.75%)
Near-complete	4 (10.25%)
Partial	0

intracranial aneurysms, which suggests that treatment with the flow-diverting pipeline embolization device is safe and efficacious for small aneurysms, with complication rates comparable with those for traditional endovascular techniques (3). Another real-world study about the safety and efficacy of the pipeline embolization device for small/medium intracranial aneurysms in China also demonstrated high surgical success rates, high occlusion rates, and low morbidity and mortality (4). Therefore, the indication of flow diversion is extended to small and medium aneurysms.

Flow diversion device for the treatment of tandem aneurysms

Tandem aneurysms are defined as multiple aneurysms located in close proximity to the same parent vessel. The clipping of tandem aneurysms can be challenging, especially when para-ophthalmic or posterior circulation sites are involved. Endovascular treatment of adjacent tandem intracranial aneurysms has been a validated option, including primary coiling, stent-assisted coiling, and flow diversion. However, it will be challenging for embolization adjacent tandem intracranial aneurysms with conventional endovascular techniques, such as primary coiling and stent-assisted coiling, because they usually require repeated catheterization of aneurysms and increase aneurysm rupture during embolization. Flow diversion provides a better reconstruction of the aneurysm neck and has lower recanalization rates, which make it more suitable to treat tandem aneurysms. Especially for small tandem aneurysms, flow diversion implantation with no coiling can achieve a high occlusion rate and low aneurysm rupture rate during the procedure. However, the treatment of tandem aneurysms with flow diversion has rarely been reported in the literature. Lin et al. (5) reported that 13 patients with 28 adjacent tandem aneurysms were treated with pipeline embolization device; complete occlusion was achieved in nine of 10 pipeline embolization device-treated aneurysms. Adeeb and his colleagues indicated that 78 tandem aneurysms underwent 34 pipeline embolization device procedures with high rates of complete occlusion, and symptomatic thromboembolic complications were encountered in 8.8% of procedures (6). A multi-institutional retrospective study released a report that the use of flow diversion for the treatment of tandem cerebral aneurysms had an acceptable safety profile, indicating that it should be considered an effective therapy after reviewing 38 tandem aneurysms of 17 patients (7).

Safety and efficacy of the Tubridge flow diverter for small/medium aneurysm

The Tubridge is actually a stent-like vessel-reconstruction device designed with a high metal coverage rate and low porosity. It diverts blood flow away from the aneurysm while preserving normal blood flow of the branch artery. It is characterized by a variety of lengths and diameters, radiopaque, flared end, retrievability, and low shortening rate.

As a new endovascular reconstruction tool, the Tubridge flow diverter also shows excellent efficacy and safety for the treatment of intracranial aneurysms, as well as a remarkably equal complete occlusion rate compared with other flow diverters. Currently, many studies have reported that Tubridge is used to treat various complex aneurysms, such as large or giant aneurysms, recurrent aneurysms, vertebral artery dissecting aneurysms, and distal aneurysms, indicating that Tubridge flow diverter can achieve good clinical and radiological outcomes (1, 8–10). However, there was no study reporting the safety and efficacy of Tubridge flow diverter for small/medium and tandem aneurysms.

In our study, we evaluate the safety and efficacy of Tubridge in the treatment of small/medium and tandem aneurysms. In total, 57 cases with 77 small/medium aneurysms underwent Tubridge flow diverter implantation (Figure 1), and the complete occlusion rate on the last angiographic follow-up was achieved in 88.46% of the small aneurysms group and 81.82% of the medium aneurysms group. There were six patients with new mild cerebral infarction after the procedure, and all cases had good clinical outcomes at the last follow-up. In addition, there were 19 patients with tandem aneurysms (a total of 39 aneurysms) treated with Tubridge flow diverters, and 89.75% of patients achieved a complete occlusion rate on the last angiographic follow-up, which was comparable with other flow diversion devices.

Compared with other flow diverter devices, Tubridge does not increase the complications, delivery, and opening difficulty of the stent. In contrast, Tubridge has a longer length and a larger diameter choice than other flow diverters, resulting in a lower stenting bridging rate and higher vascular fit. It is reported that minimum distance may affect perioperative complications and complete occlusion for tandem aneurysms (11). Undoubtedly, Tubridge has obvious advantages in the treatment of tandem aneurysms with long minimum distances compared with other flow diversion devices.

Limitations

We acknowledge that our study is a retrospective study from a single center, and no more patients and time of follow-up were included in our study, although we included parameters about patient characteristics, aneurysms, management, follow-up, imaging studies, and the evaluation of aneurysm occlusion. However, our report on small and medium aneurysms and comparison of the two types of aneurysms treated by Tubridge will make a significant contribution to the existing literature.

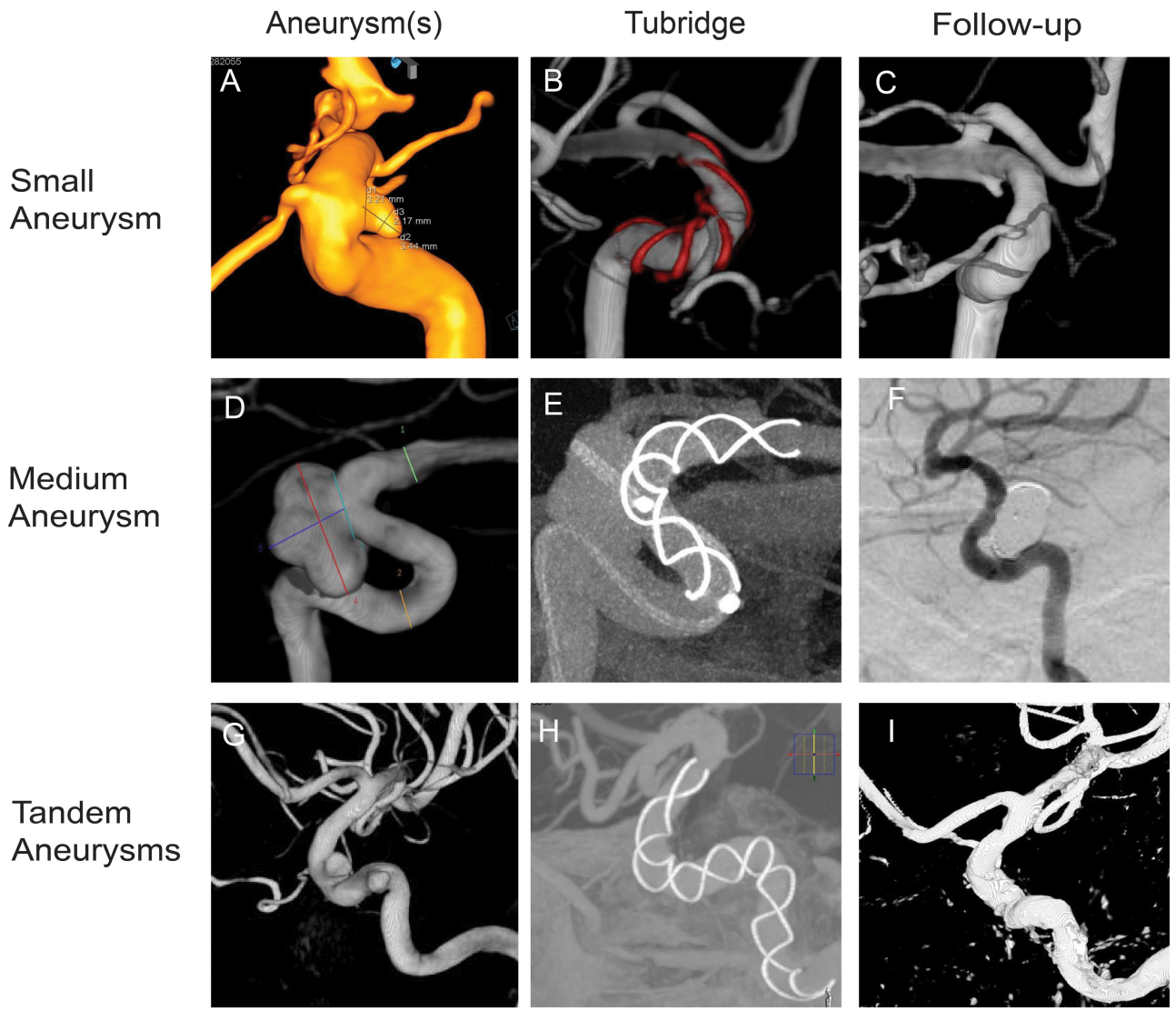

FIGURE 1
Tubridge flow diverter deployment of small, medium, and tandem aneurysms. **(A)** Small aneurysm, 3.44 mm × 2.17 mm, neck 3.21 mm; parent artery diameter, 4.5–3.3 mm. **(B)** Stent size 4.0–25. **(D)** Medium aneurysm, 10.00 mm × 7.44 mm, neck 5.99 mm; parent artery diameter, 4.2–3.0. **(E)** Stent size, 3.5–25. **(G)** Tandem aneurysms, 4.81 mm × 3.77 mm, neck 4.17 mm. 4.36 mm × 3.09 mm, neck 4.48 mm; parent artery diameter, 5.2–4.5. **(H)** stent size, 5.0–45. **(B, E, H)** Show the opening of the Tubridge flow diverters. **(C, F, I)** Show complete occlusion with the Tubridge flow diverters and coils.

Conclusion

Our preliminary experience demonstrated that the Tubridge flow diverter is a safe and effective stent for the treatment of small and medium aneurysms of the internal carotid artery. Long stents may increase the incidence of cerebral infarction. However, indications and complications require further confirmation, so a multicenter randomized controlled trial with a long-term follow-up is justified and needed.

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.

Ethics statement

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

Author contributions

WN, SY, CG, YT, and YG contributed to the study conception and design. DX, HY, LZ, and XY conducted the literature review and acquired the data. DX, HY, and LZ performed analysis, interpreted the data, and drafted the manuscript. 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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Flow diverters in the treatment of unruptured vertebral artery dissecting aneurysm: A single-center experience

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Objective: To evaluate the efficacy and safety of flow diverters (FD) in the treatment of vertebral artery dissecting aneurysm (VADA).

Methods: A total of 16 patients with 17 unruptured VADAs treated with FD from January 2017 to May 2021 were included. Data of clinical outcomes and radiographic examination were collected and assessed by the modified Rankin Scale (mRS) and O'Kelly-Marotta (OKM) grading scale.

Results: All patients were treated with a single FD. No perioperative complications occurred. The mean age was 55.1 years old. The mean size of the aneurysm was 10.4 mm. All patients had a favorable occlusion (OKM D + C3) result and the complete occlusion rate in the 6th month was 66.7% (OKM D). The mean clinical follow-up time was 7.8 months, and all patients had a good clinical outcome (mRS = 0). No procedure-related complication occurred at the last follow-up time.

Conclusion: FD is an effective and safe tool for treating unruptured VADA. Long-term prospective studies with a large sample are still needed to confirm these findings in the future.

KEYWORDS

aneurysm, vertebral artery dissection, flow diverter, endovascular treatment, embolization

Introduction

Vertebral artery dissecting aneurysm (VADA) is a rare and special vascular disease characterized by a dilation of the wall of an artery resulting from tears in the intima and elastic lamina (1). Although VADA is not one of the most commonly encountered intracranial aneurysms, it can cause high mortality and morbidity if ruptures (2). VADA is located in the posterior cranial fossa with complex anatomical structures around it (3). Traditional clipping surgery for treating VADA was reported to have a high complication, morbidity, and mortality rate (4, 5), therefore endovascular treatment (EVT), including simple coiling, stent-assisted coil embolization, or flow diverter (FD) has become the main clinical treatment for VADA in recent years (6). Among these EVT options, FD is a new treatment device based on the hemodynamic mechanism of aneurysm healing (7). It can promote aneurysm healing by improving the local hemodynamics of aneurysms without the need for intra-aneurysm coil embolization (8, 9). In addition, FD greatly simplifies the surgical procedure and reduces the compression effect caused by the aneurysm (10). FD was first approved by the Food and Drug Administration (FDA) for treating large and giant unruptured aneurysms of the internal carotid artery. In view of its excellent efficacy in the treatment of aneurysms, the clinical indication of FD has become more and more widespread and expanded to posterior circulation aneurysms, distal aneurysms, ruptured aneurysms, traumatic aneurysms, and other off-label aneurysms utilizations (11). However, the data regarding FD treating VADA is still controversial and limited so far. The goal of our study is to determine whether FD can be used effectively and safely to treat intracranial unruptured VADA.

Methods

Population data

A total of 16 patients with unruptured intracranial VADA from January 2017 to May 2021 in our institution were retrospectively included and reviewed. Digital subtractive angiography (DSA), magnetic resonance (MR), and computerized tomography (CT) angiography are usually used to aid in the diagnosis of VADA. The electronic medical record system provided the data on the patients. The Institutional Review Board of Yunnan First People's Hospital approved this study. Patients' therapeutic decisions (FD, stent-assisted coil embolization, or surgical clipping) were made after considering treatment risks, benefits, and the condition of patients. Patient informed consent is required from every patient before the procedure.

Postoperative medication

Before the FD deployment procedure, all patients received a 5-day pre-treatment of 75 mg of clopidogrel and 300 mg of aspirin daily as part of dual antiplatelet therapy (DAPT). The response to clopidogrel was monitored *via* P2Y12. Resistance to clopidogrel was defined as inhibition of more than 30% of platelets' P2Y12 receptors. Ticagrelor (90 mg, twice a day) was selected as an alternative to clopidogrel when patients have clopidogrel resistance. A total of 3,000 IU of heparin was administered before the femoral arterial sheath was placed, and then 1,000 IU per hour thereafter. The activated clotting time was monitored throughout the procedure. In the first 6 months after the procedure, the dose of 100 mg of aspirin and 75 mg of clopidogrel were continued daily to use for the first 6 months, after which 100 mg of aspirin was administered for a long time.

Endovascular procedure protocol

In general, endotracheal intubation anesthesia, a puncture was performed on the common femoral artery on the right side using the Seldinger technique. The right subclavian was usually used for the right-sided VADA, whereas the left subclavian is selected for the left-sided VADA. The subclavian artery was then inserted with a 7Fr shuttle sheath (Cordis, USA). The Pipeline flow diverter (PED^{TM}, Medtronic, Dublin, Ireland) or Tubridge flow diverter (TUB^{TM}; MicroPort, Shanghai, China) was deployed along the vertebral artery to treat the VADA. In our experience, coiling-assisted FD deployment was conducted only when the aneurysm was acutely ruptured or the maximal aneurysm length was larger than 20 mm (12). As all VADAs in our study are unruptured, no coiling was used during all operations. On a control angiogram, the wall apposition status was assessed, and ultra-compliant balloon or micro guidewire-loop technology was used in the event that better wall apposition was required.

Patient follow-up

Data on clinical outcomes were collected at the timepoint of admission and last follow-up time and were evaluated with the modified Rankin Scale (mRS) (13). DSA was routinely used for postoperative and 6-month follow-up radiologic evaluation using the O'Kelly Marotta (OKM) grading scale (14) (A—complete filling; B—incomplete filling; C—neck remnant; or D—no filling). The results of DSA were evaluated by two experienced neurointerventional surgeons. Then an annual imaging examination of DSA and computed tomography angiography (CTA) were suggested to be performed for the patients.

Results

Baseline patient characteristics

A total number of 16 patients with 17 unruptured VADAs treated with single FD were included in our study cohort. The number of male patients was 10 and the number of female patients was 6. The mean age of all patients was 55.1 years old (ranging from 38 to 74). The mean size of the aneurysm was 10.4 mm (ranging from 4.2 to 16.2). Six Patients (37.5%) were treated with a Pipeline embolization device (PED) and the other 10 patients (62.5%) were operated on using a Tubridge (TUB). Neuropathic symptoms presented in 11 patients, including headache ($n = 6$), vertigo ($n = 3$), neck pain ($n = 1$) and ataxia ($n = 1$), whereas 5 patients were asymptomatic. The mRS of all patients prior to the procedure was zero. Nine of 17 aneurysms were located in the right V4 segment of the vertebral artery (VA), and the other 8 aneurysms were located in the left V4 segment of the VA. Based on the position of the aneurysm and the PICA, three types of VADA were identified: proximal to the PICA, involving the PICA, and distal to the PICA (15). The data on basic patient characteristics were shown in Table 1.

Clinical and radiological follow-up outcomes

All 16 patients received a single FD treatment (6 PED and 10 TUB) without additional coils (Figure 1). The operative successful rate was 100%. The results of OKM grade after immediately FD deployment are as follows: A3 ($n = 6$), B3 ($n = 8$), and C3 ($n = 2$), and no perioperative ischemic or hemorrhagic complications happened. DSA follow-up was carried out in 15 patients (93.8%) over 6 months. There was no occlusion of the PICA on the follow-up DSA examination. All patients had a favorable occlusion (OKM grade D + C3) outcome. The complete occlusion rate at 6 months was 66.7% (OKM D, 10/15); the complete occlusion rate of VADA incorporated PICA was 100% (3/3, D); the complete occlusion rate of the aneurysm proximal to PICA or distal to PICA was 66.7% (4/6, D) and 50% (3/6, D), respectively. The mean clinical follow-up time was 7.8 months (3–12 months). A good clinical outcome was achieved for all patients (mRS = 0). All patients were free of procedure-related complications at the last clinical follow-up.

Discussion

VADA is a rare and treatment-challenging subtype of posterior circulation aneurysms. At present stent-assisted coiling or coil-alone embolization of the parent artery has been considered the main

TABLE 1 Clinical features of 16 patients with unruptured vertebral artery dissecting aneurysms and radiologic and clinical follow-up outcomes after flow diversion deployment.

Patient no.	Gender	Symptoms	Age	Aneurysm location	Maximal length of the aneurysm (mm)	Relation with PICA	FD type	Clinical FU months	Immediate angiography (OKM grade)	6-month FU angiography (OKM grade)	Last FU mRS	Procedure related complication
1	Male	Headache	41	R V4	8.2	Involving PICA	PED	7	A3	D	0	–
2	Female	Asymptomatic	56	R V4	11.3	Proximal to PICA	TUB	6	B3	D	0	–
3	Male	Vertigo	62	R V4	16.2	Distal to PICA	TUB	8	B3	C3	0	–
4	Male	Headache	43	L V4	15.1	Proximal to PICA	TUB	3	A3	/	0	–
5	Male	Headache	67	R V4	9	Involving PICA	PED	10	A3	D	0	–
6	Female	Asymptomatic	38	L V4	14	Proximal to PICA	TUB	6	C3	D	0	–
7	Male	Headache	48	L V4	8.5	Distal to PICA	TUB	7	B3	D	0	–
8	Female	Asymptomatic	51	L V4	14.6	Proximal to PICA	PED	12	C3	D	0	–
9	Male	Ataxia	55	R V4	7.4	Involving PICA	TUB	8	B3	D	0	–
10	Male	Asymptomatic	70	L V4	13	Distal to PICA	PED	7	B3	C3	0	–
11	Male	Vertigo	52	R V4	8.1	Distal to PICA	TUB	11	B3	C3	0	–
12	Female	Vertigo	62	R V4	6.6, 4.2	Proximal to PICA	TUB	8	A3	D	0	–
13	Female	Headache	74	L V4	11.8	Proximal to PICA	PED	7	A3	C3	0	–
14	Male	Neck pain	54	L V4	9.2	Distal to PICA	TUB	8	A3	D	0	–
15	Female	Headache	61	R V4	7.8	Proximal to PICA	PED	7	A3	C3	0	–
16	Male	Asymptomatic	48	L V4	12.2	Distal to PICA	TUB	9	B3	D	0	–

R, right; L, left; PED, pipeline embolization device; TUB, Tubridge; PICA, posterior inferior cerebellar artery; FU, follow–up; OKM, O'Kelly Marotta; mRS, modified Rankin Scale; "/", means the follow-up time is <6 months; "–", means there are no procedure-related complications in the patients.

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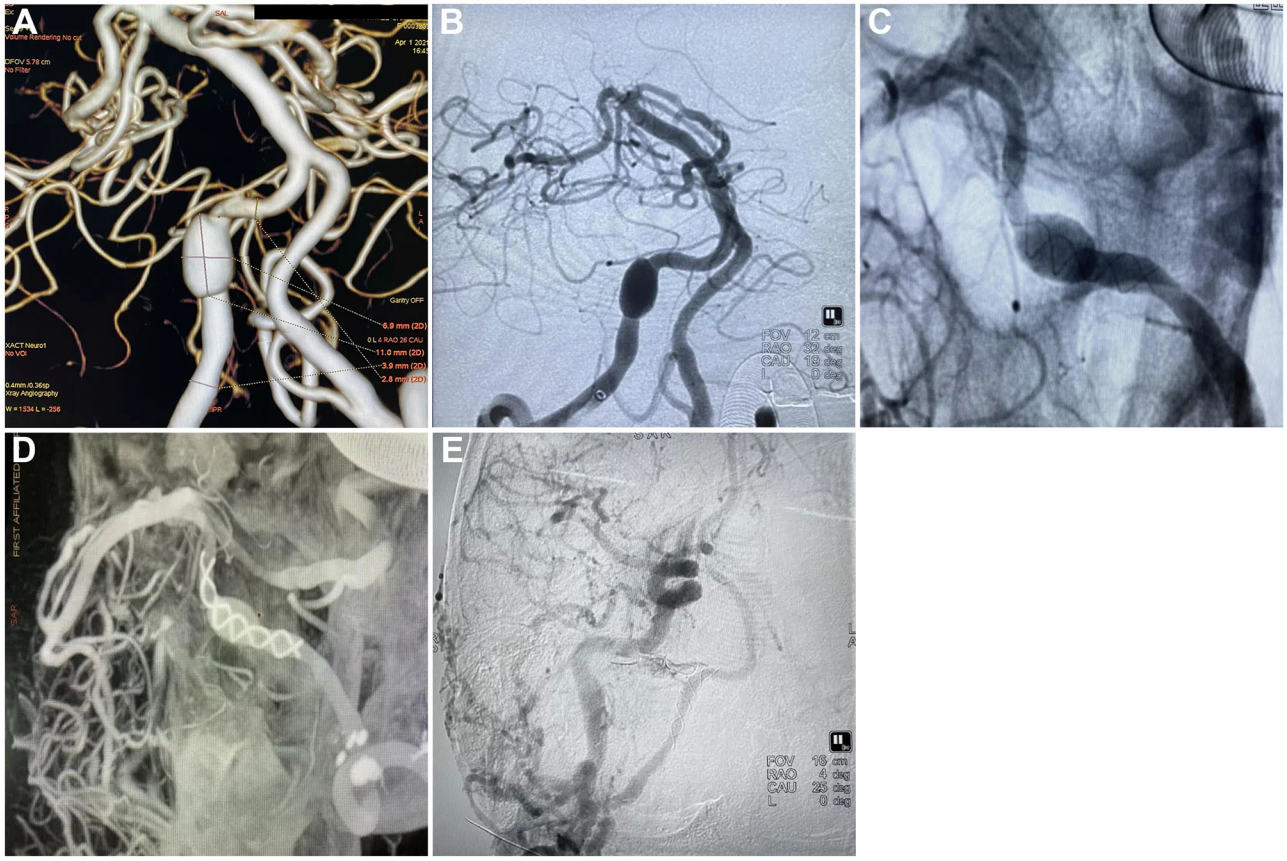

FIGURE 1
Tubridge treatment on vertebral artery dissecting aneurysm and the follow-up. **(A)** CTA scan showing the dissecting aneurysm in the right vertebral artery, section 4 (V4); **(B)** DSA showing the dissecting aneurysm in the right vertebral artery, section 4 (V4); **(C)** Release of Tubridge flow diverter (3.5 × 55 mm); **(D)** DSA showing a goof wall apposition after final deployment of the flow diverter; **(E)** Follow-up 6 month after the treatment found no silhouette of the dissecting aneurysm.

and effective therapy for VADA (16). However, this method also has the risk of aneurysm recurrence and postoperative ischemic complications (17). Before the operation, it is necessary to strictly evaluate whether the diseased side vertebral artery works dominantly for blood supply; whether the contralateral vertebral artery has sufficient blood compensation, and whether the important branch artery such as the posterior inferior cerebellar artery (PICA) is involved (18–20). FD is a new type of endovascular aneurysm treatment device developed in recent years. By reducing the blood flow in the aneurysm, creating an internal-aneurysm thrombus, the luminal healing by epithelialization along the FD stent, and diverting antegrade flow at the lesion artery, it is capable of healing aneurysms clinically (21–23). Many high-quality studies have proven the efficiency and safety of FD in intracranial complicated aneurysm therapy. A pooled analysis of three large studies-ASPIRe (Aneurysm Study of Pipeline in an Observational Registry), PUFS (Pipeline for Uncoilable or Failed Aneurysms Study), and IntrePED (International Retrospective Study of the Pipeline Embolization Device) including 1,092 patients with 1,221 aneurysms concluded that the complete occlusion rates were 75.0%, with a 5.7% major neurological morbidity rate and a 3.3% neurological mortality rate, respectively (24). Similarly, a prospective cohort study focusing on the long-term effectiveness of FD in treating large and giant wide-neck aneurysms found that the long complete occlusion rate was 93.4% at the point of 3-year follow-up, and there were no hemorrhagic or ischemic cerebrovascular events or neurological deaths reported late in the period (25).

However, few studies are reporting the application of FD in VADA treatment by now, and most of them were small sample studies. Oh et al. conducted a retrospective study including 26 VADA patients treated with FD. They found the overall complete occlusion rate was 55.6%, and only two patients occurred with delayed ischemic complications (22). Another retrospective study containing 12 cases with large VADA (>10 mm) showed a favorable occlusion (OKM grade C3 + D) in all 10 patients who were followed up (26). Similar to the previous study, our study found a complete occlusion rate of 66.6% (OKM D) at the sixth-month follow-up. However, further complete occlusion rate in a long follow-up time still needs to be investigated.

A meta-analysis including 15 articles using FD treating posterior circulation non-saccular aneurysms suggested that the periprocedural complications rate was 18% (27). Another comprehensive meta-analysis including 129 cases evaluating the treatment outcome of FD in posterior circulation non-saccular aneurysms reported similar results. They found that 23% of patients suffered periprocedural strokes, and overall mortality and morbidity were 21% and 26%, respectively (28). The patients in our study have no periprocedural stroke complications, but this result must be tested

more carefully in studies with larger samples. Although aneurysms in the vertebral artery showed better neurologic outcomes than in other locations (28), periprocedural strokes are still a remarkable risk, and the complications of using FD for VADA treatment still deserve strong alerts. It is important to pay attention to the effect of FD on the blood flow of branch vessels after it has been implanted since it contains a high metal coverage rate, and ischemic events caused by FD-covered branches play an important role in the treatment outcomes (26). It is acknowledged by most clinicians that flow diverter may cause blood stagnation or obstruction of penetrating arteries. The PICA is an important branch of the vertebral artery that may be affected by FD treatment for VADA, causing a fatal cerebellar and brainstem infarction (29). In our study cohort, the patency of PICAs was not influenced in all patients after a 6-months radiologic follow-up.

Limitations

Our study is a retrospective study with a small patient sample, therefore the statistical analysis was not able to be conducted. More randomized controlled trials or cohort studies with large samples should be conducted to confirm our results. In addition, the follow-up time of the patients in our study is relatively short, a longer follow-up ($\geq$18 months) to evaluate the effect and safety of FD in treating VADA is still necessary for the future.

Conclusion

FD may be an effective and safe endovascular choice for unruptured VADA treatment as proven by the good clinical outcome and radiological review after 6-month of follow-up. It is important, however, that further long-term and large cohort studies are necessary to confirm these findings.

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

Ethical review and approval was not required for the study on human participants in accordance with the local legislation and institutional requirements. Written informed consent from the patients/participants or patients/participants legal guardian/next of kin was not required to participate in this study in accordance with the national legislation and the institutional requirements.

Author contributions

XL, YZ, and HZ collected the data and wrote the manuscript. LJ and SY helped to analyze the data. TL and WH checked the results and coordinated and supervised the study.

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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.

Publisher's note

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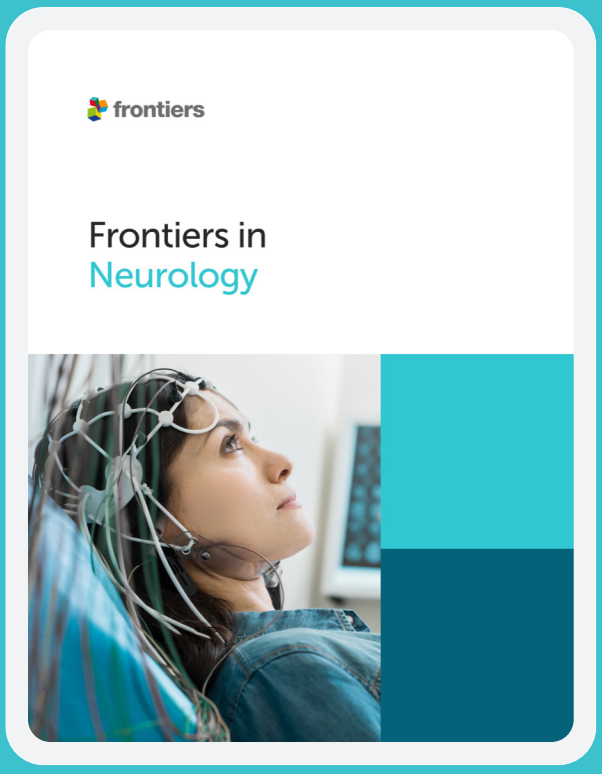

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