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Advance in vascular anomalies of head and neck region: from bench to bedside

Edited by
Deming Wang, Shancai Xu, Yu Cai, Xindong Fan, Lixin Su and Wayne Yakes

Coordinated by
Yuchen Shen

Published in
Frontiers in Neurology
Frontiers in Cardiovascular Medicine

ISSN 1664-8714
ISBN 978-2-8325-5887-4
DOI 10.3389/978-2-8325-5887-4

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Advance in vascular anomalies of head and neck region: from bench to bedside

Topic editors

Deming Wang — Vascular Anomaly Center, Department of Interventional Therapy, Shanghai Ninth People's Hospital, Shanghai Jiao Tong University School of Medicine, Shanghai, China

Shancai Xu — Department of Neurosurgery, The First Affiliated Hospital of Harbin Medical University, Harbin, Heilongjiang, China

Yu Cai — Department of Oral and Maxillofacial Surgery, School and Hospital of Stomatology, Wuhan University, Wuhan, China

Xindong Fan — Vascular Anomaly Center, Department of Interventional Therapy, Shanghai Ninth People's Hospital, Shanghai Jiao Tong University School of Medicine, Shanghai, China

Lixin Su — Vascular Anomaly Center, Department of Interventional Therapy, Shanghai Ninth People's Hospital, Shanghai Jiao Tong University School of Medicine, Shanghai, China

Wayne Yakes — The Yakes Vascular Malformation Center, Englewood, CO, United States

Topic coordinator

Yuchen Shen — Vascular Anomaly Center, Department of Interventional Therapy, Shanghai Ninth People's Hospital, Shanghai Jiao Tong University School of Medicine, Shanghai, China

Citation

Wang, D., Xu, S., Cai, Y., Fan, X., Su, L., Yakes, W., Shen, Y., eds. (2025). *Advance in vascular anomalies of head and neck region: from bench to bedside*. Lausanne: Frontiers Media SA. doi: 10.3389/978-2-8325-5887-4

Table of contents

frontiers | Frontiers in Neurology

TYPE Editorial
PUBLISHED 20 December 2024
DOI 10.3389/fneur.2024.1529950

OPEN ACCESS

EDITED AND REVIEWED BY
Diogo C. Haussen,
Emory University, United States

*CORRESPONDENCE
Xindong Fan
✉ fanxindong@aliyun.com
Wayne F. Yakes
✉ wayne.yakes@vascularmalformationcenter.com
Lixin Su
✉ sulixin1975@126.com

†These authors have contributed equally to this work

RECEIVED 18 November 2024
ACCEPTED 13 December 2024
PUBLISHED 20 December 2024

CITATION
Wang D, Shen Y, Xu S, Cai Y, Su L, Yakes WF and Fan X (2024) Editorial: Advance in vascular anomalies of head and neck region: from bench to bedside. *Front. Neurol.* 15:1529950. doi: 10.3389/fneur.2024.1529950

Editorial: Advance in vascular anomalies of head and neck region: from bench to bedside

Deming Wang[1†], Yuchen Shen[1†], Shancai Xu[2†], Yu Cai[3†], Lixin Su[1*], Wayne F. Yakes[4*] and Xindong Fan[1*]

[1]Vascular Anomaly Center, Department of Interventional Therapy, Shanghai Ninth People's Hospital, Shanghai Jiao Tong University School of Medicine, Shanghai, China, [2]Department of Neurosurgery, The First Affiliated Hospital of Harbin Medical University, Harbin, Heilongjiang, China, [3]Department of Oral and Maxillofacial Surgery, School and Hospital of Stomatology, Wuhan University, Wuhan, China, [4]The Yakes Vascular Malformation Center, Englewood, CO, United States

KEYWORDS

vascular anomalies, vascular tumor, vascular malformations, hemangioma, signaling/signaling pathways, treatment, translational research

Editorial on the Research Topic
Advance in vascular anomalies of head and neck region: from bench to bedside

We are pleased to present our Research Topic, which includes a total of 10 articles, discussing the state-of-art on vascular anomalies' research.

Vascular anomalies are abnormalities or disorders of the vascular or lymphatic system, with a relatively higher prevalence in the head and neck region. According to the International Society for the Study of Vascular Anomalies (ISSVA), vascular anomalies are classified as either vascular tumors or malformations (1). Vascular tumors can be benign, locally aggressive, or malignant. Hemangioma is considered the most common type of benign vascular tumor, which is divided into infantile and congenital hemangioma; given the onset time, both are endowed with unique natural history. Other benign vascular tumors include tufted angioma, pyogenic granuloma, spindle-cell hemangioma, and intravenous lipomas, etc. When it comes to locally aggressive tumors, kaposiform hemangioendothelioma is prone to cause thrombocytopenia among affected infants and children, known as the Kasabach-Merritt phenomenon. Malignant tumors include angiosarcoma, epithelioid hemangioendothelioma, etc.

Regarding vascular tumors, Fernández-Alvarez et al. contributed valuable perspectives on the intravenous lipomas of the head and neck through an up-to-date literature review and summary.

Different from vascular tumors, vascular malformations mostly occur congenitally. In the light of the hemodynamics, vascular malformations can be sorted into low-flow (capillary malformation [CM], venous malformation [VM], and lymphatic malformation [LM]) and high-flow (arteriovenous fistula [AVF] and arteriovenous malformation [AVM]). According to ISSVA, vascular malformations are divided into the following types: simple, combined, vascular malformations of major named vessels, and vascular malformations associated with other anomalies.

For low-flow vascular malformations, Azmoun et al., Zhang et al., and Sun et al. have introduced novel sclerosants on VMs; Yuan and Wang contributed their experiences on the electrochemical therapy combined with injection of pingyangmycin treating VMs.

Yang et al. discussed the efficacy of surgical resection, sclerotherapy, and the combination of the two in treating LMs.

For high-flow vascular malformations, Han et al. reported the efficacy and safety of embolization among scalp AVFs. Shen et al. demonstrated the promising prognosis of peripheral AVFs after coil-assisted ethanol embolization. Furthermore, Su et al. shed light on the presentation and countermeasures related to the cardiopulmonary collapse induced by ethanol embolization.

Thanks to the significant development of molecular genetics, our understanding of vascular malformations has gradually shifted from a macroscopic level to a microscopic one. Nowadays, gene mutations are the broadly acceptable etiology of vascular malformations and related syndromes, including somatic or germline types. For example, cutaneous or mucosal CM is considered the somatic mutation of *GNAQ*/*GNA11*; (2) common VM is caused by somatic mutation of *TEK*, whereas sporadic AVM results from *MAP2K1* somatic mutation (3, 4). Some genetic diseases, such as hereditary hemorrhagic telangiectasia or capillary malformation-arteriovenous malformation, happen due to the germline mutation of (*ENG*, *ACVRL1*, and *SMAD4*) and (*RASA1* and *EPHB4*), respectively (5, 6). Here, Solomon and Comi summarized the latest progress of Sturge-Weber syndrome, most commonly associated with a *R183Q* somatic mosaic mutation in the gene *GNAQ*, from a translational perspective.

Given the complex category and comprehensive system of vascular anomalies, scientists, and clinicians are still facing tremendous challenges in basic, clinical, and translational research. Nevertheless, the knowledge base related to vascular anomalies continues to accrue and further studies are needed to allow for the treatment optimization of these challenging conditions.

Author contributions

DW: Writing – original draft, Writing – review & editing. YS: Writing – original draft, Writing – review & editing. SX: Writing – original draft, Writing – review & editing. YC: Writing – original draft, Writing – review & editing. LS: Writing – original draft, Writing – review & editing. WY: Writing – original draft, Writing – review & editing. XF: Writing – original draft, Writing – review & editing.

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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frontiers | Frontiers in Neurology

TYPE Original Research
PUBLISHED 22 May 2024
DOI 10.3389/fneur.2024.1417788

OPEN ACCESS

EDITED BY
Deming Wang,
Shanghai Jiao Tong University, China

REVIEWED BY
Gaetano Gallo,
Sapienza University of Rome, Italy
Giacomo Colletti,
Vascular Birthmark Foundation, United States

*CORRESPONDENCE
Shaohua Liu
✉ lshabccba@126.com

†These authors have contributed equally to this work and share first authorship

RECEIVED 15 April 2024
ACCEPTED 10 May 2024
PUBLISHED 22 May 2024

CITATION
Azmoun S, Liu Y, Tursun M and Liu S (2024) Effect of catheter needle caliber on polidocanol foam stability in foam sclerotherapy.
Front. Neurol. 15:1417788.
doi: 10.3389/fneur.2024.1417788

Effect of catheter needle caliber on polidocanol foam stability in foam sclerotherapy

Sajjad Azmoun[1†], Yiran Liu[2†], Medina Tursun[1] and Shaohua Liu[3*]

[1]Department of Plastic, Cosmetic and Burn Surgery, Qilu Hospital of Shandong University, Jinan, China, [2]Department of Endocrinology, Qilu Hospital of Shandong University, Cheeloo College of Medicine, Shandong University, Jinan, China, [3]Department of Oral and Maxillofacial Surgery, Qilu Hospital of Shandong University, Jinan, China

Background: Although sclerotherapy is widely used to treat vascular malformations (VMs), it is associated with several challenges. One significant issue is the insufficient understanding of the influence of various factors on the stability of polidocanol (POL) foam used in sclerotherapy.

Objective: This study aimed to explore the effect of the catheter needle caliber on foam stability when using POL with or without hyaluronic acid (HA) for the treatment of VMs.

Methods and materials: The Tessari method generated sclerosant foam using POL both with and without HA. We used catheters and syringe needles of various calibers, and the resulting foam was transferred into new syringes to facilitate a comparison of foam stability. Foam half-life (FHT) was utilized as a metric to assess foam stability.

Results: The study found that narrower needle calibers produced a more stable foam when POL was used alone; however, no significant effect was observed when HA was added. Furthermore, when the foam was expelled using catheters and syringe needles of the same size, no noticeable changes in the stability were observed.

Conclusion: When choosing needles of varying calibers, their effect on foam stability should be carefully considered, particularly when the foam contains HA.

KEYWORDS

needle caliber, catheter needle, syringe needle, polidocanol, hyaluronic acid, foam stability, Tessari method

1 Introduction

Foam sclerotherapy is commonly used to treat vascular malformations (VMs), especially large VMs of the head and neck area (1–3). Foam sclerotherapy is a safe and effective therapeutic option for hemorrhoids (4). In foam sclerotherapy, achieving a stable sclerosant foam for optimal results is crucial because poor foam stability can potentially result in serious complications (5, 6). Blisters, paradoxical embolism, orbital compartment syndrome, and transient weakness of the facial nerve branch are complications that can arise when treating head and neck VMs (7).

Recently, the management of vascular anomalies affecting the maxillofacial, rectal, and gastroesophageal regions demonstrated foam's efficacy, underscoring this therapeutic technique's versatility (8).

Various factors influence the quality and stability of sclerosant foam, including the incorporation of surface-active agents (9), liquid-to-air ratio (10), type and concentration of sclerosant (11), use of different gases (12), and the pushing rate in the foam-making procedure (13).

Hyaluronic acid (HA) is a large, non-sulfated glycosaminoglycan that is the main component of the extracellular matrix (14). The addition of small amounts of HA has been demonstrated to significantly improve the overall stability of foams (15) while ensuring their safe and effective utilization in the treatment of VMs (3).

Once the sclerosant foam is prepared, the foam should be promptly injected into the veins affected by VMs, either through a syringe needle or with a catheter needle, which is mostly used for treating large VMs (16). It has been observed that foam stability varies depending on the caliber of the needle through which it is injected (6). However, the influence of the needle catheter caliber on foam stability remains unclear. This study aimed to investigate the impact of needle catheter caliber on foam stability using polidocanol (POL), a commonly used sclerosing agent, in combination with HA.

2 Materials and methods

We tested the stability of polidocanol sclerosant foam prepared with a liquid-to-air ratio of 1:4 using the Tessari technique. The experiment used a 1% solution of POL (SHAANXI TIANYU Pharmaceutical Co., Ltd.) and two 10 mL syringes (SHANDONG XINHUA ANDE Medical Supplies Co., Ltd.) with a three-way stopcock (Discofix). Eight distinct groups were developed and evenly dispersed across the two experiments. Each group used a disposable syringe with a 0.70 mm needle size and three catheter needles of various calibers. Hyaluronic acid (SHANDONG BOSHILUN FURUIDA Pharmaceutical Co., Ltd.) was used as an enhancer to improve foam stability.

2.1 Catheter needle selection

Three catheter needles (WEIHAI WEIGAO Blood Collection Supplies Co., Ltd.) with diameters ranging from largest to narrowest (0.90 mm, 0.70 mm, and 0.55 mm) were employed. A disposable syringe with a 0.70 mm needle caliber (SHANDONG XINHUA ANDE Medical Supplies Co., Ltd.) was used in our experimental setup. To standardize the length of the catheter needle, we cut 0.90 mm, 0.70 mm, and 0.70 mm disposable syringe needles to match the length of the 0.55 mm catheter needle using a cutting machine. This ensured that all the needles used in the study were identical in length (Figure 1).

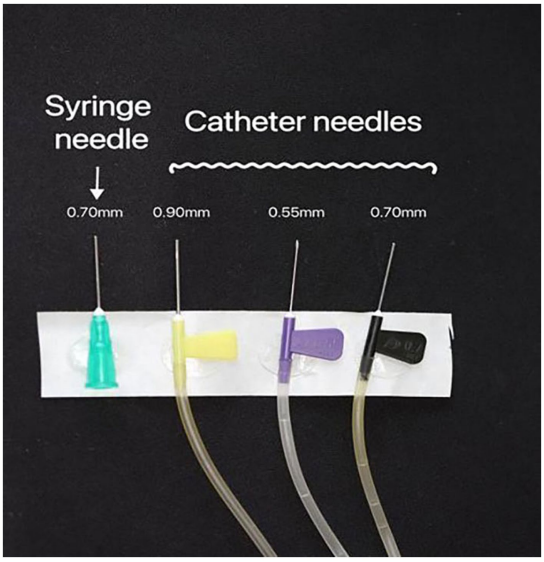

FIGURE 1
The needle catheters (0.55 mm, 0.70 mm, and 0.90 mm) and the 0.70 mm caliber disposable syringe needle were used. All the needles were trimmed to the same length.

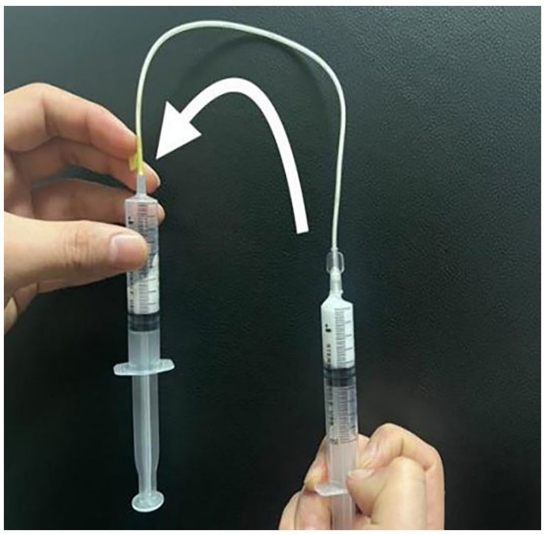

FIGURE 2
The POL sclerosant foam was transferred through a catheter needle to a new syringe.

2.1.1 Experiment 1: needle caliber and POL foam-making

Two syringes were connected to a three-way tap, with one syringe loaded with 2 mL of the POL solution and the other syringe filled with 8 mL of room air. The Tessari method was employed to produce the foam, which involved 20 cycles of pushing back and forth (13, 17). The resulting foam-containing syringe was promptly removed from the three-way tape. Using catheter needles 0.55 mm, 0.70 mm, and 0.90 mm in diameter and a syringe needle 0.70 mm in diameter, the sclerosant foam was gently transferred to an empty syringe for observation (Figure 2).

Abbreviations: VMs, vascular malformations; HA, Hyaluronic acid; FHT, foam half-life; POL, polidocanol; DSS, double-syringe system.

The transfer time of the foam was meticulously controlled at 10 s for each needle caliber.

The foam half-life (FHT) was recorded to determine its stability. The rest of the plunger's thumb was set on the table, the syringe was checked to ensure that it was steady and upright, the stopwatch was started immediately, and the drainage liquid extraction of the lower foam section was closely monitored. The FHT was recorded when 1 mL liquid emerged from the entire foam.

2.1.2 Experiment 2: needle caliber and POL + HA foam-making

For this experiment, the method from Experiment 1 was slightly modified. HA (0.05 mL) was added to 2 mL of the POL solution loaded into one syringe, whereas the other syringe was filled with 8 mL of room air. The syringes were connected to three-way tape. Apart from the addition of HA, all other aspects of the experimental procedure, including the FHT detection, were consistent between the two experiments.

Each test was conducted 4 times by the same operator to ensure consistency and reliability in the experimental process. Fresh equipment was used for each repetition to ensure the generation of pristine foam. The room temperature was maintained at 25°C to ensure homogeneity across the experiments.

ANOVA was conducted to detect any difference in FHT, where $p < 0.05$ was regarded as a significant difference.

3 Results

3.1 Experiment 1

Among the needle catheters, those with diameters of 0.90 mm and 0.70 mm, as well as a disposable syringe with a 0.70 mm needle size, showed similar FHT values. Conversely, needles with a diameter of 0.55 mm exhibited the longest FHT duration, indicating superior stability of the sclerosant foam. Table 1 shows how the size of the needle affected the stability of the POL foam across the four groups.

In the POL solution, a significant difference ($p < 0.0001$) was observed in the 0.55 mm group compared to the other groups. In contrast, no significant differences were detected among the remaining three groups (Figure 3).

3.2 Experiment 2

The impact of needle size on foam stability in the presence of HA added to POL was investigated, as outlined in Table 2. Surprisingly, our results revealed that changing the needle caliber did not significantly influence the stability of the foam produced using POL combined with HA. Statistical analysis revealed no notable differences among the foams injected through needles of 0.55 mm, 0.70 mm, or 0.90 mm and those injected through a disposable syringe with a 0.70 mm needle caliber ($p = 0.075$) (Figure 4).

Remarkably, both the 0.70 mm catheter needle and disposable syringe with a 0.70 mm needle caliber showed identical FHT.

TABLE 1 FHTs of different needle catheter calibers in POL foam ($n = 4$).

Needle caliber (mm)	FHT (s)	FHT (s)	FHT (s)	FHT (s)	FHT (s) (mean ± SD)
0.90 catheter	114	118	116	120	117 ± 2.6
0.70 catheter	115	116	116	121	117 ± 2.7
0.55 catheter	145	139	136	134	139 ± 4.8
0.70 syringe	110	119	118	119	117 ± 4.4

4 Discussion

Our findings highlight the significance of needle caliber in affecting foam stability among various factors. Specifically, when utilizing only POL sclerosant foam, we observed a shorter FHT with larger catheter needles and a 0.70 mm syringe needle, suggesting the potential for quicker dispersion and breakdown of the foam. Conversely, employing a narrower-caliber catheter needle resulted in enhanced stability.

In the second experiment, which involved POL + HA sclerosing foam, we did not observe a correlation between the needle caliber and foam stability. This finding indicates that the effect of needle caliber on foam stability varies between foam formulations with and without HA. The addition of HA significantly enhanced foam stability, thereby diminishing the influence of needle caliber on foam properties. Although the exact reason for this observation remains uncertain, we speculate that any potential effect of the needle caliber on the stability of the HA-containing foam may be too subtle to discern.

According to Burdick et al. (18), HA can be chemically altered to create various physical forms, including hydrogels, that are appropriate for preclinical and clinical use. Furthermore, the combination of POL and HA using the Tessari method for foam sclerotherapy has yielded a more stable and effective foam solution for treating VMs (3, 19).

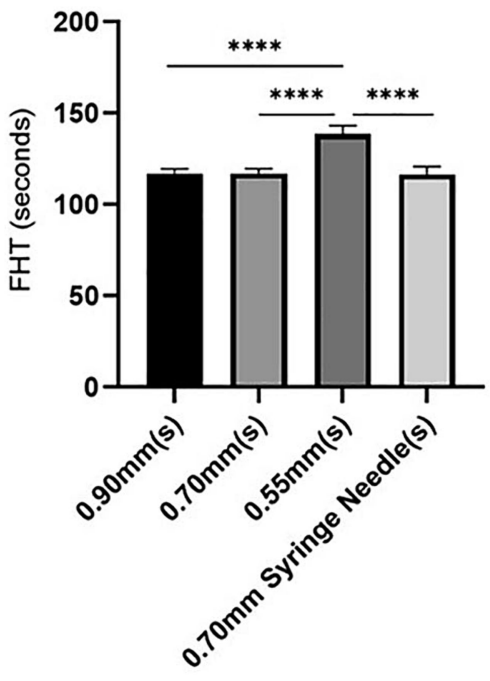

FIGURE 3
FHT in POL foam through different catheter needles and 0.70 mm syringe needle.

TABLE 2 FHTs of different needle catheter calibers in POL + HA foam (n = 4).

Needle caliber (mm)	FHT (s)	FHT (s)	FHT (s)	FHT (s)	FHT (s) (mean ± SD)
0.90 catheter	249	239	235	239	240 ± 6.0
0.70 catheter	237	233	218	236	231 ± 8.8
0.55 catheter	246	253	241	230	242 ± 9.7
0.70 syringe	229	228	237	222	229 ± 6.2

Skuła et al. (6) conducted a commendable study on the influence of needle caliber on foam stability, shedding light on the significant impact of needle caliber and length. A meticulous examination revealed that both the needle caliber and length play a role in determining foam stability. However, given the nascent stage of this research area, a plethora of avenues for further exploration remain. Throughout our experiments, we used uniformly sized needles to validate the findings. Additionally, three different sizes of catheter needle calibers were used alongside only one syringe needle, a combination that has not been previously explored in similar studies. This distinctive approach adds depth to our understanding and underscores the importance of expanding research in this field.

We also discovered that foam stability was equivalent when using either a 0.70 mm direct needle or a 0.70 mm catheter needle. Despite the unknown reasons behind this, the choice between needle types, whether a syringe needle or catheter needle, may not be influenced by their impact on stability.

There are several foam production procedures in foam sclerotherapy, such as the double-syringe system (DSS) marketed as an Easyfoam kit and the ultrasonic approach (8). Varixio is another method of creating foam that uses an automated device to inject the foam (4). The Tessari technique and the DSS are widely employed methods for generating foam sclerosants (20) because they share similar mechanisms. In this study, the Tessari method was used to create foam. If DSS had been used, we would have expected the results to be comparable.

It is essential to emphasize that foam stability is influenced by various factors, and the needle caliber is only one of them. A limitation of our study was the restricted variety of catheter needles used, with only three different sizes available from the same manufacturer. To enhance the comprehensiveness of future studies, a broader range of needle calibers from diverse manufacturers should be considered. Another limitation was the use of only POL. Future studies should incorporate other sclerosant agents at varying concentrations to provide a more comprehensive understanding of foam stability in different formulations. Furthermore, the foam preparation using the Tessari method is manual and susceptible to multiple factors. Each experiment was repeated four times. Although the results of each independent experiment were similar, conducting more repetitions may have yielded more precise results.

5 Conclusion

Our study revealed that the needle caliber had an impact on the stability of the foam produced with POL alone to some extent. However, when POL was combined with HA, the caliber of the needle did not significantly affect foam stability. It is suggested that when selecting needles of different calibers, their influence on foam stability should be considered, depending on whether the foam contains HA.

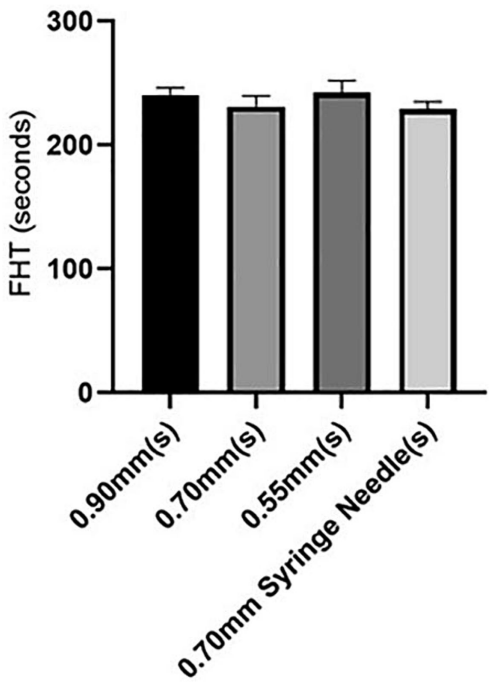

FIGURE 4
FHT in POL + HA foam through different catheter needles and 0.70 mm syringe needle.

Data availability statement

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

Author contributions

SA: Writing – original draft. YL: Writing – original draft. MT: Writing – original draft. SL: Writing – review & editing.

Funding

The author(s) declare that no financial support was received for the research, authorship, and/or publication of this article.

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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frontiers | Frontiers in Neurology

TYPE Original Research
PUBLISHED 07 August 2024
DOI 10.3389/fneur.2024.1431723

OPEN ACCESS

EDITED BY
Lixin Su,
Shanghai Jiao Tong University, China

REVIEWED BY
Douglas Couto,
Pontifical Catholic University of Parana, Brazil
Subhash Kumar,
All India Institute of Medical Sciences (Patna), India

*CORRESPONDENCE
Shao-Hua Liu
✉ lshabccba@126.com

†These authors have contributed equally to this work and share first authorship

RECEIVED 12 May 2024
ACCEPTED 30 July 2024
PUBLISHED 07 August 2024

CITATION
Zhang H-S, Liu Y-R and Liu S-H (2024) Ethanol foam: a novel type of foam sclerosant for treating venous malformations. *Front. Neurol.* 15:1431723. doi: 10.3389/fneur.2024.1431723

Ethanol foam: a novel type of foam sclerosant for treating venous malformations

Han-Shu Zhang[1†], Yi-Ran Liu[2†] and Shao-Hua Liu[1*]

[1]Department of Oral and Maxillofacial Surgery, Qilu Hospital of Shandong University, Jinan, Shandong, China, [2]Department of Endocrinology, Qilu Hospital of Shandong University, Cheeloo College of Medicine, Shandong University, Jinan, Shandong, China

Introduction: Sclerotherapy is a commonly utilized treatment approach for venous malformations. Absolute ethanol is renowned for its remarkable efficacy as a potent sclerosants, but it is potentially associated with severe complications. Foam sclerotherapy is considered superior to liquid sclerotherapy owing to its heightened efficacy and diminished incidence of complications. Thus, our objective was to devise an ethanol foam sclerosant that delivers exceptional efficacy while mitigating complications.

Methods: In the first set of experiments, we identified the suitable range of ethanol concentrations for sclerotherapy through human umbilical vein endothelial cell proliferation assays and blood clotting experiments. Next, the surfactants polysorbate 80, egg yolk lecithin, and hyaluronic acid were added to create stable ethanol foam, with their ratios meticulously optimized.

Results: The optimal concentration range of ethanol was determined to be 30–60%. Eventually, a 48% ethanol foam was successfully produced with excellent stability. Other than ethanol, the formulation included 5×10^{-3} g/mL polysorbate 80, 10^{-2} g/mL egg yolk lecithin, and 0.04 mL/mL hyaluronic acid.

Discussion: The novel ethanol foam produced here could be a promising candidate for the treatment of venous malformations.

KEYWORDS

venous malformations, sclerotherapy, absolute ethanol, foam sclerosant, ethanol foam

1 Introduction

Venous malformations (VMs) are complex congenital lesions with diverse clinical presentations that can result in significant esthetic and functional limitations and even death in some cases (1). Currently, the primary treatment strategy for VMs is sclerotherapy, which involves the administration of sclerosants into the lumen of the vessel that consequently leads to venous wall damage and occlusion of the vessel (2). However, sclerosants are easily diluted and can be washed away into the bloodstream, and this limits sufficient contact with the inner walls of the lesion (3). Some commonly used sclerosants are absolute ethanol, polidocanol, and bleomycin (4–6), among which absolute ethanol is associated with the lowest incidence of lesion re-expansion (7, 8). However, absolute ethanol can cause severe complications (9) and, reportedly, has higher complication rates than other sclerosants (10). Improving the current sclerotherapy strategy and agents could help improve the treatment outcomes and quality of life of patients with VMs.

A potential alternative to the current sclerotherapy methods is foam sclerotherapy, a unique technology and has been found to improve the efficiency of sclerotherapy. Foam

displaces blood from the lesion, thereby increasing the contact time between the sclerosant and vessel walls and improving the effect of the sclerosant (11). Another advantage of foam sclerotherapy is that it requires a lower dose of the agent. Based on the known advantages of foam sclerotherapy and absolute ethanol, we speculated that transforming ethanol from the liquid form to foam may be an ideal approach for sclerotherapy. When delivered in the form of a foam, the concentration of ethanol required will be lower, and this may reduce its associated complications while ensuring treatment efficacy. Accordingly, the aim of this study was to develop an ethanol foam sclerosant that can be used for the treatment of VMs.

2 Materials and methods

2.1 Cell proliferation experiments

We evaluated the effect of different concentrations of ethanol on the destruction of venous endothelial cells in a cell proliferation experiment using human umbilical vein endothelial cells (HUVECs; ScienCell, San Diego, California, United States).

The experiment included one blank group (no cells), one control group in which cells were cultured in endothelial cell medium (ECM, ScienCell), one control group that was treated with absolute ethanol, and nine experimental groups (treated with ethanol concentrations of 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, and 90% in volumetric fractions). First, HUVECs were seeded in 96-well plates at a density of 2.5×10^3 cells/well and cultivated in ECM for 24 h. To evaluate the transient effect of ethanol on HUVECs, ECM was immediately added to the wells after the addition of the experimental solution to dilute ethanol, which was then removed via suction. The plate was washed three times with ECM for 3 min. Next, 50 μL of ECM and 20 μL of Cell Counting Kit-8 reagent (CCK-8; Beyotime, Shanghai City, China) were added, and the plates were placed in an incubator at 37°C with a 5% CO_2 atmosphere for 1 h. The cell viability of HUVECs was determined based on absorbance of different samples at a wavelength of 550 nm using a spectrophotometer (UV-VIS, UV1800; Shimadzu, Japan).

2.2 Blood clotting experiments

To determine the blood clotting ability of ethanol at different concentrations, fresh coagulated blood from a healthy volunteer (1 mL each tube) was added to 11 centrifuge tubes comprising two control tubes (containing distilled water or absolute ethanol) and nine experimental tubes (containing ethanol at the same concentrations as those used in the cell proliferation experiments). After the sample solutions were mixed with blood, we observed changes in the color and state of the blood to determine the blood clotting ability of ethanol.

2.3 Foam production

Tessari's method was used to produce foam with a gas–liquid ratio of 3:1. We tried to determine whether all the liquid could be converted to foam. Furthermore, the foam half-life time (FHT), defined as the time required for one volume of foam to be reduced to half its original volume, was used to assess foam stability.

We used polysorbate 80 (Tween 80) (injection quantity, 500 g; Nanjing Weier Pharmaceutical Co. Ltd., Jiangsu, China) and egg yolk lecithin (PC 80) (injection quantity, 50 g; Shenyang Tianfeng Biopharmaceuticals Co. Ltd., Liaoning, China) as surfactants to produce ethanol foam in experiments A and B, respectively. In experiment A, Tween 80 was used at concentrations of 1.6×10^{-5}, 10^{-4} g/mL, 10^{-3}, 5×10^{-3} g/mL, and 10^{-2} g/mL. The fractional volumes of ethanol used were 40, 42, 44, 46, 48, 50, 52, 54, 56, 58, and 60%. In experiment B, the concentrations of PC 80 were 10^{-2} g/mL, 1.5×10^{-2} g/mL, and 2×10^{-2} g/mL. Next, the combined effect of PC 80 and Tween 80 was evaluated in experiment C. For this, we added 5×10^{-3} g/mL Tween 80 and 10^{-2} g/mL PC 80 to the ethanol solution based on the results of experiments A and B. The fractional volume of ethanol used was found to be the same in experiments A, B, and C. Finally, to improve the stability of the ethanol foam, we performed experiment D, in which hyaluronic acid (HA) (20 mg/2 mL, Sofast sodium hyaluronate injection; Shandong Bauschfruida Pharmaceutical Co. Ltd., Shandong, China) was used along with the same concentrations of PC 80 and Tween 80 as experiment C, and the fractional volume of ethanol used was 48%. We added HA at incremental concentrations of 0.01 mL/mL ranging from 0 to 0.08 mL/mL.

3 Results

3.1 Effect of ethanol on cell proliferation ability

In the HUVEC proliferation assay, the destructive effect of ethanol increased with increasing concentrations of ethanol. When the cells were treated with ethanol at concentrations above 30%, the absorbance was not significantly different from that of the blank and absolute ethanol groups (Figure 1). This indicates that all the cells were destroyed at ethanol concentrations above 30%.

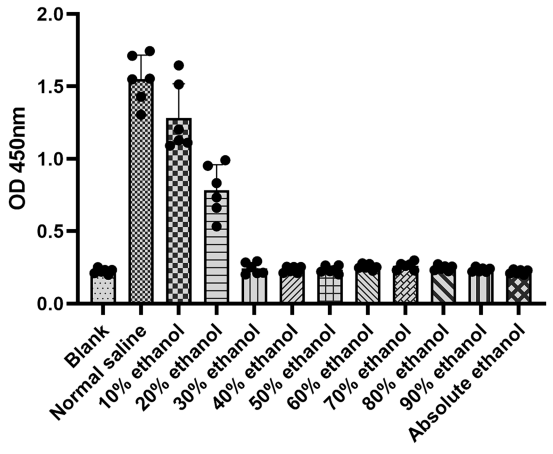

FIGURE 1
Proliferation assay of HUVECs incubated with different concentrations of ethanol.

3.2 Blood clotting ability of ethanol

The blood clotting ability was found to increase with increasing ethanol concentrations (Figure 2). When the blood was mixed with ethanol at concentrations below 60%, there was no obvious visible clotted blood. This implies that ethanol can induce clotted blood only at concentrations above 60%.

3.3 Efficiency of ethanol foam production

We successfully developed an ethanol foam that is stable enough for foam sclerotherapy. When the fractional volume of ethanol reached 50% or higher, the solution could not be converted into a foam. When the ethanol concentration was lower than 50%, the foamability was dependent on the concentration of both ethanol and the surfactants. In experiment A, the foamability decreased as the concentration of ethanol increased and increased as the concentration of Tween 80 increased. In all the groups from experiment B, only a portion of the liquid in the syringe could form foam. In experiment C, all groups with ethanol concentrations lower than 50% produced foam. In experiment D, the FHT of the ethanol foam increased as the HA concentration increased (Figure 3). When the dose of HA was greater than 0.04 mL/mL, the foam was dense and homogeneous, with an FHT longer than 3.5 min. Hence, we considered an HA concentration of 0.04 mL/mL to be optimal for ethanol production.

4 Discussion

In this study, we have described a protocol to produce ethanol foam, a novel type of sclerosant. We were able to produce stable foam at an ethanol concentration of 48%. This could eliminate the need to use absolute ethanol for sclerotherapy and help avoid its serious side effects. The potential clinical application of this foam warrants investigation in future studies.

Our findings indicated that when the ethanol concentration exceeded 30%, the ethanol solution had a comparable effect on HUVECs to that of absolute ethanol. Thus, the optimal concentration of ethanol foam is higher than 30%. Additionally, we observed that solutions with ethanol concentrations below 60% had a minor impact on blood clotting. Hence, we surmised that ethanol foam with an ethanol concentration under 60% would not cause severe clotted blood and would produce fewer side effects than absolute ethanol. Based on these findings, we chose solutions with ethanol concentrations between 30 and 60% for foam production. Interestingly, we discovered that ethanol at concentrations less than 50% could be transformed into foam. It has been previously reported that ethanol molecules begin to aggregate at concentrations above 50% on account of changes in the microstructure of ethanol solutions that occur with changes in the concentration of ethanol (12, 13). Further, ethanol foam at concentrations over 48% was found to have poor stability. Considering the differences between *in vivo* and *in vitro* conditions, we determined that, among the experimental concentrations, a 48% fractional volume of ethanol was the ideal concentration at which the solution could be made into a stable foam and still have a potent effect.

A key factor affecting foam stability is the surfactant effect, which can reduce the surface tension and increase foaming efficiency (14). Therefore, we chose Tween 80, a type of surfactant that has good biocompatibility for use as a pharmaceutical adjuvant, according to the US Pharmacopoeia (15), to produce ethanol foam. To evaluate the foaming efficiency of Tween 80, the critical micelle concentration (CMC), a characteristic value that represents the formation of surfactant micelles, was adopted in our

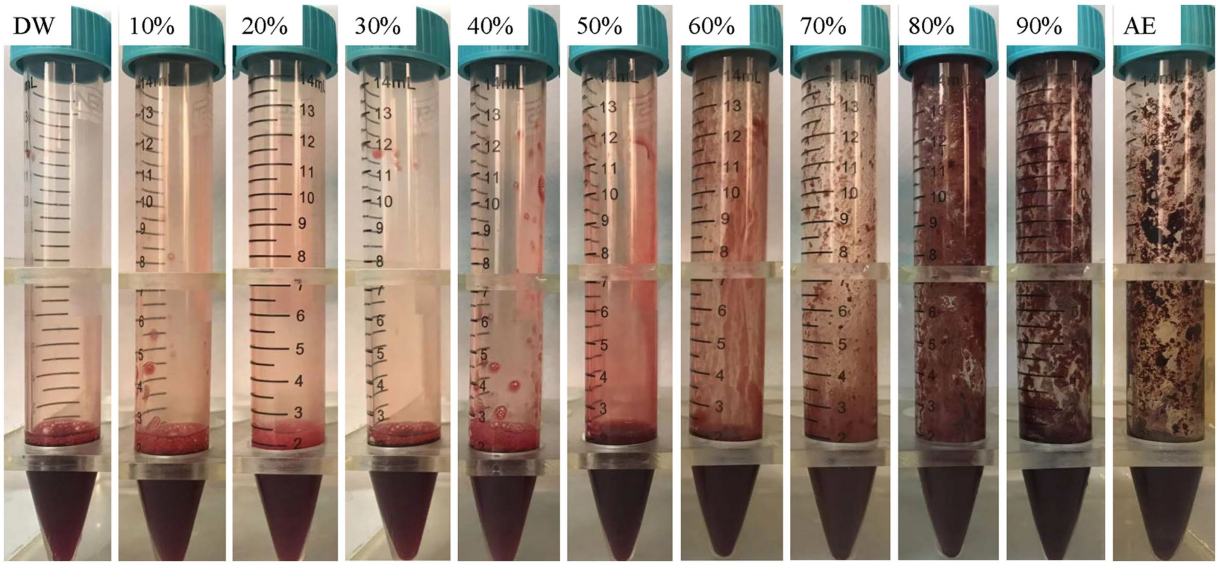

FIGURE 2
Blood clotting ability of ethanol at different concentrations. DW, distilled water; AE, absolute ethanol.

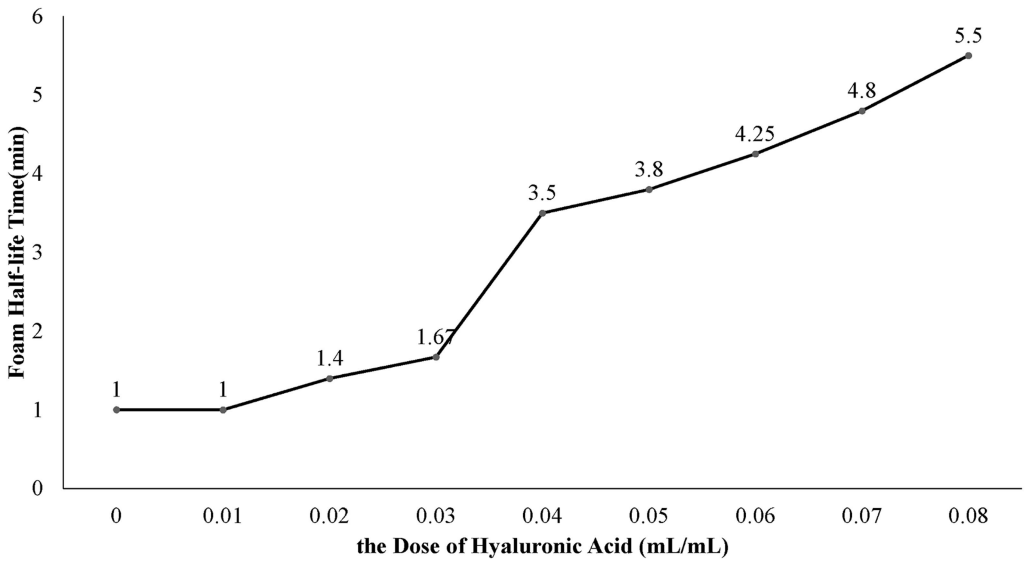

FIGURE 3
Effect of hyaluronic acid at different concentrations on ethanol foam half-life time.

study. When the foam concentration is below the CMC, the foaming efficiency generally increases with increasing concentration until the concentration reaches or exceeds CMC slightly (14). In this study, we used Tween 80 at a concentration of 5×10^{-3} g/mL.

Mixtures of two or more surfactants have been demonstrated to have synergistic effects on micelle formation (14, 16), so we chose PC 80 as another surfactant to be combined with Tween 80. PC 80 is a pharmaceutical adjuvant approved by the FDA that is mainly used in pharmaceutical products as a dispersing, emulsifying, and stabilizing agent and is included in intravenous injections (15). Based on the findings in experiment B that there were no significant differences in foam formation between different concentrations of PC 80, we chose a lower concentration of 10^{-2} g/mL to prevent a decrease in the ethanol concentration.

It is recognized that high surface viscosity contributes to stable foam (17). Solutions with higher concentrations of Tween-80 have higher surface viscosity. However, excessive Tween 80 has also been associated with severe adverse effects (15), and it was recommended that its daily intake be restricted to 25 mg/kg body weight by the World Health Organization in 1974 (18). Considering this dose and the clinical use of Tween 80, we used a low concentration of Tween 80 (5×10^{-3} g/mL) to ensure safety. However, the ethanol foams prepared with 5×10^{-3} g/mL Tween 80 and 10^{-2} g/mL PC-80 exhibited poor stability. To enhance the stability of the foam, we added HA to the solution. HA, a type of biodegradable viscose that is nontoxic and nonimmunogenic (19), is reported to produce no generalized complications when intravenously injected as one of the elements of a foam sclerosant (20). The addition of HA was beneficial in our experiment, as the FHT increased with increasing concentrations of HA (Figure 3). We found that an HA concentration of 0.04 mL/mL is optimal for produce ethanol foam.

To conclude, we have developed a novel ethanol foam that has potential as a sclerosant for treating VMs. In the future, the positive response and good tolerance of this ethanol foam for treating VMs need to be proved in both animal experiments and clinical observation.

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 humans were approved by Research Ethics Committee of Qilu Hospital Shandong University. The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study.

Author contributions

H-SZ: Conceptualization, Formal analysis, Investigation, Methodology, Writing – original draft. Y-RL: Conceptualization, Formal analysis, Investigation, Methodology, Writing – original draft. S-HL: Conceptualization, Funding acquisition, Writing – review & editing.

Funding

The author(s) declare that financial support was received for the research, authorship, and/or publication of this article. This study was supported by Development Funding for Novel Clinical Technology, Qilu Hospital of Shandong University.

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.

A patent based on this work, A Method to Produce Ethanol Foam in Treating Venous Malformations, has been authorized by the Chinese National Intellectual Property Administration and United States Patent and Trademark Office.

Publisher's note

Supplementary material

The Supplementary material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2024.1431723/full#supplementary-material

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frontiers | Frontiers in Neurology

TYPE Original Research
PUBLISHED 16 August 2024
DOI 10.3389/fneur.2024.1444896

OPEN ACCESS

EDITED BY
Xindong Fan,
Shanghai Jiaotong University School of Medicine, China

REVIEWED BY
Marco Fresa,
Centre Hospitalier Universitaire Vaudois (CHUV), Switzerland
Junyi Zhu,
Huazhong University of Science and Technology, China

*CORRESPONDENCE
Tao Wang
✉ wangtao1984@sdu.edu.cn
Shaohua Liu
✉ lshabccba@126.com

†These authors have contributed equally to this work and share first authorship

RECEIVED 06 June 2024
ACCEPTED 06 August 2024
PUBLISHED 16 August 2024

CITATION
Sun Z, Liu Y, Chen A, Wang T and Liu S (2024) Efficacy and safety of hyaluronic-polidocanol foam in sclerotherapy for head and neck venous malformations.
Front. Neurol. 15:1444896.
doi: 10.3389/fneur.2024.1444896

Efficacy and safety of hyaluronic-polidocanol foam in sclerotherapy for head and neck venous malformations

Zhaoyang Sun[1,2†], Yiran Liu[3†], Anwei Chen[1], Tao Wang[1*] and Shaohua Liu[1*]

[1]Department of Oral and Maxillofacial Surgery, Qilu Hospital of Shandong University, Jinan, Shandong, China, [2]Department of Oral and Maxillofacial Surgery, Weifang People's Hospital, Weifang, Shandong, China, [3]Department of Endocrinology, Qilu Hospital of Shandong University, Cheeloo College of Medicine, Shandong University, Jinan, Shandong, China

Background: Foam sclerotherapy is currently the first-line treatment for venous malformations (VMs). Hyaluronic acid-polidocanol (HA-POL) foam has been used in the treatment of head and neck VMs recently; however, its clinical efficacy and safety have yet to be further evaluated, and the impact of age and other related factors on its safety is still unclear.

Objective: To assess the efficacy and safety of HA-POL foam in the treatment of head and neck VMs.

Methods and materials: We performed a single-center retrospective review of all patients with VMs involving the head and neck region undergoing HA-POL foam sclerotherapy from February 2015 to February 2022 in the Oral and Maxillofacial Surgery Department of Qilu Hospital Shandong University. Patients' medical records were collected and all patients enrolled were followed up for 1–6 months (group 1), part of them were followed up for 3–9 years (group 2).

Results: A total of 223 patients with head and neck VMs were enrolled in the study, with 36 patients who were followed for 3–9 years. Total response rate in group 1 was 96.41% ($n = 215$), of which 30.94% ($n = 69$) of the patients met the criteria of "resolution," and 65.47% ($n = 146$) of the patients had "significant improvement." In group 2, the total response rate was 72.22% ($n = 26$), of which the rates of the patients met the criteria of "resolution" and patients had "significant improvement" were all 36.11% ($n = 13$)0.144 (64.57%) patients experienced complications like localized swelling, pain and fever, and no serious complications occurred. The risk of developing complications after treatment was independent of age, and was weakly associated with the dose of HA-POL foam.

Conclusion: The HA-POL foam sclerotherapy is safe and effective in the treatment of head and neck VMs.

KEYWORDS

polidocanol foam, sclerotherapy, hyaluronic acid, venous malformations, sclerosant

1 Introduction

The treatment of head and neck venous malformations (VMs) requires multidisciplinary collaboration, and available treatments include surgery, laser therapy, sclerotherapy, and vascular intervention (1, 2). Extensive or radical surgical resection is often difficult to achieve due to the complicated histological structures involved in the head and neck region (3).

Foam sclerotherapy is currently the preferred therapy for VMs (4), which is characterized by minimal invasive operation, high efficiency and safety. Polidocanol is a widely used foam sclerosant agent.

It has been recognized that the sclerosing ability is highly influenced by foam stability (5, 6), the addition of Hyaluronic acid (HA) to polidocanol foam (HA-POL foam) can effectively prolong the stability of polidocanol foam (7–9). However, the safety and efficacy of HA-POL foam has been less studied. A single-center retrospective study including 70 patients conducted by Chen et al. confirmed that the application of HA-POL foam sclerotherapy for the treatment of head and neck VMs is safe and effective (10). However, the sample size of this study was small, resulting in a relatively low level of evidence.

Considering that serious adverse events of foam sclerotherapy (11), such as deep vein thrombosis, superficial vein thrombosis, and pulmonary embolism, already have a high morbidity in the elderly (12), the safety of HA-POL foam sclerotherapy in the elderly should be given special attention. Similarly, the characteristics of children in terms of physiology, pharmacology, growth and development differ greatly from those of adults, and guiding the use of drugs in children on basis of the results of safety and efficacy studies based on adults may lead to unpredictable and serious consequences (13, 14). Therefore, in view of the particularity of children and the elderly, it is necessary to explore the relationship between age and the efficacy and safety in foam sclerotherapy.

Therefore, we performed a retrospective review with a larger sample size, to assess the efficacy and safety of HA-POL foam in the treatment of head and neck VMs, especially in the children and the aged.

2 Methods and materials

2.1 Study design

A single-center retrospective study was conducted on patients with head and neck VMs treated with HA-POL foam sclerotherapy at the Department of Oral and Maxillofacial Surgery, Qilu Hospital, Shandong University, between February 2015 and February 2022. The study was approved by the Ethics Committee of Qilu Hospital, Shandong University. In group 1, all enrolled patients were classified into 3 age groups, 0–18 years, 19–59 years and ≥ 60 years according to the age of the first visit. The diagnosis of VMs was based on medical history, clinical manifestations, MRI, ultrasound, and other ancillary examination findings according to the classification criteria of the International Society for the Study of Vascular Anomalies (ISSVA) on vascular diseases. Besides, the following patients were excluded: (1) Patients with other vascular diseases or VMs in other sites treated at the same time; (2) Patients treated with other sclerosants or other forms of treatment within 6 months (including 6 months).

2.2 Foam preparation

The Tessari method was adopted for the preparation of HA-POL foam: two 10 mL sterile disposable syringes (WEGO, Weihai, China) were connected at 90° through a medical three-way valve (B. Braun Melsungen AG 34209 Melsungen, Germany). 2 mL of 1% POL liquid (SHANXI TIANYU Pharmaceutical Co., Ltd) and 0.1 mL of 1% HA (20 mg/2 mL Sofast, Sodium Hyaluronate Injection, Shandong Bausch-fruida Pharmaceutical Co Ltd., Shandong, China) were drawn into one of the 10 mL syringes, and the other was filled with 8 mL of air. The two syringes were pushed back and forth for at least 20 times at room temperature in a 4:1 air-liquid ratio to produce HA-POL foam, and the foam was used immediately for sclerotherapy.

2.3 Sclerotherapy process

Sclerotherapy is performed using either a two-needle technique or a multiple-needle technique using winged needles (Shandong Ande Healthcare Apparatus Co., Ltd., China), depending on the patients age and the size of the lesion. The treatment was aided with ultrasound-guiding if necessary. One sterile winged needle was inserted into the lesion, with venous blood was withdrawn to make sure the correct position. A second winged needle connected with a 10 mL syringe would be punctured into the other part of the lesion before the HA-POL foam was slowly injected into the lesion, the injection would cease until foam was observed in the second syringe. If the treatment was ultrasound-guided, the injection was stopped when the lesion was full filled with HA-POL foam under ultrasound, and the dose of foam sclerosing agent used was recorded. The dose of foam for a single sclerotherapy injection should not exceed 30 mL. After injection, sterile gauze was used to compress the entry point by mild pressure to avoid spillage of sclerosing agent through the entry point and to control bleeding. The patient was asked to rest for at least 10 min after treatment. The interval between treatments is 1 month. Signs of discontinuation of sclerotherapy include: (1) clinical assessment that the lesion has disappeared or decreased in size, the symptoms have disappeared or resolved, and that continuation of the treatment will not result in a better therapeutic outcome; and (2) the patient or the patients' guardian voluntarily requesting. All patients were followed up for 1–6 months (group 1), part of them were followed for 3–9 years (group 2).

2.4 Clinical efficacy and safety assessment

We obtained the following data from the patients' medical records, and follow-up results: gender, age at first treatment, location of the lesions, course of treatments, volume of foam sclerosant used, treatment response, and complications of post-treatment.

After sclerotherapy, the efficacy and safety were evaluated at the last follow-up visit. Clinical efficacy was evaluated according to a modified scoring system proposed by Achauer et al.: "Cure" indicated that the clinical manifestations of VMs had completely disappeared; "Significant improvement" indicates a continuous reduction in lesion size by 50% or more, or that the original dysfunction had completely

returned to normal; "no effect" indicates a recurrence or no improvement in the size and the functional impairment caused by the lesion.

The occurrence of complications during and after sclerotherapy were collected in the medical records and during follow-up, and the types, time of occurrence of complications were recorded for safety assessment.

2.5 Statistical analysis

Descriptive statistics were used in the statistical analysis, where continuous variables were described by means ± standard deviation and categorical variables were described by numerical values (percentages). We applied SPSS 23.0 software package to analyze the data by statistical methods of binary Logistics linear regression and Pearson correlation analysis.

3 Results

3.1 Patients' characteristics

Total of 223 patients were enrolled in group 1 (Table 1), of whom 78 patients were male and 145 patients were female. The average age of the patients at first treatment was 29.91. Number of patients in age group of 0–18 years, 19–59 years and ≥ 60 years were 75,137 and 11 patients, respectively. There were total 36 patients underwent further follow-up in group 2, details are given in Table 2.

Sites of lesions included the face, tongue, lips, neck, parotid gland, periorbital, nose, mental region, palate, temporal region, floor of the mouth, gums, and oropharynx, with 32 of the patients' lesions were multiple (Table 3).

In group 1, there was a total of 380 treatment sessions for all 223 patients (Table 1), with an average of 1.7 sessions each (range 1–12). The average volume of HA-POL foam used per treatment was 9.82 mL, ranging from 1.20 mL to 30.00 mL.

TABLE 1 Clinical date of patients with head and neck venous malformations.

Characteristic	Number	%	Standard deviation
Sex ($n = 223$)			
Female	145	65.02%	
Male	78	34.98%	
Age ($n = 223$)	29.91 (0–75)		17.77
Age group ($n = 223$)			
0–18 years	75	33.60%	
19–59 years	137	61.43%	
≥60 years	11	4.93%	
Treatment session ($n = 380$)	1.70		1.41
Volume of foam ($n = 380$)	9.82		6.31

3.2 Clinical efficacy

The overall efficiency in group 1 was 96.41% ($n = 215$), of which 30.94% ($n = 69$) of the patients achieved "Cure," and 65.47% ($n = 146$) achieved "Significant improvement." There were 3.59% ($n = 8$) patients had no response. Results of Pearson correlation analysis showed that age was not related to the efficacy of treatment [point two-column correlation coefficient: $R = 0.078$, $p > 0.05$].

Of the 8 patients who were "no effect," 3 patients had multiple lesions, accounting for 37.50%. Therefore, it was considered that the multiple lesions might affect the results of the treatment. Therefore, the patients were categorized into "Effective(including "Cure" and "Significant improved)" ($n = 215$) and "Ineffective" ($n = 8$) groups according to the treatment effect, the statistical results showed that whether the lesions were multiple or not did not affect the efficacy of treatment, and the difference was not statistically significant [9.38% vs. 2.62%, OR = 3.848, *95%CI* (0.873, 16.971), $p > 0.05$], and the lesion sites did not affect the efficacy($p > 0.05$).

In group 2, the overall efficiency was 72.22% ($n = 26$), of which the rates of the patients met the criteria of "resolution" and patients had "significant improvement" were all 36.11% ($n = 13$). There were 10

TABLE 2 Clinical date of patients with head and neck venous malformations (group 2).

Characteristic	Number	%
Sex ($n = 36$)		
Female	27	75.00%
Male	9	25.00%
Age ($n = 36$)	30.25	
Treatment session ($n = 51$)	1.42	
Volume of foam	10.42	
Cure	13	36.11%
Significant improvement	13	36.11%
No effect	10	27.78%

TABLE 3 Locations of the head and neck venous malformation lesions.

Location of VMs	Number	%
Face	73	32.74%
Tongue	39	17.49%
Lips	41	18.39%
Multiple	32	14.35%
Neck	8	3.59%
Parotid region	5	2.24%
Periorbital	5	2.24%
Nose	4	1.79%
Mental region	4	1.79%
Temporal region	3	1.35%
Palate	3	1.35%
Floor of mouth	3	1.35%
Gums	2	0.90%
Oropharynx	1	0.90%

(27.78%) patients who had "no effect," of which 7 patients had recurrence (Table 2).

3.3 Risk assessment of complications

There were 141 patients experienced localized swelling, which was the most common complication. Two patients had localized pain, and 1 patient had fever. All patients experienced gradual relief and recovery within 2–3 days. No patient developed serious complications such as localized skin and mucosal ulcers, pulmonary embolism, allergic and allergic-like reactions, deep vein thrombosis, shock. No patient whose lesion involved parotid area and periorbital area developed complications of facial nerve dysfunction and visual impairment after treatment. Data of complications is detailed in Table 4.

A 27-year-old female patient with lesions in the buccal mucosa who had suffered from shock during pingyangmycin sclerotherapy years ago did not experience any complications. A 35-year-old male patient with a history of uremia received twice treatments, and no complication occurred. The results of the above study demonstrated that the use of HA-POL foam sclerotherapy for the treatment of VMs in the head and neck region is safe.

3.4 Correlation analysis between age and safety

We categorized all the patients into three age groups according to their age, 0–18 years, 19–59 years and ≥ 60 years, and compared the post-treatment complications among patients of different age groups, respectively, to investigate the safety of HA-POL foam sclerotherapy. The difference of the risk of complication between three groups was not statistically significant. Results are detailed in Table 5.

Although patients in the age group of 19–59 years had the highest probability of complications after treatment, followed by the patient of age group ≥60 years, and the patient of age group 0–18 years had the lowest risk, the difference was not statistically significant, and the results of the correlation analysis showed that the risk of complications did not correlate with the patients age [point two-column correlation coefficient: $R = 0.149$, $p > 0.05$]. It is evident that HA-POL foam sclerotherapy for head and neck VMs is safe for all age groups.

TABLE 4 Complications of HA-POL foam sclerotherapy.

Complication	Number (%)
Localized swelling	141 (63.36%)
Pain	2 (0.90%)
Fever	1 (0.45%)
Skin and mucosal ulcer	0 (0.00%)
Bacterial infection	0 (0.00%)
Cutaneous necrosis	0 (0.00%)
Pulmonary embolism	0 (0.00%)
Anaphylaxis and anaphylactoid reactions	0 (0.00%)
Deep vein thrombosis	0 (0.00%)
Shock	0 (0.00%)
Never damage	0 (0.00%)
Visual impairment	0 (0.00%)

3.5 Correlation between the volume of HA-POL foam and safety

The mean volume of HA-POL foam used per patient was 9.82 ± 6.31 mL. The single-treatment dose of foam sclerosant used was weakly and positively correlated with the risk of complications [point two-column correlation coefficient: $R = 0.209$, $p < 0.05$]. That is, the higher the volume of HA-POL foam used in a single treatment, the higher the risk of complications such as local swelling and pain after treatment. Therefore, in the clinical application of foam sclerotherapy for the treatment of VMs in the head and neck region, controlling the volume of foam sclerotherapy used in a single treatment helps to improve the safety of the treatment.

4 Discussion

The site and size of VMs lesions limits the choice of treatment method, and in this study, the highest percentage of patients with lesions located in the cheeks was 32.74%, followed by the tongue (17.49%) and lips (18.39%). VMs in the head and neck region often involve important anatomical structures, making the lesion cannot be completely resected, and surgery is also accompanied by risks of adjacent nerve damage, bacterial infection and scar formation (2). Percutaneous sclerotherapy is currently the most widely used treatment for VMs (15). In this study, the overall treatment efficiency of HA-POL foam sclerotherapy was 96.41% in group 1, among them, 30.94% of the patients were "cured," 65.47% were "significantly improved." We found that whether the lesions involved multiple sites or not did not affect the efficacy of the treatment, and the treatment response of lesions in different site had no difference. The results certified that HA-POL foam sclerotherapy is very effective in the treatment of head and neck VMs, and the therapeutic efficacy is not limited by the complex anatomical structure.

Considering the short follow-up time, we performed a further follow-up study, and finally 36 patients were followed up for 3–9 years. In this group with a long follow-up time, the treatment efficiency decreased significantly, with an overall response rate of 72.22%. It is worth noting that the rate of patients meeting "cure" criteria has increased. Considering fewer patients were enrolled, whether this difference is meaningful needs further investigation. In addition, among the 10 patients had "no effect," half of the patients reached the "cured" and "significantly improved" criteria after treatment but had recurrence. The high recurrence rate suggests that the reduction in treatment response rate may be closely associated with recurrence, but this also needs to be confirmed by further studies.

Compared with liquid sclerosant, foam sclerosant can achieve better treatment response by increasing the contact area and contact time between the drug and the lesions, and enhance safety by reducing the dose of sclerosant (8, 16). It is believed that increasing the stability of the sclerosing agent foam correlates with better therapeutic outcomes. There are many factors affecting the stability of sclerosant foam (17, 18), and our previous study confirmed that the addition of a small dose of HA can significantly increase the stability of POL foam (9). HA is a linear glycosaminoglycan, as a

TABLE 5 Analysis of relationship between age group and complications after HA-POL foam sclerotherapy.

Age group	Complication (n = 141)	No complications (n = 82)	Total (n = 223)	p-value
Age group				0.424
0–18 years	43 (57.33%)	32 (42.67%)	75	0.190
19–59 years	91 (66.42%)	46 (33.58%)	137	
≥60 years	7 (63.64%)	4 (36.34%)	11	0.851

natural polymer involved in the formation of the extracellular matrix, it is widely found in human body (19, 20). Research has proven that intravenous application of HA is safe for humans (9, 21, 22).

In a study by Chen et al. (10), 70 patients with VMs of the head and neck treated with HA-POL foam sclerotherapy were enrolled and the results of the study showed a 100% total response rate, of which "Resolution" was achieved in 21 cases (30%) and a significant response in 49 patients (70%). Localized swelling was the most common post-treatment complication but it resolved within 2–3 days, and one patient developed localized mucosal ulceration after treatment, with no other serious complications. However, this study included a small sample size and did not mention the efficacy and safety of HA-POL foam sclerotherapy in different age groups, especially in children and the elderly. VMs, as congenital lesions, often occur in children, who have complex physiological, developmental, psychological, and pharmacological characteristics, and their metabolism of specific drugs is different from that of adults, which may lead to poor therapeutic efficacy, side effects, and drug poisoning. S.P. Mooijaart et al. suggested that the physiological differences between the elderly and the young, such as altered renal function, hepatic function, and body composition of the elderly affects the metabolism of the body and the clearance of the drug, in addition to the fact that the elderly patients are exposed to drug interactions due to the simultaneous application of multiple medications (23). Children and the elderly deserve special attention when assessing the safety and efficacy of a drug or treatment. It is necessary to explore the relationship between age and the safety of HA-POL foam sclerotherapy.

In our study, after HA-POL foam sclerotherapy, intra-and post-treatment adverse events occurred in 144 patients (64.57%), of which localized swelling had the highest incidence of 63.36% and was the most common complication after HA-POL foam sclerotherapy, followed by pain and fever, but with a very low percentage of 0.90 and 0.45%, respectively. There were no serious adverse events such as localized skin mucosal ulcers, superficial tissue necrosis, infection, deep vein thrombosis, pulmonary embolism, or shock in this study. All patients presented with uncomfortable symptoms gradually relieved and recovered within 2–3 days. We also categorized the enrolled patients into three age groups: 0–18 years, 19–59 years, and ≥60 years, and compared the risk of complication between different groups, respectively. The results showed that the risk of complications after HA-POL foam sclerotherapy was consistent between patients in the 0–18 years age group and the 19–59 years age group, and the difference was not statistically significant. The risk of complications in group of ≥60 years was 63.64%, and all of them were localized swelling and resolved soon after treatment, no serious adverse complications occurred. There was no statistically significant difference in the risk of complications in patients ≥60 years of age compared to patients 19–59 years of age, indicating HA-POL foam sclerotherapy is safe for children and the elderly population as well.

Based on the above findings about different age groups, we further explored the correlation between age and the risk of complications after HA-POL sclerotherapy, and the results showed that there was no correlation between age and the risk of complications, demonstrating the application of HA-POL foam to treat head and neck VMs has a high level of safety for all age groups.

In this study the effect of the dose of foam sclerotherapy used in a single treatment on the safety of the treatment was investigated. The volume of sclerosing agent foam used per treatment was determined by the treating physician based on the size of the lesion, but the maximum volume of foam used in a single session was not to exceed 30 mL to ensure the safety of the treatment. In the 223 patients enrolled in this study, the average HA-POL foam volume used in a single session for each patient was 9.82 mL (from 1.20 mL to 30.00 mL). The results showed that there is a weak positive correlation between the volume of foam sclerosant used in a single treatment and the risk of complications. That means the higher the volume of HA-POL foam sclerosant used in a single treatment, the higher the risk of complications. Therefore, controlling the volume of HA-POL foam in a single treatment is one of the keys to ensure the safety of treatment.

The limitations of this study included the use of a single-center clinical retrospective study, the absence of some case data, and the fact that most of the patients did not undergo a second MRI and ultrasound check after treatment to accurately assess the change in lesion volume. This study did not include patients treated with POL foam sclerotherapy alone to form a controlled trial. Otherwise, the short follow-up time limits the accuracy of the study findings. Although we did further long-term study, the small number of patients enrolled is still insufficient to illustrate treatment efficacy. There is a need for larger prospective clinical studies or randomized controlled trials to provide more convincing results on the efficacy and safety of HA-POL in the treatment of head and neck venous malformations.

5 Conclusion

In this study, we demonstrated that the application of HA-POL foam sclerotherapy for the treatment of head and neck VMs is safe and effective, and that the efficacy and safety of this treatment are not affected by age, including children and the elderly. The volume of HA-POL foam used in a single treatment session was weakly correlated with the risk of complications, so careful control of drug dosage can help to improve the safety of the treatment.

Data availability statement

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

Ethics statement

The studies involving humans were approved by the Medical Ethics Committee of Qilu Hospital of Shandong University. The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study.

Author contributions

ZS: Writing – review & editing, Writing – original draft, Validation, Software, Methodology, Formal analysis, Data curation, Conceptualization. YL: Writing – review & editing, Writing – original draft, Validation, Data curation, Conceptualization. AC: Writing – review & editing, Visualization, Validation, Conceptualization. TW: Writing – review & editing, Visualization, Validation, Supervision, Resources, Project administration, Funding acquisition, Conceptualization. SL: Writing – review & editing, Visualization, Validation, Supervision, Resources, Project administration, Methodology, Funding acquisition, Conceptualization.

Funding

The author(s) declare that no financial support was received for the research, authorship, and/or publication of this article.

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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frontiers | Frontiers in Neurology

TYPE Mini Review
PUBLISHED 19 August 2024
DOI 10.3389/fneur.2024.1447960

OPEN ACCESS

EDITED BY
Wayne Yakes,
The Yakes Vascular Malformation Center,
United States

REVIEWED BY
Osamah Alwalid,
Sidra Medicine, Qatar

*CORRESPONDENCE
Verónica Fernández-Alvarez
✉ UO72421@uniovi.es

RECEIVED 12 June 2024
ACCEPTED 02 August 2024
PUBLISHED 19 August 2024

CITATION
Fernández-Alvarez V, Linares-Sánchez M, Mäkitie AA, Suárez C, de Bree E, Karatzanis A, Takes RP, Strojan P, Rinaldo A and Ferlito A (2024) Intravenous lipomas of head and neck: an exceptional entity and its clinical implications.
Front. Neurol. 15:1447960.
doi: 10.3389/fneur.2024.1447960

Intravenous lipomas of head and neck: an exceptional entity and its clinical implications

Verónica Fernández-Alvarez[1]*, Miriam Linares-Sánchez[2], Antti A. Mäkitie[3], Carlos Suárez[4], Eelco de Bree[5], Alexander Karatzanis[6], Robert P. Takes[7], Primoz Strojan[8], Alessandra Rinaldo[9] and Alfio Ferlito[10]

[1]Department of Vascular and Endovascular Surgery, Torrecardenas University Hospital, Almeria, Spain, [2]Department of Vascular and Endovascular Surgery, Cabueñes University Hospital, Gijon, Spain, [3]Department of Otorhinolaryngology – Head and Neck Surgery, Research Program in Systems Oncology, University of Helsinki and Helsinki University Hospital, Helsinki, Finland, [4]Department of Otorhinolaryngology, University of Oviedo, Oviedo, Spain, [5]Department of Surgical Oncology, Medical School of Crete University Hospital, Heraklion, Greece, [6]Department of Otorhinolaryngology, Medical School of Crete University Hospital, Heraklion, Greece, [7]Department of Otorhinolaryngology and Head and Neck Surgery, Radboud University Medical Center, Nijmegen, Netherlands, [8]Department of Radiotherapy, Institute of Oncology, Ljubljana, Slovenia, [9]ENT Unit, Policlinico Città di Udine, Udine, Italy, [10]Coordinator of the International Head and Neck Scientific Group, Padua, Italy

Intravenous lipomas (IVLs) of the head and neck are uncommon benign tumors that develop within the venous walls, often detected incidentally during imaging for unrelated issues. While usually asymptomatic, these IVLs can cause congestive venous symptoms like swelling, paresthesia or pain in the head and neck and upper limbs, or even venous thromboembolism. The precise diagnosis of IVLs is predominantly achieved through computed tomography (CT) and magnetic resonance imaging (MRI), with CT being the most frequently used method. Symptomatic patients generally undergo open surgery with excision of the IVL followed by venous reconstruction, which has shown safe and effective outcomes. However, the management of asymptomatic IVLs remains controversial due to the limited number of reported cases. Despite this, there is a notable trend toward recommending surgical removal of IVLs to prevent complications and rule out malignancy, driven by the challenges of differentiating IVLs from malignant tumors using imaging alone. This review highlights the key differential imaging characteristics of IVLs and the main surgical techniques to remove the tumor and repair the vascular defect. Further research is necessary to establish a robust, evidence-based approach for treating asymptomatic IVLs, balancing the risks of surgery against the potential for future complications.

KEYWORDS

lipoma, intravenous lipoma, primary venous tumor, superior vena cava, head and neck

1 Introduction

Lipomatous tumors in the head and neck region are rare, exhibiting a wide spectrum of biological behaviors, from completely benign to malignant with metastatic potential. Ordinary lipoma, the most prevalent benign tumor in adults, constitutes approximately 30–50% of all soft tissue tumors and predominantly occur in the subcutaneous tissue of the upper body and proximal extremities (1–4), with around 13–17% located in the head and neck region (1).

However, intravenous lipomas (IVLs) are extremely rare primary venous tumors originating intravascularly. While these lipomas are most commonly found in the heart (5), their occurrence in central veins is exceptionally uncommon (6). The inferior vena cava (IVC) is the most common location for IVLs, with few cases reported in the head and neck region (6). Many IVLs are asymptomatic and are often discovered during imaging studies for other conditions, while others mimic deep vein thrombosis by causing compressive or occlusive symptoms (5, 7–9). Although IVLs have a favorable prognosis, their clinical course is not well understood. Due to the scarcity of reported cases, the indication for surgical intervention is controversial, particularly in asymptomatic patients, given the uncertain risk of thrombus formation, venous occlusion, and embolization. The aim of this mini-review is to clarify the natural history and optimal management strategies for IVL, thereby enhancing clinical decision-making and patient outcomes. Key points for imaging diagnosis are summarized, surgical techniques are briefly outlined, and associated patient outcomes are presented.

2 Literature review, primary anatomical locations, and demographic trends

A literature search was conducted across three major databases (PubMed, Elsevier, Google Scholar) using the terms "lipoma" AND ("intravascular" OR "intravenous" OR "superior vena cava" OR "brachiocephalic" OR "subclavian" OR "jugular"). If additional studies were identified from the references of previously published reviews, they were included in the analysis.

Only 24 cases of IVL were identified until May 2024 during the above literature search.

The majority of reported IVL cases in the head and neck region involved the superior vena cava (SVC), often extending to the brachiocephalic, subclavian or jugular veins (2, 4, 6–17). IVLs may also occur within the SVC without extension to adjacent veins (18–22). Additionally, isolated cases of jugular (5) or brachiocephalic vein lipomas (23–27) have also been documented. With the exception of cases reported by Kamdar et al. (11) and Fung (27), right-sided veins are typically involved. Regarding gender distribution, IVLs exhibited a male predominance with a ratio of 3:1 compared to females, while they are detected at an earlier age in women (mean age: 53.2 years, range: 39–70 years) compared to men (mean age: 58.5 years, range: 47–73 years) (2, 4–27). The occurrence rate of IVLs is unknown but it was estimated to be found, as an incidental finding, in 0.35–0.5% among the general population undergoing contrast-enhanced CT (4, 28).

Table 1 summarizes the case reports from the literature describing IVLs involving the SVC and cervical veins.

3 Pathophysiological mechanisms and potential contributing factors

The risk factors for IVLs remain somewhat unclear due to the limited literature on this condition and the absence of experimental data. However, several authors have suggested that obesity, liver cirrhosis, hepatic tumors, renal angiomyolipomas, direct venous injury, and prolonged corticosteroid use may be associated with the presence of IVLs (7, 13, 29, 30).

Genetic factors are believed to play a significant role. However, while approximately 7–14% of patients with ordinary lipomas develop multiple lipomas, familial multiple lipomas are observed in about 30% of cases (1), suggesting a hereditary predisposition, only Thorogood et al. (8) have reported a case of SVC IVL associated with multiple cutaneous lipomas.

Santos et al. (13) have proposed a hypothesis regarding the potential role of immunologic phenomena associated with sarcoidosis, which could impact the structural components of vessel walls. This hypothesis is based on the plausible differentiation of vascular wall-resident multipotent stem cells, including mesenchymal stem cells, into adipocytes. Despite the few adipocytes typically present in the venous media layer, according to their assumption, these factors may contribute to the abnormal growth of fatty tissue within veins.

4 Natural history of IVLs and variants

4.1 Natural progression of IVLs

Several hypotheses have been proposed about the origin of IVLs. Initially, IVLs were believed to originate within the vein wall, with potential expansion into the vascular lumen or extraluminal invasion into surrounding adipose tissue (2, 6, 9, 13, 22). The first documented case of an IVL dates to 1962, reported by Tsardakas, involving the endothelium of the saphenous vein (31). However, subsequent reports by other authors have depicted cases where lipomas exhibited both intravascular and extravascular components (4, 5, 24). This duality has prompted the formulation of two theories to elucidate this peculiar presentation, positing intraluminal origin from the vein wall or extraluminal origin via invagination of adjacent adipose tissue (13). According to the former theory, the tumor grows into the vein wall protruding both internally and externally (4, 13, 23, 24, 29, 30, 32). The latter hypothesis suggests a perivascular tissue origin, infiltration into the vein wall, and subsequent protrusion into the lumen. Lomeo et al. (4) provided a detailed description of how the tumor arose from perivascular tissue and then intruded into the vein by invagination without infiltrating the wall. The CT scan revealed that initially, the mass was located outside the right subclavian vein; however, after a 2 cm distance, it traversed the venous wall and positioned itself within the vein lumen as it approached the SVC. The transmural vascular invasion of the IVL into the vein was described as a dumbbell-shaped extension of the tumor (24).

4.2 Pericaval fat collections as normal variants

Concerning fat mass-like lesions, localization adjacent to or projecting into the subdiaphragmatic portion of the intrahepatic IVC is recognized as a normal variant by some authors (28). Miyake et al. (28) first described these focal fat collections in 1992, found in 0.5% of 2,227 patients undergoing a CT examination. Subsequently, Perry et al. (30) reported similar findings in seven cases, terming them "lipomas." Although these masses appeared intraluminal due to their acute angle with respect to the cava wall, speculation persisted

TABLE 1 Cases reported from the literature describing IVLs involving the SCV and cervical veins.

Author (year)	Age Gender	Location	Symptoms	Imaging studies	Size (mm)	Surgical repair
Vinnicombe et al. (1994) (6)	42/F	R BCV SVC	Fatigue, facial and hand edema	CT: rounded mass of fat attenuation reducing the lumen of R BCV and SVC. Venography: Lobulated filling defect, widening SVC.	100×50 ×50	NE
Thorogood et al. (1996) (8)	73/M	R BCV SVC	No	CT: mass of fat density within the lumen of the SVC and the R BCV. MRI T1-weighted: high signal mass. STIR sequence confirmed the fatty nature.	NE	No excision
Trabut et al. (1999) (19)	55/M	SVC	No	CT: findings not specified.	NE	NE
Lomeo et al. (2007) (4)	60/M	R SCV SVC	No	CT: Extravascular fatty mass adjacent to the R SCV with an intravascular SVC component. Echocardiography: mass adjacent to the SVC. Duplex US: no sign of thrombosis in the R SCV/SVC.	100	Direct primary suture
Moore et al. (2008) (23)	58/M	R BCV	No	CT: filling defect with fatty attenuation within the R BCV. MRI: confirmed fatty nature of the mass.	NE	No excision
Ryu et al. (2009) (10)	47/M	R SCV R BCV	No	CT: oval-shaped mass with fat attenuation. MRI T1 weighted: fatty mass based on the R SCV growing into the R BCV.	10×35	No excision
Kamdar et al. (2009) (11)	63/M	L IJV SVC	No	CT: fatty mass partially occluding L IJV and extending into the SCV. MRI T1-weighted: hyperintense mass that loses signal with fat saturation.	NE	Ligation of IJV
Mordant et al. (2010) (12)	55/F	R SCV R BCV SVC	No	CT: Intraluminal nonenhancing tumor. MRI: fatty intravascular lesion. Venography: total occlusion of the R SCV and BCP and SVC with abnormal collaterals.	90×50	End-to-end anastomosis between BCV and SVC
Bravi et al. (2012) (18)	63/M	R SCV SVC	Left-sided abdominal and right shoulder pain	CT: fatty mass within the lumen of SVC extending from right atrium to R SCV. MRI: uniform signal drop on fat-suppressed sequences. Echocardiogram: dilatated right atrium and a filling defect in the final portion of SVC.	130	Pericardial patch
Santos et al. (2012) (13)	47/F	R BCV SVC	No	CT: nonenhancing intraluminal polypoid mass with fat attenuation from the R BCV to SVC.	NE	No excision
Lococo et al. (2013) (24)	61/M	R BCV	No	CT: well-defined mass of fat density in the thoracic inlet space which invaded the R BCV.	41×23	PTFE patch
Yoon et al. (2013) (5)	39/F	R IJV	No	CT: fat attenuation mass in the caudal R IJV. Dupplex US: loosely attached, mobile, well-circumscribed hypoechoic mass.	10×10 ×12	Oversewn of both IJV ends
Iqbal et al. (2014) (25)	51/M	R BCV	No	CT: fatty mass (−129 HU). MRI: intravascular lipoma with no signs of malignancy. Duplex US: no evidence of venous stasis or compression.	13	No excision
Concatto et al. (2015) (20)	58/M	SVC	No	CT: hypodense elongated lesion with fat density within the SVC. MRI: confirmed the fatty nature of the lesion.	110	NE

(Continued)

TABLE 1 (Continued)

Author (year)	Age Gender	Location	Symptoms	Imaging studies	Size (mm)	Surgical repair
Tanyeli et al. (2015) (21)	48/M	SVC	Right upper extremity swelling and paresthesia	CT: lesion of fat density within the SVC. MRI: intraluminal mass, causing enlargement and partial occlusion of the SVC.	50×20	NE
Vetrhus et al. (2017) (26)	60/F	R BCV	No	CT: filling defect with fatty attenuation within the R BCV.	17x8x 12	No excision
Wahab et al. (2017) (22)	70/F	SVC	No	MRI: filling defect at the junction of the RA and SVC. TEE: partially obstructing round, echogenic mass at the SVC and RA junction.	26×16×16	NE
Beliaev et al. (2019) (7)	49/F	R IJV R SCV SVC	No	CT: low density mass with smooth contours in the SVC, attached to the junction of the R SCV and IJV by a narrow stalk.	95×25	Direct primary suture
Elen et al. (2019) (14) Soetisna et al. (2022) (15)	54/M	SVC RA	No	CT: elongated lesion with low density (−102 HU) arised from SVC to RA. MRI: big capsulated mass, hyperintense at T1-weighted image but hypointense at fat suppression technique, with no enhancenment. Ecocardiography: large mass at RA.	120×50 ×40	Direct primary suture
Sundaram et al. (2020) (16)	58/M	R IJV R BCV SVC	Facial edema and right upper extremity venous congestion	CT: intraluminal mass in the IJV and BCV extending into SVC. Dupplex US: large pedunculated hyperechoic mass attached to R IJV and extending to R BCV. Diminished flow in the IJV.	50	Direct primary suture
Podobed (17) (2021)	53/F	R BCV SVC	Facial and right hand edema	CT: hypodense elongated lesion with fat density within the SVC.	NE	NE
Knop et al. (9) (2021)	59/M	R IJV R BCV SVC	No	CT: low density intraluminal mass R BCV extending to IJV and SVC.	NE	No excision
Cohen et al. (2) (2023)	64/F	R BCV SVC	No	CT: low density mass in the SVC extending to the R BCV with mild enhancement after contrast administration. MRI: fatty encapsulated tumor conditioning filling defect in SVC and R BCV.	76	Pericardial patch
Fung (2023) (27)	70/M	L BCV	No	CT: well-circumscribed hypodense lesion in the L BCV with fat density.	10×8	No excision

R BCV, right brachiocephalic vein; L BCV, left brachiocephalic vein; SVC, superior vena cava; R SCV, right subclavian vein; R IJV, right internal jugular vein; L IJV, left internal jugular vein; RA, right atrium; PTFE, polytetrafluoroethylene; TEE, transesophageal echocardiogram; US, ultrasound; NE, not specified.

regarding their external origin (30). Han et al. (33) attributed the appearance of pericaval fat collections to rightward angulation of the IVC and narrowing of the intrahepatic IVC. The stability of fat collections on follow-up CT scans in the majority of reported cases supports the notion that these findings likely represent entirely extraluminal lesions mimicking intraluminal masses. Thus, they are considered unusual but normal variants with no clinical significance, negating the need for patient follow-up (34).

5 Clinical presentation: how IVLs show up

IVLs are often asymptomatic and are commonly detected incidentally during imaging studies conducted for unrelated reasons (8, 9). When symptoms do occur, they are usually attributable to the location and tumor's size, resulting in venous thrombosis, obstructive venous symptoms, or mediastinal syndromes due to compressive effects (6, 21, 23). Although SVC lipomas or IVLs in the head and neck region are rare compared to IVC counterparts, they may produce symptoms related to venous obstruction within the SVC drainage territory. This can manifest as SVC syndrome, swelling in the head, face, neck, and arms, as well as upper limb paresthesia, shoulder pain, and venous thromboembolism (6, 7, 12, 15, 17, 18, 21). In the literature review, only 21% of cases were associated with symptoms (6, 16–18, 21). Among them, facial and upper extremity edema have been reported as the main symptom of head and neck IVLs.

In cases involving larger IVLs within the SVC, there have been reports of intraluminal thrombus formation, such as the case documented by Bravi et al. (18) where an IVL within the SVC led to a

subtotal occlusion extending into the right atrium, accompanied by thrombosis of the suprahepatic IVC and the portal vein. Similarly, Lococo et al. (24) reported a case of a fatty neoplastic thrombus completely occluding the brachiocephalic vein. It is postulated that the subsequent turbulent flow may promote thrombus formation and occlusion (18, 30).

6 Diagnostic imaging of IVLs and histopathologic findings

6.1 Key imaging features of IVLs

IVLs can be diagnosed using various imaging modalities, including sonography, CT, MRI, transthoracic/transesophageal echocardiogram, or venography (16). Among reported cases of IVLs in the head and neck region, CT and MRI are commonly employed for characterizing the mass (1).

Upon examination of chest X-rays, the identification of a widened superior mediastinum may signal the presence of a SVC IVL, as documented by Vinnicombe et al. (6). Sonographically, IVLs typically present as intraluminal hyperechoic masses with or without thin septa. Duplex venous sonography can show a patent vein or diminished flow if the lipoma is causing near obstruction (4, 9, 16, 25). However, MRI and CT are the most reliable imaging techniques for confidently identifying adipose tissue in these lesions (1). CT imaging may depict a well-defined, hypoattenuating intraluminal mass consistent with fat, often lacking contrast enhancement except for its fibrous capsule (1, 16, 35) (Figures 1A,B). Contrast CT is particularly effective in determining fat coefficients by calculating Hounsfield units (HU) with given values between −30 to −150 HU, facilitating non-invasive diagnosis of IVLs in major venous vessels (9, 36). CT also aids in distinguishing lipomas from other soft tissue tumors based on fat density and also in identifying the presence of an intravenous thrombus by calculating the densitometry of the intraluminal mass (36, 37). CT has been performed in all reported cases of IVL except the one reported by Wahab et al. (22). This case involved the superior vena cava and right atrium and was diagnosed using only MRI and echocardiography. On MRI, IVLs appear as well-circumscribed lesions with signal characteristics similar to subcutaneous fat across all imaging sequences. Fat-specific MRI sequences appear to offer the highest specificity for diagnosing IVLs compared to other modalities confirming their fatty nature through significant loss of signal intensity on fat suppression sequences. They exhibit high signal intensity on T1-weighted images and also on T2-weighted images, although the intensity on T2-weighted images may be slightly lower compared to T1-weighted images (16, 38) (Figure 1C). However, MRI was performed in less than the half of the reported cases (2, 8, 10–12, 14, 15, 18, 21–23, 25).

6.2 Additional imaging modalities

In addition to standard imaging techniques, other modalities can offer valuable insights into the diagnosis and characterization of IVLs. Transthoracic and transesophageal echocardiography can provide useful tissue information, including echogenicity, calcification, vascularity, and evaluation of right atrium extension, aiding in the diagnosis of lipomas (2). Nonetheless, echocardiography was performed in only 4 of the total reported cases. Another imaging technique which may demonstrate a filling defect in the SVC or jugulosubclavian venous confluence with collateral development is the SVC venography (6, 12). Due to its invasiveness and limited value compared to CT or MRI, venography is not commonly used. Additionally, fludeoxyglucose positron emission tomography (FDG-PET) is suggested as a technique which can aid in differentiating malignant from benign lipomatous tumors and between different liposarcoma subtypes, though its use in IVLs of the head and neck has not been reported (1).

6.3 Histopathological analysis of IVLs

IVLs are characterized by distinctive histological features. Macroscopically, IVLs present as well-circumscribed, pale yellow, lobulated fatty masses occupying the vein lumen, which may or may not be associated with thrombus formation (5, 6). Microscopically, IVLs exhibit well-differentiated tumor predominantly composed of mature white adipose cells with non-centrally located nuclei and thin fibrous septa in some areas, encapsulated by collagenous tissue. IVLs typically lack necrosis, hemorrhage, or calcifications (14, 15).

6.4 Differential diagnosis

In addition to lipomas, the differential diagnosis of intravascular masses containing fat encompasses a spectrum of benign and malignant conditions such as thrombus formation, other primary tumors, and secondary tumor extension (39).

Among benign tumors, leiomyomas, originating from smooth muscle cells of the endothelium, represent the most prevalent venous tumors (3, 4). Another benign entity, fibrolipoma, characterized by neoplastic fat cells within dense collagen, has been reported, including a unique case involving the femoral vein (40). Hemangiomas, deriving from endothelial cells, have also been documented, with Hu et al. (41) reporting a rare case of a massive unicameral cardiac hemangioma associated with a persistent left SVC.

Among malignant tumors, leiomyosarcomas, arising from smooth muscle tissue of the endothelium, are the most common primary tumors of the vena cava, often leading to luminal obliteration (30). Fibrosarcomas, originating from connective tissues, and endotheliomas and hemangioendotheliomas, derived from endothelial cells, are also to be considered. Although venous angiosarcomas are rare, reported cases suggest their potential presence, characterized by mesenchymal cells with epithelioid morphology, focal nuclear atypia in adipocytes, vascular channels, and CD31 endothelial marker positivity (42). Liposarcoma, the malignant variant of lipoma, typically appear on CT as heterogeneous masses with areas of fat density interspersed with soft tissue density. They usually include thick septa and nodular or globular areas of non-adipose tissue that show heterogeneous patterns of signal intensity and enhancement due to necrosis, hemorrhage, myxoid changes or cellular areas. On T1-weighted images generally exhibit intermediate to low signal intensity and tend to show heterogenous high signal intensity on T2-weighted images. Fat-suppressed sequences and gadolinium-enhanced sequences can show heterogeneous enhancement, reflecting areas of vascularization and necrosis (35, 38). Cytogenetic analysis may play a crucial role in establishing the

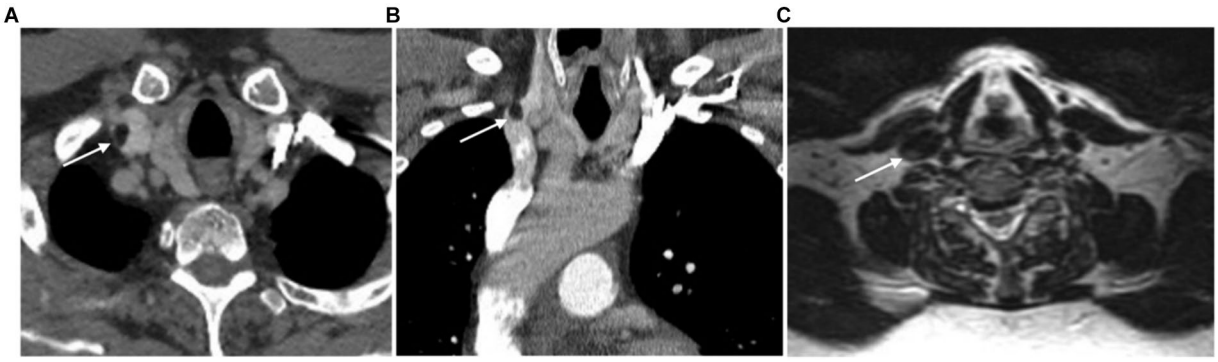

FIGURE 1
Axial **(A)** and coronal **(B)** images of a CT scan of the chest, revealing a 10 mm, well-defined, hypodense mass at the right jugulosubclavian venous confluence (white arrows). This lesion is consistent with the characteristics of an intravascular lipoma, exhibiting fat attenuation (-97 HU) and no evidence of significant contrast enhancement. On an axial T2-weighted MRI sequence without fat saturation **(C)**, the lipoma appears as a hyperintense, homogeneous mass.

diagnosis (1). Head and neck intravenous location of liposarcoma has not been reported in the literature so far (26).

7 Management of IVLs: from observation to intervention

7.1 Surgical and non-surgical treatment options

Treatment guidelines for IVLs have not yet been established, most likely due to their rarity. Given that most IVLs are asymptomatic and exhibit slow growth, some authors suggest that invasive treatment may not be necessary for asymptomatic cases (2, 8–10, 13, 23, 25, 26, 36). However, regular follow-up with imaging examinations is essential to monitor any changes in the tumor over time (38). Nevertheless, other authors state that surgical resection is crucial to rule out malignancies and prevent the potential risk of thrombus formation, embolization, penetration of the right atrium and venous occlusion (2, 12, 17). This viewpoint supports the surgical removal of asymptomatic IVLs, particularly when the patient is fit for surgery and the lesion's location allows for a safe approach without risking damage to nearby structures, thereby making the risk–benefit balance favorable in these cases (2, 12, 17, 18). This is especially recommended for large lipomas or those that are mobile, as they pose a risk for future pulmonary thromboembolism (43). Another factor endorsing this position is that, despite no reported cases of intravenous liposarcoma in the literature (26), surgical management in asymptomatic patients may be necessary to exclude malignancy in scenarios where CT or MRI cannot reliably differentiate between benign lipomas and well-differentiated liposarcomas (2), or where the lesion displays radiologic features of vascular invasiveness and association with a fatty thrombus, which are highly suggestive of malignancy. Surgical excision not only provides a definitive histological diagnosis but also prevents these risks, with no major complications reported in the performed surgeries. Furthermore, Mordant and colleagues argue that excision should be mandatory since surgical treatment is safe without the need of lifelong anticoagulation (12, 20).

Management of IVLs in other regions varies. Although no published reports exist on tumor resection for IVLs of the IVC (29, 36, 43, 44), half of the cases involving the renal vein have undergone surgery (35, 45). Additionally, all published cases of iliofemoral IVLs have been treated with surgical resection (3, 32, 40, 46–48).

7.2 Surgical excision techniques

The surgical approach for excising IVLs in the head and neck should be carefully considered and supported by adequate preoperative anatomical imaging. Its primary challenge is the proximity of relevant anatomical structures, therefore, when planning intervention, it is crucial to balance achieving complete tumor removal with minimizing the risk of complications and unnecessary functional and cosmetic morbidity (1).

The resection techniques described in the literature vary depending on the anatomical localization and extent of the tumor. It should also be noted that some published cases do not describe the surgical technique employed. Nonetheless, a median sternotomy combined with transcervical approach has been the most frequently used surgical approach, as it allows control of all major thoracic veins, minimizes the risk of tumor embolization, limits blood loss, and permits en bloc resection of the tumor if necessary (2, 4, 12, 16, 17, 24). Some reports describe the use of cardiopulmonary bypass to excise SVC IVLs when they extend into or are proximal to the right atrium (14–16, 18, 22).

To remove the IVL, a longitudinal (6, 16) or transverse (12) venotomy can be performed, and the tumor can then be pulled down and excised (6, 11, 18). The venous wall may be primary repaired with a running 6/0 or 7/0 polypropylene suture (4) or using a patch of polytetrafluoroethylene (24) or pericardium for surgical defect closure (2, 18). Another method for tumor removal is en bloc resection followed by end-to-end anastomosis between the two severed venous ends (12) or, in cases of IVLs isolated in the internal jugular vein, by ligation (5, 11).

Special mention is given to Cohen et al. (2), who planned a hybrid approach for an IVL extending from the jugular and subclavian vein to the SVC. They performed an endovascular technique to control the

right brachiocephalic vein via the right brachial vein with a 12 mm balloon prior to venotomy to prevent the risk of tumor embolization and minimize blood loss during the en bloc excision of the IVL.

7.3 Post-treatment outcomes and follow-up

Among the 16 surgical patients reported in the literature, the administration of antiplatelet agents (2, 5, 21) or anticoagulants (4, 16, 18, 22) in the immediate postoperative period is noted in only 7 cases, as well as in the non-surgical case reported by Santos et al. (13), associated with sarcoidosis and long-term corticosteroid therapy.

Most cases after surgical removal had an uneventful recovery. Two postoperative complications were reported: a pulmonary embolism one week after discharge (21) and Dressler's syndrome on postoperative day 25 (2).

Short-term follow-up imaging should be considered to assess for central vein stenosis or occlusion. Notably, many authors did not specify the surveillance regimen, and those who did typically indicated short-term follow-up with an average duration of 10 months (range 1–36 months) (2, 4, 5, 7, 12–16, 18). No evidence of tumor recurrence was observed during follow-up. Based on this, Sundaram et al. (16) suggested that due to the low incidence of tumor recurrence, long-term follow-up does not appear to be necessary.

8 Conclusion

IVLs represent rare benign neoplasms that grow into the venous wall. While often asymptomatic, they have the potential to induce congestive venous symptoms and venous thromboembolism. CT and MRI are the most valuable imaging techniques for confident identification of IVLs, with CT being the most frequently used throughout the literature. For symptomatic patients, surgical excision via median sternotomy and cervicotomy with subsequent venous reconstruction represents the main treatment strategy. The management of asymptomatic patients, however, remains controversial due to the limited number of reported cases. Despite this, our mini-review underscores a prevailing trend toward the surgical removal of IVLs. This inclination is driven by the necessity to accurately exclude malignancy based on cross-sectional imaging alone and to mitigate the risks of venous thromboembolism, particularly in larger or mobile lipomas. Our findings highlight that this proactive approach is substantiated by a remarkably low complication rate and the documented absence of recurrence following surgical excision. Further research is needed to accurately determine the real risk of complications and morbidity in asymptomatic IVL patients in order to establish an evidence-based approach for individual treatment selection.

Author's note

This article was written by members and invitees of the International Head and Neck Scientific Group (http://www.ihnsg.com).

Author contributions

VF-A: Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Software, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. ML-S: Software, Writing – review & editing, Writing – original draft, Investigation, Data curation. AM: Writing – review & editing, Writing – original draft. CS: Writing – review & editing, Writing – original draft. EB: Writing – review & editing, Writing – original draft. AK: Writing – review & editing, Writing – original draft. RT: Writing – review & editing, Writing – original draft. PS: Writing – review & editing, Writing – original draft. AR: Writing – review & editing, Writing – original draft. AF: Project administration, Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision.

Funding

The author(s) declare that no financial support was received for the research, authorship, and/or publication of this article.

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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frontiers | Frontiers in Neurology

TYPE Original Research
PUBLISHED 21 August 2024
DOI 10.3389/fneur.2024.1425395

OPEN ACCESS

EDITED BY
Xindong Fan,
Shanghai Jiaotong University School of Medicine, China

REVIEWED BY
Gerson de Oliveira Paiva-Neto,
Federal University of Amazonas, Brazil
Benjamin Yim,
John Muir Medical Center, United States
Abdullah M. Al-Qudah,
University of Pittsburgh Medical Center, United States

*CORRESPONDENCE
Xukai Wang
✉ wangxukai757892@sina.com

RECEIVED 29 April 2024
ACCEPTED 02 August 2024
PUBLISHED 21 August 2024

CITATION
Yuan W and Wang X (2024) Therapeutic evaluation of electrochemical therapy combined with local injection of pingyangmycin for the treatment of venous malformations in the tongue.
Front. Neurol. 15:1425395.
doi: 10.3389/fneur.2024.1425395

Therapeutic evaluation of electrochemical therapy combined with local injection of pingyangmycin for the treatment of venous malformations in the tongue

Weili Yuan[1] and Xukai Wang[2]*

[1]Department of Stomatology, The Fourth Affiliated Hospital of China Medical University, Shenyang, Liaoning, China, [2]Department of Oral and Maxillofacial Surgery, School of Stomatology, China Medical University, Shenyang, Liaoning, China

Background: Venous malformations are congenital developmental abnormalities that consist of enlarged dysplastic blood vessels. The tongue is a common site of venous malformations in the head and neck region. The aim of the present study was to evaluate the therapeutic effect of using electrochemical therapy (ECT) combined with local injection of pingyangmycin (PYM) for venous malformations in the tongue.

Methods: 60 patients (20 male and 40 female; age range, 8 to 68 yr) with venous malformations in the tongue were treated with a combination of ECT and PYM injection or with local injection of PYM alone in the department of oral and maxillofacial surgery of the stomatological hospital of China Medical University from January 2013 through June 2019. Among them, 30 patients (group A) were treated with ECT combined with PYM injection for tongue venous malformations and 30 patients (group B) were treated with local injection of PYM alone for tongue venous malformations. The size of the lesions in the two groups varied from $3.5 \times 3 \times 3$ to $8 \times 6 \times 5$ cm. There was no statistical difference in the volume of the lesions between group A and group B ($p > 0.05$). There was no statistical difference in the age between the two groups ($p > 0.05$). A repeated treatment of ECT combined with PYM injection or PYM injection alone was administered for venous malformations of tongue in the group A and group B. According to the size of the lesions, the amount of ECT was 5–10 C/cm^2. The injection dose of PYM was 3 ~ 5 mL and the injection concentration of PYM was 1.6 mg/mL for adults and 1.0 mg/mL for children. Glucocorticoids were given to prevent postoperative swelling. The therapeutic interval was 3 months for ECT combined with PYM injection and 2 to 4 weeks for PYM injection alone. Hemisphere measurements were used to measure the size of the lesions. 4-scale score and feedback from the patients were used to evaluate the clinical efficacy.

Results: During the follow-up period from 6 months to 3 years, 60 patients achieved different degree of improvement, with a total effective rate of 85%. 30 patients in the group A received ECT combined with local injection of PYM, with an effective rate of 97%. 30 patients in the group B received local injection of PYM alone, with an effective rate of 73%. The effectiveness of ECT combined with PYM injection in the group A was significantly higher than that of PYM injection alone in the group B ($p < 0.05$). Postoperative symptoms such as

local pain, swelling and fever often occurred in the patients, and the symptoms generally disappeared after 5 to 7 days. No mucosa necrosis or nerve damage was found. Postoperative subjective sensation and function of the tongue were normal.

Conclusion: Electrochemical therapy combined with local injection of pingyangmycin was a reliable, safe and minimally invasive method for the treatment of venous malformation in the tongue. The treatment modality has fewer complications and is worth of further promotion in clinic.

KEYWORDS

electrochemical therapy, pingyangmycin, venous malformation, tongue, sclerotherapy

Introduction

Vascular malformation is a kind of vascular abnormality caused by the abnormal morphology of vascular tissue, which is composed of blood vessels with abnormal arrangement of endothelial cells (1). The abnormal blood vessels involved could be classified into capillary malformations, venous malformations, arteriovenous malformations, lymphatic malformations, and mixed malformations (2). Tongue is a common site of venous malformation in the head and neck. Typical symptoms of venous malformations of the tongue are bleeding, pain and swelling as well as impairments of speaking, swallowing or even breathing (3). In the past, the treatment of tongue venous malformations included laser therapy, conventional surgery, sclerotherapy, interventional embolization and other methods, but the indications of the above methods were limited and the effect of clinical treatment was not ideal. In recent years, our team used electrochemical therapy combined with local injection of pingyangmycin or local injection of pingyangmycin alone in the treatment of tongue venous malformations in 60 patients in the department of oral and maxillofacial surgery of the stomatological hospital of China Medical University. We conducted a retrospective case–control study of the efficacy of the two therapeutic methods, as reported below.

Methods

Study design and participants

60 patients (20 male and 40 female; age range, 8 to 68 yr) with venous malformations in the tongue were treated with a combination of ECT and PYM injection or with local injection of PYM alone in the department of oral and maxillofacial surgery of the stomatological hospital of China Medical University from January 2013 through June 2019. A random sequence was generated using a computer program to assign the 60 patients in a 1:1 ratio to the two groups (group A and group B) of 30 patients each. The patients in the group A were treated with ECT combined with local injection of PYM for tongue venous malformation and the patients in the group B were treated with local injection of PYM alone for tongue venous malformation. There was no statistical difference in the age between the two groups ($p > 0.05$). The size of the lesions in the two groups varied from $3.5 \times 3 \times 3$ to $8 \times 6 \times 5$ cm, as measured by Doppler ultrasonography. There was no statistical difference in the volume of the lesions between group A and group B ($p > 0.05$). Venous malformations occurred in both the body and the lateral margin of tongue in 23 cases (38%). Venous malformations occurred solely in the body of tongue in 3 cases (5%). Venous malformations occurred solely in the lateral margin of tongue were 7 cases (12%). Venous malformations occurred solely in the abdomen of tongue were 12 cases (20%). Venous malformations occurred in both the abdomen and the lateral margin of tongue in 4 cases (7%). Multiple venous malformation of tongue occurred in 11 cases (18%). The demographics and relevant treatment of the patients in the two groups were shown in Table 1. All the lesions were ≥ 3 cm in diameter. There were 15 patients with high-return flow venous malformations in the group A and 8 patients with high-return flow venous malformations in the group B. The clinical manifestations of tongue venous malformations were as follows: (1) The lesions protruded from the surface of the tongue; (2) The surface mucosa of the lesions was blue-purple; (3) The lesions were soft and could be compressed, and the high-return flow venous malformations can be restored to their original state after being compressed for 5 s. We can confirm the diagnosis by asking the history, palpating the lesion site, taking enhanced CT, and examining magnetic resonance. None of the patients received any treatment before the surgery. The research plan was reviewed and approved by the medical ethics committee of the Stomatological Hospital of China Medical University. The treatment plan was approved by the patients and their families, and informed consent was signed prior to the treatment.

Inclusion and exclusion criteria

In order to ensure the patients' safety, the inclusion criteria should be strictly followed as below: (I) the patient had not received any other drug treatment before the treatment; (II) according to the patient's history and clinical characteristics, combined with color Doppler ultrasound, enhanced CT or MRI, the patient was diagnosed as having the tongue venous malformation; (III) the results of chest anteroposterior and lateral radiographs, electrocardiogram, blood routine test, coagulation test, and liver and kidney function tests were normal; (IV) the patients with complete clinical data had good compliance and were able to complete various examinations; (V) the patients and their families signed informed consent before the treatment.

The exclusion criteria were any of the following: (I) according to the classification of vascular diseases proposed by Waner and Suen (2), hemangioma and other vascular malformations were present. (II) the patients with acute inflammation or mucositis of the tongue; (III) the patients with platelet crisis or coagulation dysfunction; (IV) the patients with severe liver and kidney dysfunction; (V) a history of drug allergy to pingyangmycin or bleomycin.

Therapeutic instruments and drugs

The therapeutic instrument used was VECHT-2 electrochemical hemangioma therapeutic apparatus (Number AOL-07004, Beijing Weili Heng Technology Development Co., LTD.), platinum electrode needle (diameter 0.7 cm, unipolar length 15 cm, bipolar length 5 cm); The sclerosing agent used was pingyangmycin hydrochloride injection (8 mg/dose, Jilin Aodong Pharmaceutical Group Yanji Co., LTD.).

Treatment methods

Preparation of pingyangmycin injection solution

For tongue venous malformation, the usual injection concentration for adults was 1.6 mg/mL. The preparation of pingyangmycin injection solution (1.6 mg/mL) was as follows: 8 mg pingyangmycin dissolved in 5 mL mixed solution of lidocaine and normal saline (lidocaine mixed with 0.9% NaCl solution at a ratio of 1: 1); The injection concentration for children was 1.0 mg/mL. The preparation of pingyangmycin injection solution (1.0 mg/mL) was as follows: 8 mg pingyangmycin was dissolved in 8 mL mixed solution of lidocaine and normal saline (lidocaine mixed with 0.9% NaCl solution at a ratio of 1: 1), and the single injection dose was 3–5 mL. We have stated that there was no vasopressor drugs, such as epinephrine in the lidocaine since the vasopressor drugs would interfere in the therapeutic effect of electrochemical therapy.

TABLE 1 Summary of the demographics and relevant treatment of the patients.

Demographics	*n* (%)
Gender	
Male	20 (33)
Female	40 (67)
Age (years)	
Mean	39.8
Range	8–68
Follow-up duration (months)	
Median	15
Range	6–36
Age at treatment initiation (years)	
<18	6 (10)
≥18	54 (90)
Maximum diameter of the lesion (cm)	
<5	25 (42)
≥5	35 (58)
Location	
The body of tongue	3 (5)
The lateral margin of tongue	7 (12)
Both the body and the lateral margin of tongue	23 (38)
The abdomen of tongue	12 (20)
Both the abdomen and the lateral margin of tongue	4 (7)
Multiple venous malformation of tongue	11 (18)
Previous treatment	0 (0)

Electrochemical therapy combined with pingyangmycin injection

The surgeon chose general or local anesthesia according to the patient's systemic condition and needs. We selected unipolar or bipolar ECT according to the size of the lesions (for the lesions ≥5 cm in diameter, select unipolar ECT). For the patients with general anesthesia, we routinely disinfected the surgical site, made the sterile towel spreading and then pulled out the tongue from the mouth, which could expose the malformed lesions; For the patients with local anesthesia, after routine disinfection and sterile towel spreading, the tongue body was pulled out and local anesthetic drugs (lidocaine injection without the vasopressor drugs) were injected into the base and surrounding area of the lesions. Then the operation was performed after the anesthetic took effect. Our team have used the color Doppler ultrasound, enhanced CT or MRI to accurately locate the insertion position of the electrodes in the venous malformations of the tongue before the operation. The cannulas with the platinum electrode needles were inserted from the normal tissue into the base of the venous malformation in order to block the blood flow in the lesions. The surgeon distributed the electrode needles in parallel with the positive and negative electrodes and at intervals (4). The needle distance was 1.0 ~ 1.5 cm, and the inserting depth was adjusted appropriately. When the internal blood return could be seen in the cannula, the needle core was extracted and the platinum electrode needle was inserted. The surgeon must pay attention to appropriate placement of the cannula outside the normal mucosal tissue to avoid the exposure of the electrode needle to burn the normal mucosal tissue during the operation. During the treatment process, we used bipolar ECT to intermittently administer electrochemical therapy and electrical power was applied once every 3 s, which last 15 s each time for each power-on with cumulative electrical power supply for 2–3 min; the treatment dose during the unipolar ECT surgery was 5–10 C/cm^2. The surgeon could also observe the changes in the lesions, and stop the electrical power when the lesions became hard or the mucosal surface color was normal. The blood and gas accumulation in the lesion cavity was removed by squeezing the lesion. The platinum needles and the cannulas were removed and the needle holes were closed with absorbable suture. Subsequently, the concentration and dose of pingyangmycin were selected according to the patient's age and the lesion size. The injection method of pingyangmycin was as follows: after routine local disinfection, a syringe for 5 mL was used to inject from the normal mucosal tissue to the tongue venous malformation. Blood in the lesion cavity was drained as far as possible, and the needle head was kept in the lesion. The syringe containing pingyangmycin solution was then replaced and the pingyangmycin solution was evenly injected into the lesion cavity. According to the location of the lesion, the patient's age, and the extent and depth of the lesion involvement, 3–5 mL pingyangmycin solution

was injected. After the injection, the local pinhole was pressed with a sterilized gauze for 10 min to prevent the injection solution from spilling out. If the lesion involved a large area or had a huge volume, a multi-point injection or multiple regional injection was given and then finger or ring pressure was used to compress the lesion region for 15–30 min to block the blood flow and prolong the local residence time of pingyangmycin. Postoperative prophylactic antibiotic therapy wasn't needed since the procedure were conducted under means that granted biosecurity. Glucocorticoids were given to prevent postoperative swelling. The therapeutic interval was 3 months for electrochemical therapy combined with pingyangmycin injection until the lesion was cured or good curative effect was obtained. At each follow-up visit, the lesion volume, surface color, and texture changes were recorded in detail. The treatment continued or discontinued according to the degree of the lesion regression or adverse reactions, respectively.

Local injection of pingyangmycin alone

The concentration and dose of pingyangmycin were selected according to the patient's age and the lesion size. The injection method of pingyangmycin was as follows: after routine local disinfection, a syringe for 5 mL was used to inject from the normal tongue mucosal tissue to the tongue venous malformation. Blood in the lesion cavity was drained as far as possible, and the needle head was kept in the lesion. The syringe containing pingyangmycin solution was then replaced and the pingyangmycin solution was evenly injected into the lesion cavity. According to the location of the lesion, the patient's age, and the extent and depth of the lesion involvement, 3–5 mL pingyangmycin solution was injected. After the injection, the local pinhole was pressed with a sterilized gauze for 10 min to prevent the injection solution from spilling out. Small superficial venous malformations could be injected until the surface of the lesion became pale. If the lesion involved a large area or had a huge volume, a multi-point injection or multiple regional injection was given and then finger or ring pressure was used to compress the lesion region for 15–30 min to block the blood flow and prolong the local residence time of pingyangmycin. In our study, small lesions were cured by only one injection, larger lesions were injected between three and five times, and the cumulative injection dose totaled less than 40 mg. The vital signs of the patients were closely observed for at least 30 min after the injection, and those patients without abnormal allergic symptoms and signs were allowed to leave the hospital. Postoperative prophylactic antibiotic therapy wasn't needed since the procedure were conducted under means that granted biosecurity. Glucocorticoids were given to prevent postoperative swelling. The injection was repeated 15–30 days later according to the regression of the lesion. At each follow-up visit, the lesion volume, surface color, and texture changes were recorded in detail. The treatment continued or discontinued according to the degree of the lesion regression or adverse reactions, respectively.

Evaluation criteria of curative effect

We used hemisphere measurement (5) to record the sizes of the lesions before and after the treatment. We used the classification of Achauer et al. as the evaluation criteria of curative effect (6), and the patients' feedback to evaluate the curative effect. The classification of Achauer et al. was as follows: I(poor) = lesion volume decreased by less than 25%, the size of the lesions did not change or continue to expand; II (moderate) = lesion volume decreased between 26 and 50%; III (good) = lesion volume decreased between 51 and 75%, the appearance markedly improved; and IV (excellent) = lesion volume decreased between 76 and 100%, the lesions disappeared completely and no recurrence occurred after 1 year of follow-up. Among them, grade III (good) and IV (excellent) were rated as effective treatment, and grade I(poor) and II (moderate) were rated as ineffective treatment. The classification of Achauer as the evaluation criteria of curative effect was shown in Table 2.

Statistical method

SPSS 22.0 statistical software was used for analysis, and counting data were analyzed by Chi-Square test. $p < 0.05$ was considered statistically significant.

Results

Overall efficacy evaluation

During the follow-up period from 6 months to 3 years, 60 patients achieved different degree of improvement, with a total effective rate of 85%. 30 patients in the group A received electrochemical therapy (ECT) combined with local injection of pingyangmycin (PYM), with an effective rate of 97%. 30 patients in the group B received local injection of pingyangmycin alone, with an effective rate of 73%. The effectiveness of ECT combined with PYM injection in the group A was significantly higher than that of PYM injection alone in the group B ($p < 0.05$). The treatment results of the two groups with different treatment methods were shown in Tables 3–5. Postoperative symptoms such as local pain, swelling and fever often occurred in the patients, and glucocorticoids were given to prevent postoperative swelling. The postoperative fever (<38°C) was considered to be caused by injection of pingyangmycin, and the symptoms disappeared without special treatment. The symptoms generally disappeared after 5 to 7 days. No mucosal necrosis or nerve damage was found. Postoperative subjective sensation and function of the tongue were normal. The pictures of typical cases were shown in Figures 1–7.

Typical cases

Case 1: The patient was a 59-year-old male. The venous malformation of the left lingual margin and lingual body lasted for more than 10 years, and the progressive enlargement of the lesion

TABLE 2 The classification of Achauer as the evaluation criteria of curative effect.

Achauer classification	Ineffective treatment		Effective treatment	
	I (Poor)	II (Moderate)	III (Good)	IV (Excellent)
Volume decreased	≤25%	26–50%	51–75%	76–100%

TABLE 3 Comparison of the efficacy of two different methods for the treatment of venous malformations in the tongue [*N* (%)].

Group	*N*	Effective			Ineffective		
		Excellent	Good	Total	Moderate	Poor	Total
ECT + PYM	30	23 (77)	6 (20)	29 (97)	1 (3)	0 (0)	1 (3)
PYM	30	12 (40)	10 (33)	22 (73)	5 (17)	3 (10)	8 (27)
Total	60	35 (58)	16 (27)	51 (85)	6 (10)	3 (5)	9 (15)

ECT + PYM stands for electrochemical therapy combined with local injection of pingyangmycin; PYM stands for local injection of pingyangmycin.

TABLE 4 Summary of the patients' characteristics and outcomes by electrochemical therapy combined with local injection of pingyangmycin for the treatment of tongue venous malformation.

Patient No.	Gender	Age at Onset, years	Size (cm[a]) prior to treatment	Size (cm[a]) after treatment	Location of the lesion	Type of return flow	Follow up, months	Response
1	M	59	8×6×5	3.5×2×1.5	LLM + LLB	High	36	Excellent
2	M	42	5×4.5×3	0×0×0.5	RLM + RLB	High	18	Excellent
3	M	56	6×5×3.5	0×0×0.5	LLM + LLB	High	24	Excellent
4	M	35	5×4.5×2.5	0×0×0	LLM + LLB	High	12	Excellent
5	F	38	6.5×6×2.5	0×0×0.5	Multiple	Low	18	Excellent
6	F	26	4.5×3.5×2	0×0×0	RLA	High	12	Excellent
7	F	45	4×3×2.5	2×2×1	LLM	High	18	Excellent
8	F	15	5.5×5×2	0×0×0.5	Multiple	High	12	Excellent
9	F	32	4.5×3×1.5	0×0×0	RLA	High	12	Excellent
10	F	52	3.5×3×3	1×1×0.5	LLA	Low	12	Excellent
11	F	38	3.5×3.5×3	0×0×0	LLB	Low	12	Excellent
12	F	55	7×6.5×5	0×0×0	RLM + RLB	Low	36	Excellent
13	M	45	6.5×6×3.5	0×0×0.5	Multiple	High	24	Excellent
14	F	48	4×3.5×2	2.5×2×1	LLM + LLB	High	18	Excellent
15	F	8	3.5×3×3	0×0×0	LLM	Low	6	Excellent
16	F	25	3.5×3×3	0×0×0	LLM + LLB	Low	12	Excellent
17	F	38	3.5×3×3	1.5×1.5×1	RLM	Low	12	Excellent
18	M	8	4×3×2	0×0×0	LLB	Low	12	Excellent
19	M	8	3.5×3×3	2.5×2×1	LLM + LLB	Low	12	Excellent
20	F	48	4.5×4×2.5	1×1×0.5	RLM + RLB	Low	18	Excellent
21	F	58	4×3×2.5	2×2×0.5	RLA + LLA	Low	12	Excellent
22	M	56	6.5×5×3	0×0×0.5	LLM + LLB	Low	24	Excellent
23	F	32	5×4.5×2	0×0×0	Multiple	Low	18	Excellent
24	M	30	6×4.5×3	3.5×3.5×2	RLA	High	24	Good
25	M	35	8×6×3.5	6×4×2	RLM + RLB	High	24	Good
26	F	55	6×4.5×2.5	4.5×3.5×2	Multiple	Low	12	Good
27	F	68	7×6×5	5×4.5×3	LLM + LLB	High	18	Good
28	F	66	8×6×5	6×5×3	Multiple	High	24	Good
29	M	33	5.5×5×2.5	4×3.5×2	RLM + RLB	High	12	Good
30	F	60	7×4.5×2.5	5.5×4×2	Multiple	Low	12	Moderate

[a]Data presented a length/width/depth. M, male; F, female. LLM stands for the left lingual margin; LLB stands for the left lingual body; RLM stands for the right lingual margin; RLB stands for the right lingual body; LLA stands for the left lingual abdominal; RLA stands for the right lingual abdominal; Multiple stands for that the lesions occurred in the multiple locations in the tongue.

affected eating and speech. The lesion of the left lingual margin and lingual body recovered after 5 s compression, which was a high-return flow venous malformation. After ECT combined with PYM injection, the lesion was significantly reduced 3 months after the treatment, and completely cured. The pictures of the lesion before and after the treatment were shown in Figure 1.

TABLE 5 Summary of the patients' characteristics and outcomes by local injection of pingyangmycin alone for the treatment of tongue venous malformation.

Patient No.	Gender	Age at Onset, years	Size (cm[a]) prior to treatment	Size (cm[a]) after treatment	Location of the lesion	Type of return flow	Follow up, months	Response
1	F	68	8×6×5	5×3×2	LLM + LLB	Low	18	Excellent
2	F	35	3.5×3×3	0×0×0	RLA	Low	12	Excellent
3	F	46	5×4.5×3	3×3×1	RLM + RLB	Low	18	Excellent
4	F	50	6×4.5×2	2×1×0.5	LLM + LLB	Low	12	Excellent
5	F	18	3.5×3×3	0×0×0	RLA	Low	12	Excellent
6	F	45	3.5×3×3	0×0×0	LLM	Low	12	Excellent
7	F	56	5×4.5×2	0×0×0	LLM + LLA	Low	24	Excellent
8	F	52	3.5×3×3	0×0×0	RLM + RLA	Low	18	Excellent
9	M	8	3.5×3.5×3	0×0×0	LLM + LLB	Low	12	Excellent
10	F	36	3.5×3×3	0×0×0	LLM	Low	12	Excellent
11	F	40	5×3×2.5	0×0×0.5	RLA + LLA	Low	18	Excellent
12	F	20	4.5×3×2	0×0×0	RLB	Low	12	Excellent
13	F	55	6×4×1.5	5×3×1	Multiple	Low	18	Good
14	F	46	5×2.5×2	4×2×1.5	RLM + RLA	Low	24	Good
15	F	48	5×3.5×2	3×3×1.5	RLM + RLB	Low	18	Good
16	F	38	5.5×4.5×2	4×3×1.5	Multiple	Low	24	Good
17	M	23	3.5×3.5×2	3×2.5×1.5	RLA	Low	18	Good
18	M	25	3.5×3×2.5	3×2×2	LLM + LLB	Low	12	Good
19	M	12	4.5×4×2	3.5×3×1.5	RLA + LLA	Low	12	Good
20	F	35	6×3.5×2	4×2.5×2	LLM + LLA	Low	18	Good
21	M	27	5.5×5×2.5	4.5×3.5×2	LLM + LLB	Low	12	Good
22	M	32	3.5×3×2.5	3×2.5×1.5	RLM + RLB	Low	12	Good
23	F	30	8×5.5×4.5	7×5×4	Multiple	High	18	Moderate
24	M	28	8×6×3	7×5.5×2.5	RLA + LLA	High	24	Moderate
25	F	55	6×5.5×3.5	5×4.5×3	LLM + LLB	High	18	Moderate
26	F	56	3.5×3×2	3.2×2.3×2	LLM	High	12	Moderate
27	F	26	5×3.5×2.5	4×3×2	LLA	High	12	Moderate
28	M	50	6×5×3	5×4.5×3	LLM	High	18	Poor
29	F	48	5.5×5×3	5×5×2.5	LLM + LLB	High	12	Poor
30	M	65	8×6×5	7×5×3	Multiple	High	12	Poor

[a]Data presented a length/width/depth. M, male; F, female. LLM stands for the left lingual margin; LLB stands for the left lingual body; RLM stands for the right lingual margin; RLB stands for the right lingual body; RLA stands for the right lingual abdominal; LLA stands for the left lingual abdominal; Multiple stands for that the lesions occurred in the multiple locations in the tongue.

Case 2: The patient was a 42-year-old male. The venous malformation of the right lingual margin and lingual body lasted for more than 6 years, and the progressive enlargement affected eating and speech. The lesion of the right lingual margin and lingual body recovered after 5 s compression, which was a high-return flow venous malformation. After ECT combined with PYM injection, the lesion was significantly reduced 3 months after the treatment, and completely cured. The pictures of the lesion before and after the treatment were shown in Figure 2.

Case 3: The patient was a 56-year-old male. The venous malformation of the left lingual margin and lingual body lasted for more than 5 years, and the progressive enlargement of the lesion affected eating and speech. The lesion of the left lingual margin and lingual body recovered after 5 s compression, which was a high-return flow venous malformation. After ECT combined with PYM injection, the lesion was significantly reduced 3 months after the treatment, and completely cured. The pictures of the lesion before and after the treatment were shown in Figure 3.

Case 4: The patient was a 35-year-old male. The venous malformation of the left lingual margin and lingual body lasted for more than 3 years, and the progressive enlargement of the lesion affected eating and speech. The lesion of the left lingual margin and lingual body recovered after 5 s compression, which was a high-return flow venous malformation. After ECT combined with PYM injection, the lesion was significantly reduced 3 months after the treatment, and completely cured. The pictures of the lesion before and after the treatment were shown in Figure 4.

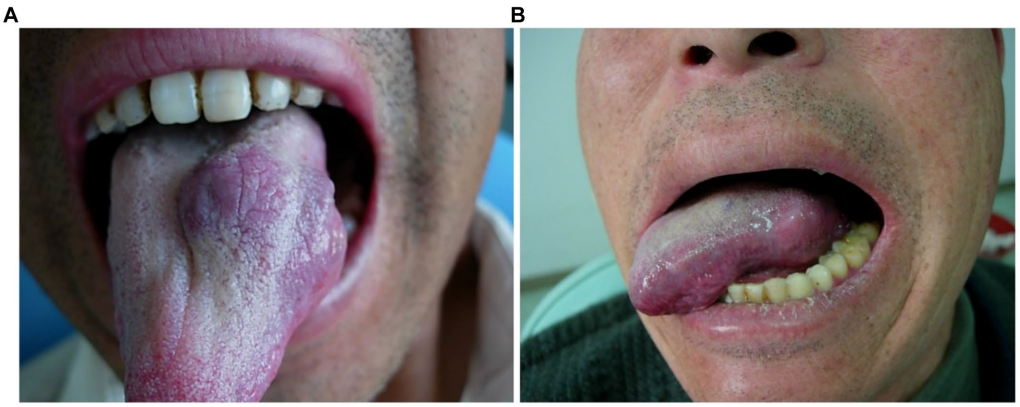

FIGURE 1
Morphological changes of venous malformation of the tongue in case 1 before and after the treatment. **(A)** Preoperative morphology of venous malformation of the left lingual margin and lingual body. **(B)** Postoperative morphology of the left lingual margin and lingual body 3 months after ECT with PYM injection.

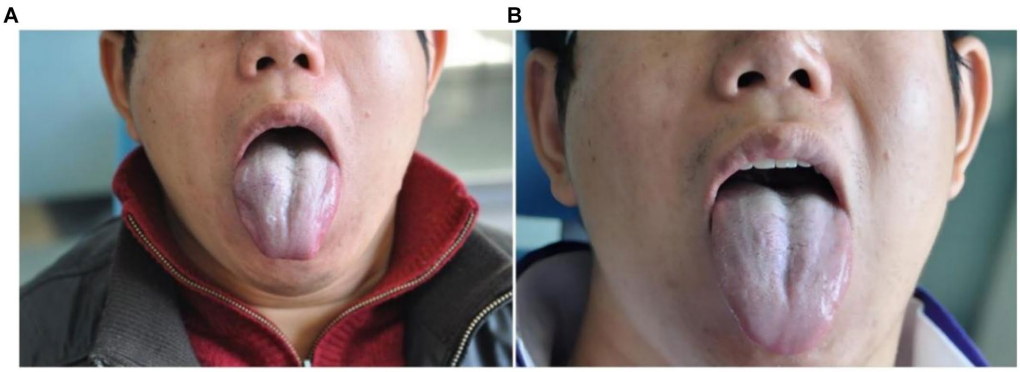

FIGURE 2
Morphological changes of venous malformation of the right lingual margin and lingual body in case 2 before and after the treatment. **(A)** Preoperative morphology of venous malformation of the right lingual margin and lingual body. **(B)** Postoperative morphology of the right lingual margin and lingual body 3 months after ECT with PYM injection.

Case 5: The patient was a 38-year-old female. The multiple venous malformations of the right lingual margin and lingual body lasted for more than 3 years, and the progressive enlargement of the lesions affected eating and speech. The multiple venous malformations of the right lingual margin and lingual body might occasionally cause bleeding. The multiple lesions of the right lingual margin and lingual body did not recover after 5 s compression, which were the low-return flow venous malformations. After ECT combined with PYM injection, the lesions were significantly reduced 3 months after the treatment, and completely cured. The pictures of the lesions before and after the treatment were shown in Figure 5.

Case 6: The patient was a 26-year-old female. The venous malformation of the right lingual abdominal lasted for more than 5 years, and the progressive enlargement of the lesion affected eating and speech. The lesion of the right lingual abdominal recovered after 5 s compression, which was a high-return flow venous malformation. After ECT combined with PYM injection, the lesion was significantly reduced 3 months after the treatment, and completely cured. The pictures of the lesion before and after the treatment were shown in Figure 6.

Case 7: The patient was a 23-year-old female. The venous malformation of the right lingual margin lasted for more than 2 years, and the progressive enlargement of the lesion affected eating and speech. The lesion of the right lingual margin did not recover after 5 s compression, which was a low-return flow venous malformation. After local injection of pingyangmycin alone, the lesion was significantly reduced 2 months after the treatment, and completely cured. The pictures of the lesion before and after the treatment were shown in Figure 7.

Discussion

Based on the cell biological characteristics of vascular diseases, Mulliken and Glowacki proposed in 1982 to clearly divide them into two categories: hemangioma and vascular malformation, which has been widely accepted by the scholars around the world. Hemangioma

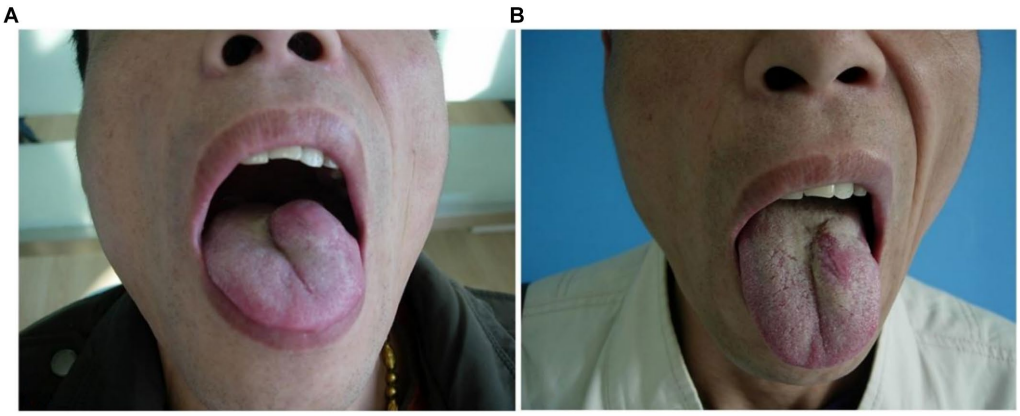

FIGURE 3
Morphological changes of venous malformation of the left lingual margin and lingual body in case 3 before and after the treatment. **(A)** Preoperative morphology of venous malformation of the left lingual margin and lingual body. **(B)** Postoperative morphology of the left lingual margin and lingual body 3 months after ECT with PYM injection.

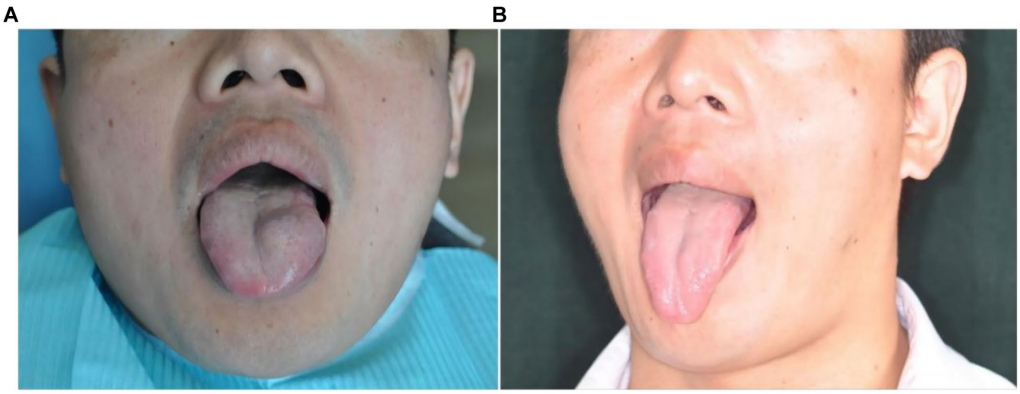

FIGURE 4
Morphological changes of venous malformation of the left lingual margin and lingual body in case 4 before and after the treatment. **(A)** Preoperative morphology of venous malformation of the left lingual margin and lingual body. **(B)** Postoperative morphology of the left lingual margin and lingual body 3 months after ECT with PYM injection.

and vascular malformation were two kinds of lesions with different biological characteristics, and there were some essential differences between them in pathology: (1) Hemangioma had the characteristics of the proliferation of vascular endothelial cell. It was a kind of true tumor, and it grew rapidly after birth. The main pathological change of proliferative hemangioma was the proliferation of endothelial cell, which resulted in narrowed vascular lumen. And the endothelial cells on the surface of the lumen were wrinkled and not smooth. (2) Vascular malformations were congenital developmental abnormalities that consist of enlarged dysplastic blood vessels. Vascular malformations did not have the characteristics of the proliferation of vascular endothelial cell. The vascular endothelium and lining of vascular malformations did not have the proliferative tendency. And they did not belong to true tumors. Vascular malformations had the characteristics of thick lumen diameter, smooth lumen wall and rapid blood flow (7). Venous malformation was the most common vascular malformation in oral and maxillofacial region (8). According to the imaging characteristics of the returning veins, venous malformations could be divided into high-return flow and low-return flow types (9, 10). Venous malformations were the most common type of vascular malformations in the tongue (3). Tongue venous malformations might not be detected at birth and grew slowly with age. When combined with infection or external stimulation, the lesions could appear pain, obvious enlargement, swelling, bleeding and other symptoms. If large tongue venous malformations developed to affect eating, speech and breathing, they should be treated as soon as possible.

In the past, the treatment methods for tongue venous malformations included laser, surgical resection, sclerotherapy and interventional embolization, but the above treatment methods had limited indications and unsatisfactory therapeutic effect. Laser was only suitable for superficial mucosa and small venous malformations, but it had poor therapeutic effect on deep and extensive venous malformations (11, 12). Surgical resection was suitable for localized lesions. Invasive lesions required a wide range of resection, which could lead to loss of tongue function, lingual nerve damage, or massive bleeding (13, 14). Interventional embolization therapy was usually used as a palliative and

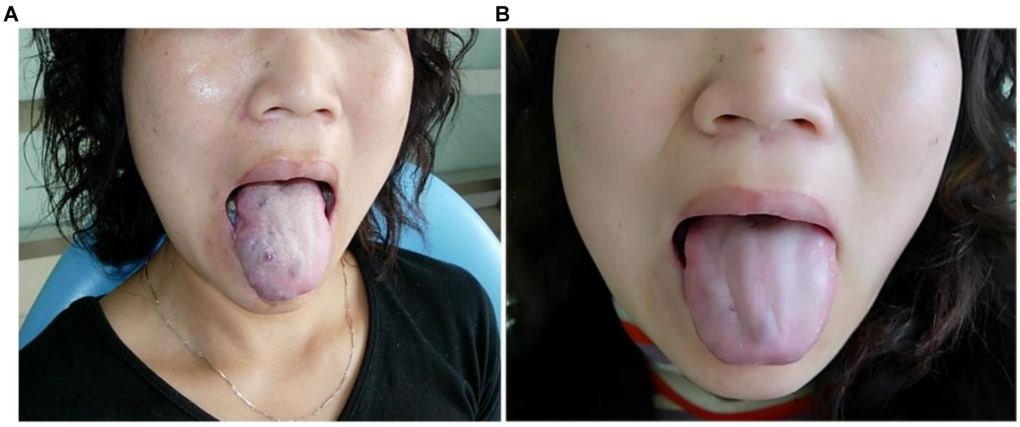

FIGURE 5
Morphological changes of the multiple venous malformations of the right lingual margin and lingual body in case 5 before and after the treatment. **(A)** Preoperative morphology of the multiple venous malformations of the right lingual margin and lingual body. **(B)** Postoperative morphology of the right lingual margin and lingual body 3 months after ECT with PYM injection.

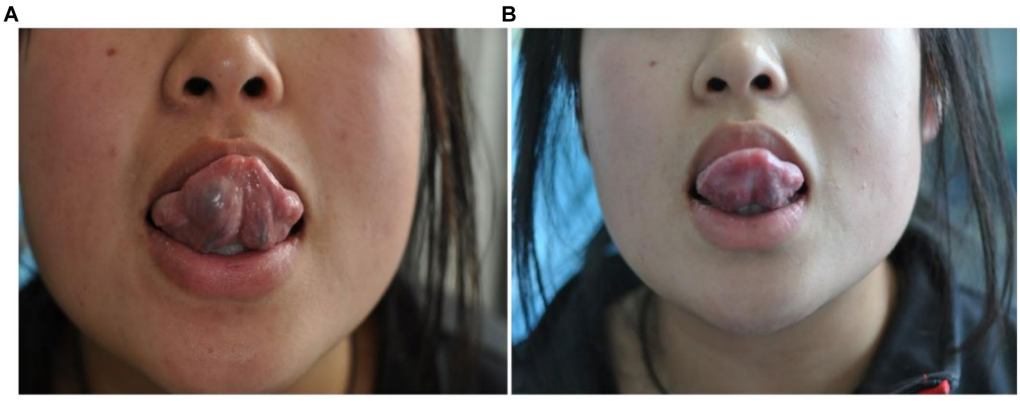

FIGURE 6
Morphological changes of the venous malformation of the right lingual abdominal in case 6 before and after the treatment. **(A)** Preoperative morphology of the venous malformation of the right lingual abdominal. **(B)** Postoperative morphology of the right lingual abdominal 3 months after ECT with PYM injection.

preoperative treatment, and its complications were more severe, including ischemic necrosis of the tissue, persistent severe pain, loss of vital organ function, and even death from heart and lung failure (15).

Electrochemical therapy was established on the basis of the biological closed electric circuits (BCEC) proposed by the Swedish scholar Nordenstrom (16). The mechanism of electrochemical therapy of vascular malformations included: (1) The direct current electrode was directly inserted into the platinum needle in the diseased cavity, and a certain intensity of bioelectric field was formed in the diseased cavity after being energized, which could result in electrolyte disturbance, acid–base imbalance, and local electrochemical and electrophysiological changes. The negatively charged Cl^- ions released by electrolyte NaCl and H_2O after electrolysis moved to the positive electrode region, which made the pH of the positive electrode region drop to 1–2 (showing strong acidity). The positively charged Na + electrolysed moved to the needle area of the negative electrode, and bonded with OH^- ion to form strongly alkaline NaOH, which increased the pH of the negative electrode region to 12–13, presenting a strong alkaline state. Red blood cells and platelets in the vascular tissues were seriously damaged and hemagglutinins were released. Then the lesions showed solid changes. (2) Direct current enhanced the permeability of the cell membrane, which caused the ions to move and diffuse in the electric field and produced oxygen and chlorine. The oxygen and chlorine directly killed the diseased cells; (3) Direct current changed the internal and external environment of the cells, destroyed the activity of cell enzymes, and led to the denaturation of the protein; (4) By the electrolysis, spot osmosis, electrophoresis and other functions, the distribution of intercellular ions concentration were changed. There were tissue dehydration and contraction of large blood vessels and capillaries in the positive electrode region. And there was extensive formation of microvascular thrombosis in the positive electrode region. While in the negative electrode region, there were interstitial edema, a large amount of accumulated fluid, compressed capillaries, and obstructed tissue blood flow. (5) According to the literature report, the volume of endothelial cells was significantly reduced and the vascular lumen was blocked at the beginning of electrochemical therapy. After the electrochemical

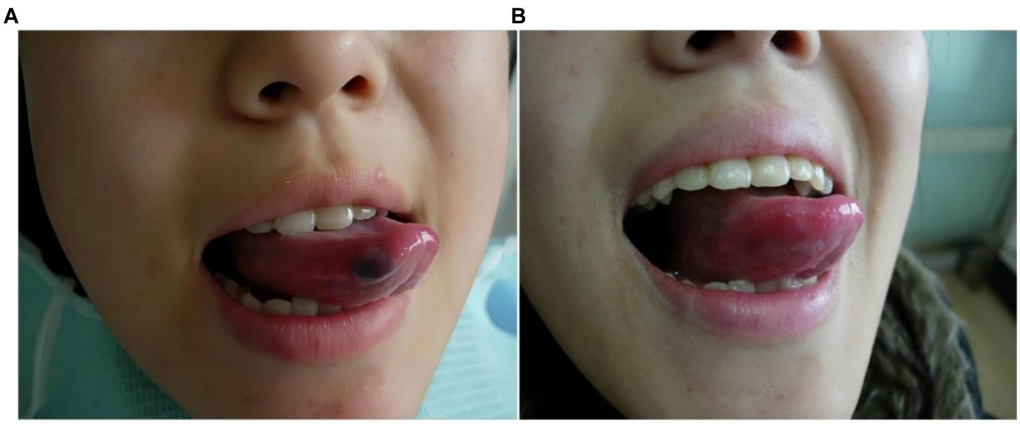

FIGURE 7
Morphological changes of the venous malformation of the right lingual margin in case 7 before and after the treatment. **(A)** Preoperative morphology of the venous malformation of the right lingual margin. **(B)** Postoperative morphology of the right lingual margin 2 months after local injection of PYM alone.

therapy, the structure of the lesion disappeared completely and the endothelial nucleus was dissolved and destroyed. The lesion became a uniform denatured-necrotic tissue. (6) Other studies had shown that electrochemical therapy could induce cell apoptosis, promote the necrosis of tumor, and inhibit the growth of tumor (17–19).

At present, the most used method for venous malformations is the sclerosing agent pingyangmycin, applied as local injection sclerotherapy (11). Pingyangmycin has a chemical structure similar to bleomycin A5, and because of its safety, convenience and effective characteristics, intralesion injection of pingyangmycin has been widely used in the treatment of oral and maxillofacial-head and neck venous malformations (20). Studies have shown that the main mechanisms of pingyangmycin in the treatment of venous malformations were as follows: pingyangmycin played its therapeutic effect by binding to DNA of vascular endothelial cells, which caused DNA strand breakage of vascular endothelial cells and inhibited the metabolism of vascular endothelial cells. This could result in the atrophy and degeneration of vascular endothelial cells and the specific damage to vascular endothelial cells and the vascular wall. It could also induce the proliferation of vascular smooth muscle cells and endothelial cells and thicken the vascular wall, which could narrow and eventually block the vascular lumen. Some studies have also found that pingyangmycin can destroy the vascular endothelial cells and promote the expression of adhesion molecules on the surface of endothelial cells, or release a variety of growth factors. Pingyangmycin can also promote inflammatory cell adhesion, infiltration, and inflammatory chemotaxis, and lead to the release of inflammatory factors and tissue fibrosis factors. This can promote the fibrosis of the tissue and eventually lead to the occlusion of vascular lumen (21, 22).

However, pingyangmycin was a kind of mild sclerosing agent. Due to its short retention time and limited action time in the lesion cavity, local injection of pingyangmycin alone was generally ineffective in the treatment of venous malformations with the high-return flow lesions, and other auxiliary measures or even multiple injections were needed for the deep and extensive venous malformations. In our study, we found that local injection of pingyangmycin alone had excellent therapeutic effect for the superficial mucosal or the localized venous malformations and local injection of pingyangmycin alone could also have very good effect for the low-return flow venous malformations. However, local injection of pingyangmycin alone had very poor therapeutic effect for the large, deep and extensive venous malformations or the high-return flow lesions. 8 patients with high-return flow venous malformations in the group B had poor therapeutic effect by the method of local injection of pingyangmycin alone in our study. The results of our study showed that the effective rate of local injection of pingyangmycin alone was 73%, while that of electrochemical therapy combined with local injection of pingyangmycin was 97%, and the difference between the two groups was statistically significant ($p < 0.05$). 15 patients with high-return flow venous malformations in the group A had very good therapeutic effect by the method of electrochemical therapy combined with local injection of pingyangmycin. On the one hand, electrochemical therapy led to the swelling, degeneration and destruction of vascular endothelial cells in the lesion. It could also increase the permeability of cell membrane and make widespread thrombosis in the lesion. On the other hand, pingyangmycin stayed in the lesion cavity for a long retention time along with electrochemical therapy. The concentration of pingyangmycin in the lesion cavity increased and accelerated the destruction of vascular endothelial cells. While pingyangmycin was playing its therapeutic effect in the lesion, pingyangmycin also aggravated the chemical killing effect of direct current of electrochemical therapy, destroyed the pathological structure more thoroughly, promoted the coagulation in the lesion cavity, and led to the complete disappearance of blood flow. Finally the sclerosed vascular tissue was absorbed, so as to achieve the excellent therapeutic effect.

The common adverse reactions of pingyangmycin injection in the treatment of venous malformations are usually mild, and include swelling and pain, fever, skin reaction (local itching), gastrointestinal reaction, and local ulceration and necrosis, while anaphylactic shock, pulmonary fibrosis, and leucopenia are rare (23, 24). To reduce the occurrence of adverse reactions, we added lidocaine to the solution to reduce swelling and pain, and meanwhile lidocaine could also reduce the occurrence of anaphylactic reaction. Postoperative glucocorticoid therapy could reduce the swelling response. In our treatment, the swelling response usually went away in about 1 week. When the temperature of the patients with fever was higher than 38.5°C, the symptoms were improved after taking antipyretic drugs. The biggest

concern of pingyangmycin injection treatment for a long time was its pulmonary toxicity, which was closely related to the injection dose (24). Generally, the total dose used for the treatment of vascular malformations was not more than 160 mg, and the dosage of pingyangmycin in our study was far less than 160 mg, so there was no toxicity to the lung. The patients did not develop pulmonary fibrosis in our study. The adverse reactions of electrochemical therapy in the treatment of vascular malformations were rare, and some adverse reactions might occur clinically which included postoperative swelling, fever (<38°C), bleeding, infection, and nerve damage at the lesion site. The above adverse reactions could be restored to normal after symptomatic treatment.

Based on our treatment experience for venous malformation of tongue by electrochemical therapy combined with local injection of pingyangmycin, the following conclusions were drawn: (1) Electrochemical therapy of tongue venous malformation needed to be performed by the trained professional surgeons to ensure the safety of the patients. It was important to have a complete history and thorough examination before performing any surgery. (2) According to our experience, for the lesions in the posterior 1/3 of the tongue, the use of electrochemical therapy under general anesthesia was better and safer. The lesions could be fully exposed, and the treatment was more accurate. (3) The needles in parallel with the positive and negative electrode were inserted evenly at intervals, and the distance between the electric needles was 1.5 cm. (4) The relationship between the lesion and the peripheral nerve should be clearly determined, and the peripheral nerve should be avoided when inserting the electric needles. (5) The surgeon should properly place the insulated cannulas with the platinum electrode needles, slowly increase the current and voltage during the treatment and reasonably set the total amount of electricity required for the treatment to avoid the skin burns. (6) In the course of the treatment, sterile gauze were used to evenly squeeze the diseased tissue. The surgeon tried to drain the blood and gas in the lesion, make the lesion cavity smaller and restore the shape and flatness of normal tissue as far as possible. (7) The treatment time of electrochemical therapy was mainly determined by the size of the lesions. Generally, when the surface skin color of the lesion turned white or the lesion became slightly hard, and when there was brownish black viscous liquid flowing out of the cannulas of the platinum electrode needles, it can be regarded as an indication of electrochemical therapy cessation. (8) The needle holes after the removal of the electric needles should be properly treated, such as gauze compression of the needle holes or non-invasive suture ligation to avoid secondary bleeding. (9) The size of the lesions and the age of the patients determined the concentration and the injection times of pingyangmycin. For tongue venous malformation, the usual injection concentration for adults was 1.6 mg/mL. The injection concentration for children was 1.0 mg/mL. If the lesion involved a large area or had a huge volume, a multi-point injection or multiple regional injection was given. In our study, small lesions were cured by only one injection, and larger lesions were injected between three and five times.

In conclusion, electrochemical therapy combined with local injection of pingyangmycin for the treatment of tongue venous malformation had the advantages of minimally invasive treatment, few postoperative adverse reactions, and significant clinical efficacy, which was easy to be accepted by the patients. This method is safe and effective for all kinds of tongue venous malformations. It is the first choice of treatment especially for the high-return flow venous malformations in the tongue. The treatment modality is worthy of further promotion in clinic. However, this study has several limitations, including the small sample size and the retrospective design. In the future, additional prospective randomized studies with the large sample size are necessary to confirm the efficacy and safety of electrochemical therapy combined with local injection of pingyangmycin for the treatment of tongue venous malformation.

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 humans were approved by the medical ethics committee of School and Hospital of Stomatology, China Medical University. The studies were conducted in accordance with the local legislation and institutional requirements. Written informed consent for participation in this study was provided by the participants' legal guardians/next of kin. Written informed consent was obtained from the individual(s), and minor(s)' legal guardian/next of kin, for the publication of any potentially identifiable images or data included in this article.

Author contributions

WY: Writing – original draft, Writing – review & editing. XW: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Resources, Supervision, Validation, Visualization, Writing – review & editing.

Funding

The author(s) declare that no financial support was received for the research, authorship, and/or publication of this article.

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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frontiers | Frontiers in Cardiovascular Medicine

TYPE Original Research
PUBLISHED 03 September 2024
DOI 10.3389/fcvm.2024.1449480

OPEN ACCESS

EDITED BY
Pasqualino Sirignano,
Sapienza University of Rome, Italy

REVIEWED BY
Marcello Andrea Tipaldi,
Sapienza University of Rome, Italy
Gianluca Faggioli,
University of Bologna, Italy
Gemmi Sufali
University of Bologna, Italy, in collaboration with GF

*CORRESPONDENCE
Xindong Fan
✉ fanxindong@aliyun.com
Xitao Yang
✉ xitao123456@126.com

†These authors have contributed equally to this work

RECEIVED 15 June 2024
ACCEPTED 20 August 2024
PUBLISHED 03 September 2024

CITATION
Shen Y, Han Q, Wang D, Su L, Wen M, Fan X and Yang X (2024) Coil-assisted ethanol embolization of traumatic arteriovenous fistulas: a 10-year retrospective study. Front. Cardiovasc. Med. 11:1449480. doi: 10.3389/fcvm.2024.1449480

Coil-assisted ethanol embolization of traumatic arteriovenous fistulas: a 10-year retrospective study

Yuchen Shen†, Qianyun Han†, Deming Wang†, Lixin Su†, Mingzhe Wen, Xindong Fan* and Xitao Yang*

Vascular Anomaly Center, Department of Interventional Therapy, Shanghai Ninth People's Hospital, Shanghai Jiao Tong University School of Medicine, Shanghai, China

Purpose: This study aimed to evaluate the efficacy and safety of ethanol embolization in treating traumatic arteriovenous fistulas (TAVFs).
Materials and methods: From March 2012 to April 2020, 42 consecutive patients (29.9 ± 15.1 years, range: 3–68 years) with peripheral TAVFs underwent ethanol embolization. All patients underwent clinical and imaging follow-ups (40.0 ± 25.9 months, range: 3–90 months). The mean time to onset of symptoms after trauma was 5.4 ± 5.9 months (range: 0.5–30 months). Among the patients, 27 (64.3%) reported that the TAVFs occurred after blunt trauma, 10 (23.8%) presented after penetrating trauma (with 4 patients involving penetration by infusion indwelling needles), and 3 (7.1%) had a history of surgery. Treatment effects, devascularization rates, and complications were evaluated at follow-ups conducted at 1–3 month intervals.
Results: Seventy-one embolization procedures were performed, with a mean of 1.6 ± 0.7 procedures per patient. Thirty-four patients received coil-assisted ethanol embolization. Absolute ethanol was used in all procedures, with an average volume of 7.1 ± 4.2 ml per procedure (range: 1–18 ml); 28 patients (28/42, 66.7%) received coil embolization in 36 procedures (36/71, 50.7%). Upon re-examination, 39 patients (92.9%) achieved 100% devascularization; of these, 29 patients (74.4%) with Schobinger stage II TAVFs improved to stage I or became asymptomatic. Overall, 30 cases (66.7%) achieved a complete response, while the other 12 cases (33.3%) showed a partial response. In addition, no major complications were observed postoperatively, apart from minor complications.
Conclusions: Coil-assisted ethanol embolization can effectively manage TAVFs with an acceptable risk of mild complications.

KEYWORDS
arteriovenous fistula, trauma, embolization, ethanol, coil

Introduction

Arteriovenous fistulas (AVFs) are abnormal channels between adjacent arteries and veins. Traumatic arteriovenous fistulas (TAVFs) refer to AVFs caused by trauma (1). The most common cause of TAVFs is penetrating injuries from sharp instruments (2). With the widespread development of various new percutaneous vascular puncture techniques, medically induced injuries are becoming a more common cause (3).

Patients with TAVFs tend to have a history of trauma (4). Due to prolonged abnormal arteriovenous communication, local and distal hemodynamic disorders and disturbances occur in the lesion, leading to local tissue compression, hyperplasia, massive opening of the collateral circulation, and expansion of the bruit circulation. TAVFs are almost impossible to self-heal. To date, various treatment options for TAVFs have been introduced, including surgical resection, ligation of feeding arteries, and interventional therapies (5–7). Inadequate surgical resection or ligation of only the supply artery, which ultimately reconstructs the flow pattern of the TAVFs due to induced preferential dilatation of collateral vessels, makes the treatment ineffective (8). Developments in interventional radiology have revolutionized previous treatment methods and have produced satisfactory results in the treatment of congenital arteriovenous malformations (AVMs). Coil-assisted ethanol embolization has demonstrated better long-term clinical and radiological results with an acceptable risk of morbidity compared to mechanical embolization alone (granular material, n-butyl cyanoacrylate, Onyx). It has evolved as the primary modality for managing congenital AVMs (9, 10). However, the suitability of the technique for TAVFs still needs to be explored. The purpose of the present study was to retrospectively assess the safety and effectiveness of ethanol embolization in the treatment of TAVFs.

Materials and methods

This study received approval from the Institutional Review Board of Shanghai Ninth People's Hospital, Shanghai Jiao Tong University School of Medicine. Informed consent was obtained from all patients who participated in the study. The flow diagram is shown in Figure 1.

Patients

A retrospective review of medical records, photographs, and radiological imaging results of 42 consecutive patients who underwent ethanol embolization between March 2012 and April 2020 was performed. Forty-two patients were included, comprising 19 ales and 23 females, with a mean age of 29.9 ± 15.1 years (range: 3–68 years). The mean time to morbidity after trauma was 5.4 ± 5.9 months (range: 0.5–30 months). Of the 42 patients, 23 (54.8%) had previously undergone unsuccessful treatments, such as incomplete surgical resection, transarterial embolization, and sclerotherapy, at other hospitals (Table 1).

Of the 42 patients, 27 (64.3%) reported that the TAVFs developed after blunt trauma, 10 (23.8%) presented after penetrating trauma (with 4 patients experiencing penetration with infusion indwelling needles), 3 (7.1%) had a history of surgery, and 2 (4.8%) caused by repeated dislocation of the temporomandibular joint. All outpatients were initially diagnosed based on clinical manifestations, followed by a color duplex ultrasound to evaluate the hemodynamic characteristics of vascular lesions. Preoperative contrast-enhanced computed tomography (CT) was used to make a definite diagnosis and assess the anatomical features of TAVFs in detail.

The indications for treatment include the presence of subjective clinical symptoms that make daily life uncomfortable (e.g., swelling, troublesome tinnitus, pulses), complications (e.g., secondary varicose veins), and progressive enlargement over time. The clinicians recorded the patients' sex, age, lesion location, previous treatments, clinical findings, and Schobinger stage (11).

Angiographic and embolization techniques

According to previous reports, ethanol embolization was initiated under general anesthesia to control pain (12). Briefly, baseline angiograms were obtained using the femoral artery approach to assess the extent and hemodynamic characteristics of TAVFs and to determine whether transarterial or direct puncture access would be used (Figures 2A,B).

A dominant outflowing vein (DOV) of TAVF is defined as the dilated vein originating from the nidus with the maximum and fastest flow (13). If angiography identified the DOV (Figure 2C), we penetrated directly with an 18-G puncture needle. A 2.1-F microcatheter (Asahi, Seto, Japan) was then inserted into the DOV, and venography was used to confirm the correct location of the microcatheter. Next, the three-dimensional mechanically detachable coils (Micro Therapeutics, Irvine, CA, USA) and synthetic fiber-attached stainless steel coils (Cook Medical, Bloomington, IN) were delivered via the microcatheters until repeat venography represented decreased blood flow (Figures 2D,E). For patients without a significant DOV, coils were placed in the nidus.

Absolute ethanol was injected at a dose of 0.1 ml/kg body weight per injection, with a maximum of 1 ml/kg body weight per procedure. An angiogram was performed 5–10 min after each ethanol injection to determine whether the AVFs were effectively embolized. If the nidus was still noted on angiography, repeated ethanol injections were required (Figure 2F).

Postoperative management

Management after ethanol embolization included intravenous infusion of fluids and dexamethasone. The dose of intravenous dexamethasone (0.1 mg/kg every 8 h for the first 3 days) was gradually reduced over 7 days after ethanol embolization to reduce swelling. If hemoglobinuria was observed postoperatively, hydration was provided with intravenous lactated Ringer's solution (2,000 ml or 30 ml/kg for children weighing <60 kg). Ranitidine (Zantac; Sanofi, Hangzhou, China) was administered to prevent gastric or duodenal ulceration.

Follow-up modality

Patients were followed up at regular intervals of 1–3 months after the initial treatment with physical examinations. The color duplex ultrasound or contrast-enhanced CT was performed for

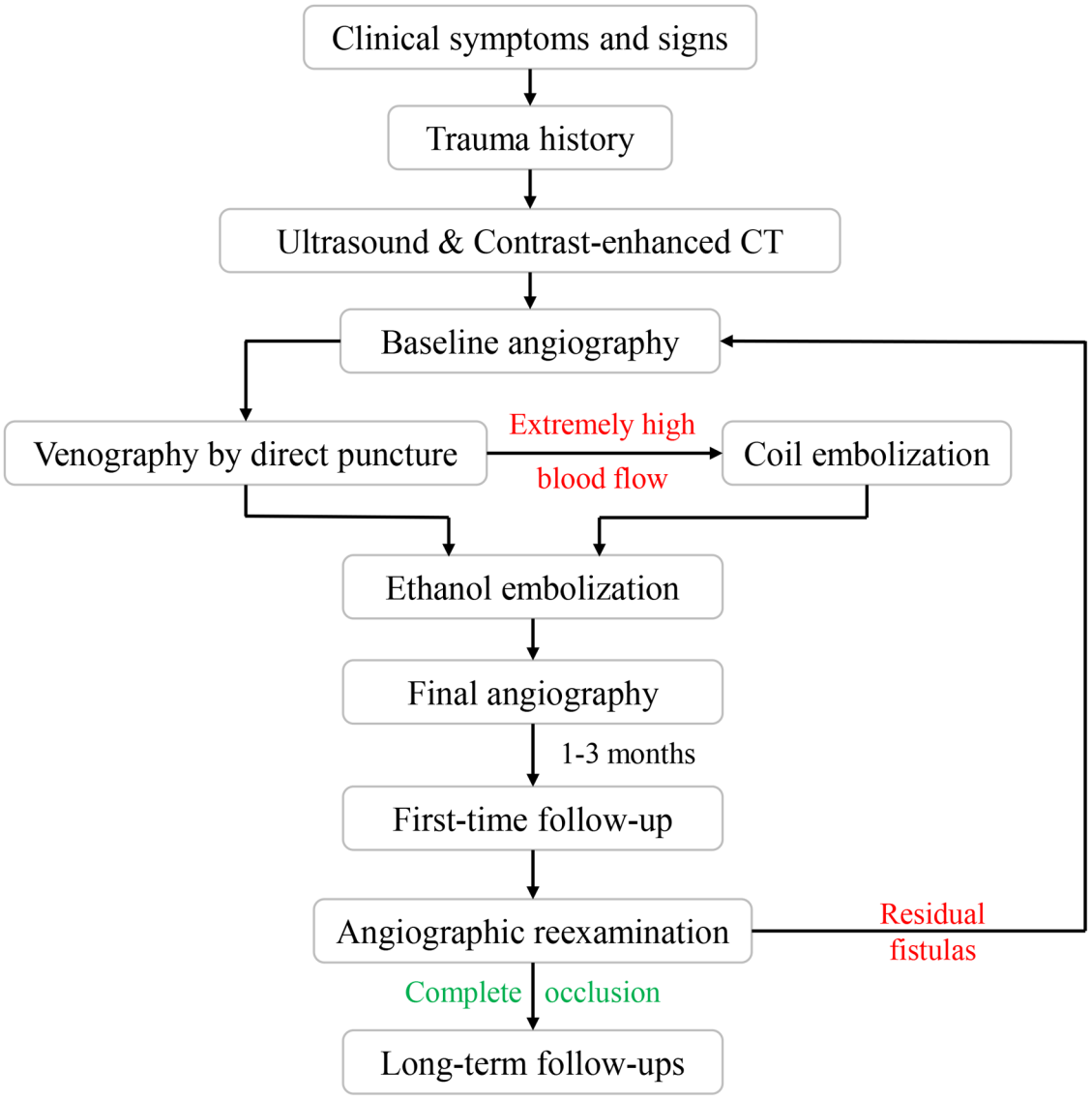

FIGURE 1
Flow diagram for ethanol embolization of traumatic arteriovenous fistulas.

outpatients. Angiographic re-examination was regularly carried out during the patient's first follow-up. Angiography was also recommended if the clinical outcomes of symptoms and signs of the patients improved or worsened during long-term follow-ups (Figures 2E,F). Additional embolotherapy was required if residual fistulas were detected on angiography.

Evaluation of clinical outcomes

The devascularization of the TAVFs was evaluated by comparing preoperative and re-examined angiography results. Two independent radiologists assessed the degree of devascularization, classifying it into four levels: 100%, 76%–99%, 50%–75%, and <50% (Figures 3, 4). Therapeutic outcomes were classified into complete response (complete resolution of symptoms with 100% devascularization of the AVFs), partial response (improvement of clinical symptoms with 50%–99% devascularization of the AVFs), no response (no change in clinical symptoms or signs with <50% devascularization of the AVFs), and worsening (deterioration of clinical symptoms regardless of the devascularization of the AVFs). Complete and partial responses were judged to have practical therapeutic benefits.

The detected complications, classified as minor or major, related to the embolization procedure were analyzed. Minor complications included non-permanent adverse sequelae, such as transient nerve injury or spontaneously healed skin necrosis. Major complications included permanent adverse sequelae or death, all of which need medical intervention.

All data are reported as the mean and standard deviation (SD).

TABLE 1 Clinical data and outcomes of ethanol embolization in treating patients with traumatic arteriovenous fistulas.

Patient No./sex/age (years)	Location	Etiology	Time of onset after trauma (months)	No. of procedures	Embolic material (No.)	Ethanol use per session (ml)	Devascularization rate (%)	Therapeutic outcome	Complications (No.)	Follow-up time (months)
1/F/57	Left maxillofacial region	Stab wound	4	1	E (1), C (1)	5	100	CR	No	6
2/M/56	Left pterygopalatine fossa infratemporal fossa	Stab wound (sharp instrument)	30	3	E (3), C (2)	10, 5, 2	100	CR	No	69
3/M/11	Forehead, left orbital periorbital	Impact injury	4	3	E (3), C (3)	8, 6, 3	100	PR	No	24
4/F/14	Right forehead and the root of the nose	Impact injury	9	1	E (1)	6	100	CR	No	6
5/F/17	Left foot	Impact injury (external objects)	10	3	E (3), C (2)	9, 5, 4	100	CR	No	16
6/F/31	Right eyebrow arch	Impact injury (external objects)	2	2	E (2), C (1)	8, 3	100	CR	No	16
7/M/28	Left upper eyelid and periorbital region	Impact injury	2	1	E (1)	2.5	100	CR	No	26
8/F/30	Right forehead scalp	Impact injury	10	1	E (1)	10	100	CR	No	26
9/M/25	Left eyebrow arch	Impact injury (external objects)	1	2	E (2)	6, 1	76–99	PR	No	22
10/M/25	Left chest and back	Impact injury (fall)	6	3	E (3), C (2)	16, 10, 4	100	PR	No	13
11/F/21	Right calf	Impact injury (heavy object)	6	2	E (2), C (2)	15, 8	100	CR	No	9
12/F/21	Upper lip	Impact injury (external objects)	14	2	E (2)	6, 6	100	PR	Blister	5
13/M/33	Left temporal scalp	Impact injury (heavy object)	10	1	E (1), C (1)	18	100	PR	No	6
14/F/44	Right thigh	Stab wound	2	1	E (1)	6	100	CR	No	6
15/M/17	Left fifth thoracic pedicle, left sixth rib	Surgery	4	2	E (2), C (2)	5, 3	50–75	PR	No	3
16/F/50	Right temporomandibular joint area	repeated dislocation of the temporomandibular joint	5	1	E (1), C (1)	4.5	100	CR	No	26
17/M/26	Occipital scalp	Impact injury (stick)	5.5	3	E (3), C (1)	10, 6, 3	100	PR	No	56
18/M/68	Right thigh	Stab wound	3.3	1	E (1), C (1)	8	100	CR	No	90
19/F/68	Left forehead scalp	Impact injury (fall)	1.8	2	E (2), C (1)	10, 4	100	PR	No	43;
20/M/30	Occipital scalp	Impact injury (fall)	2	1	E (1)	8	100	CR	No	84
21/M/35	Frontoparietal scalp	Impact injury (stick)	19	1	E (1)	8	100	PR	No	84
22/M/42	Preauricular region of the left ear	Impact injury (sharp instrument)	2.5	1	E (1), C (1)	15	100	CR	No	38
23/M/30	Preauricular region of the left ear	Impact injury (sharp instrument)	1.8	2	E (2), C (1)	11, 3	100	PR	No	61
24/M/16	Lower lip	Impact injury (fall)	8	2	E (2)	6, 2	100	PR	Blister	61
25/M/31	Left temporomandibular joint area	Repeated dislocation of the mandible	3	2	E (2), C (1)	15, 6	100	CR	No	72

(*Continued*)

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TABLE 1 Continued

Patient No./sex/age (years)	Location	Etiology	Time of onset after trauma (months)	No. of procedures	Embolic material (No.)	Ethanol use per session (ml)	Devascularization rate (%)	Therapeutic outcome	Complications (No.)	Follow-up time (months)
26/M/42	Interbrow region	Impact injury (fall)	2	1	E (1), C (1)	8	100	CR	No	24
27/F/41	Left temporal scalp	Impact injury (foreign object)	20	1	E (1), C (1)	8	100	CR	No	42
28/M/23	Right temporal scalp	Stab wound	1	1	E (1), C (1)	1	100	CR	No	80
29/M/38	Left temporal scalp	Impact injury (foreign object)	3	2	E (2), C (1)	13, 6	100	CR	No	53
30/M/22	Right forehead scalp	Impact injury (foreign object)	1	3	E (3),	14, 8, 6	100	CR	No	49
31/M/18	Right forehead scalp	Impact injury (wooden stick)	0.5	2	E (2)	8, 3	100	CR	No	79
32/M/6	Left frontal scalp	Puncture wound with infusion indwelling needle	3	1	E (1)	5	100	CR	No	50
33/M/28	Right temporal and frontal regions	Impact injury (foreign object)	2.5	2	E (2), C (1)	14, 8	100	CR	No	40
34/M/24	Right temporal and frontal regions	Impact injury (foreign object)	2	1	E (1), C (1)	7	100	CR	No	76
35/M/25	Left temporal and frontal regions	Impact injury (foreign object)	8.5	2	E (2), C (1)	8, 4	100	CR	No	80
36/M/50	Left temporal and parietal scalp	Impact injury (foreign object)	6	1	E (1)	10	100	CR	No	35
37/M/6	Right forearm	Puncture wound with infusion indwelling needle	4	1	E (1), C(1)	1	100	CR	No	20
38/M/3	Right forehead scalp	Puncture wound with an infusion indwelling needle	1.5	1	E (1), C (1)	2	100	CR	No	20
39/M/25	Left forearm	Puncture wound with an infusion indwelling needle	2	1	E (1), C (1)	1.5	100	CR	No	40
40/F/21	Left maxillofacial region	Surgery (jaw orthodontic surgery)	2	1	E (2), C (1)	13, 7	100	CR	No	35
41/M/33	Right maxillofacial region	Surgery (resection of benign tumor)	2.5	3	E (3), C (2)	18, 13, 7	100	CR	No	48
42/F/25	Left hand	Stab wound (sharp instrument)	1	1	E (2)	3. 1.5	76–99	PR	No	40

C, coil; CR, complete response; E, ethanol; NR, no response; PR, partial response.

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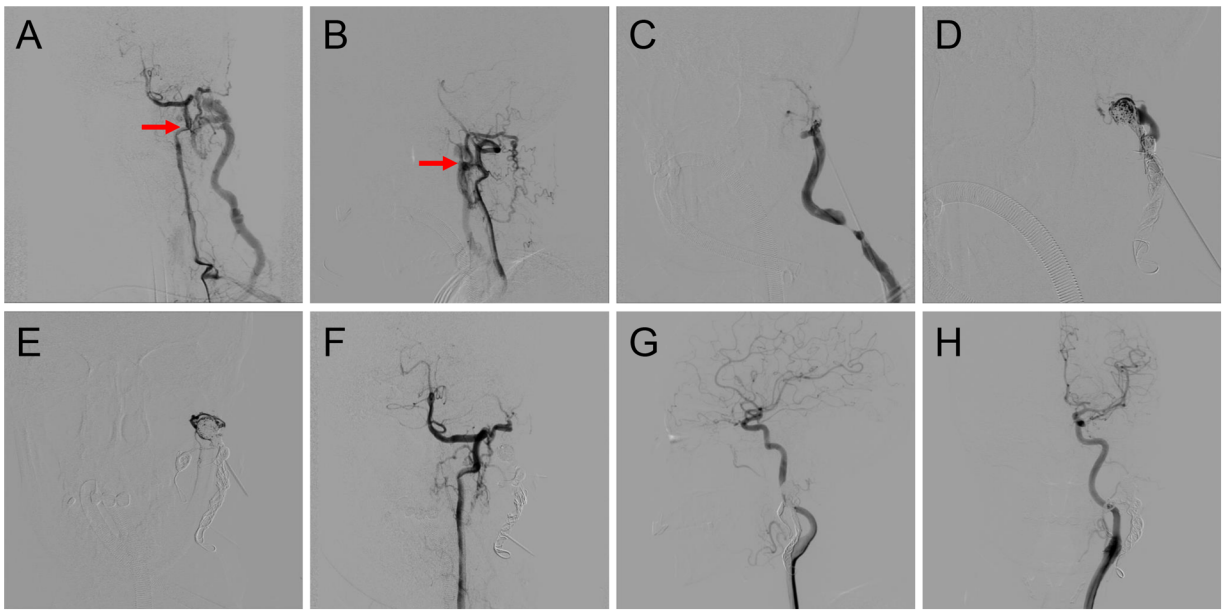

FIGURE 2
Procedure of coil-assisted ethanol embolization of traumatic arteriovenous fistulas. (A,B) Anteroposterior and lateral views of baseline angiography. (C) Direct puncture of the nidus. (D) Configuration of coils. (E) Angiography indicating the reduction of blood flow. (F) Final angiography after ethanol injection showing 100% devascularization. (G,H) Anteroposterior and lateral views of angiography 1.5 years postoperatively. Red arrows: arteriovenous shunts.

Results

Baseline data of patients with traumatic arteriovenous fistulas

The locations of TAVFs of the present cohort were as follows: head and neck (33/42, 78.6%), lower extremities (4/42, 9.5%), upper extremities (3/42, 7.1%), and trunk (2/42, 4.8%) (Table 1). Patients' clinical manifestations included pulsatile mass (41/42; 97.6%), secondary vasodilation (40/42; 95.2%), trill (28/42, 66.7%), elevated skin temperature (20/42, 47.6%), persistent tinnitus (7/42; 16.7%), pain (3/42; 38.1%), and limb ulceration (2/42; 4.8%). According to the Schobinger classification, 39 out of 42 patients (92.9%) were classified as Schobinger stage II, whereas 3 patients (7.1%) were classified as Schobinger stage III (Table 2).

Embolization modality of patients with traumatic arteriovenous fistulas

In total, 71 embolization procedures were conducted, with a mean of 1.6 ± 0.7 procedures per patient. Among the 42 patients, 20 (47.6%) underwent a single embolization session, 15 (35.7%) underwent two sessions, and 7 (26.7%) underwent three sessions. Notably, 28 patients (28/42, 66.7%) had extremely high-blood flow TAVFs, for which coil embolization was carried out in 36 procedures (36/71, 50.7%). Absolute ethanol was administered in all procedures, with an average volume of 7.1 ± 4.2 ml per procedure (1–18 ml) (Table 1).

Postoperative outcomes of patients with traumatic arteriovenous fistulas

Angiography showed that 39 patients (92.9%) achieved 100% devascularization, while 2 patients (4.8%) achieved 76%–99% devascularization; the remaining patient had 50%–75% devascularization (2.4%). Among 39 patients initially diagnosed with Schobinger stage II, 29 (74.4%) improved to stage I (or became asymptomatic). Two out of three (66.7%) patients with stage III TAVFs improved to stage II after coil-assisted ethanol embolization. No recurrence was observed during imaging or clinical follow-ups (Table 2). According to angiographic re-examination and clinical manifestations, 30 cases (66.7%) achieved a complete response, while the other 12 (33.3%) showed a partial response (Table 1).

No major complications were reported. Thirty-four patients (34/42, 81.0%) developed focal swelling at the treatment area postoperatively, which subsided within 2 weeks. Two patients (2/42, 4.8%) developed blisters on their lesions shortly after treatment, which recovered spontaneously after 1 week. No patient experienced superficial skin necrosis and transient hemoglobinuria. Also, no abnormal feelings or neurological dysfunction associated with the embolization procedure were noted. Finally, no procedure-related mortality occurred during the perioperative phase for any of the patients.

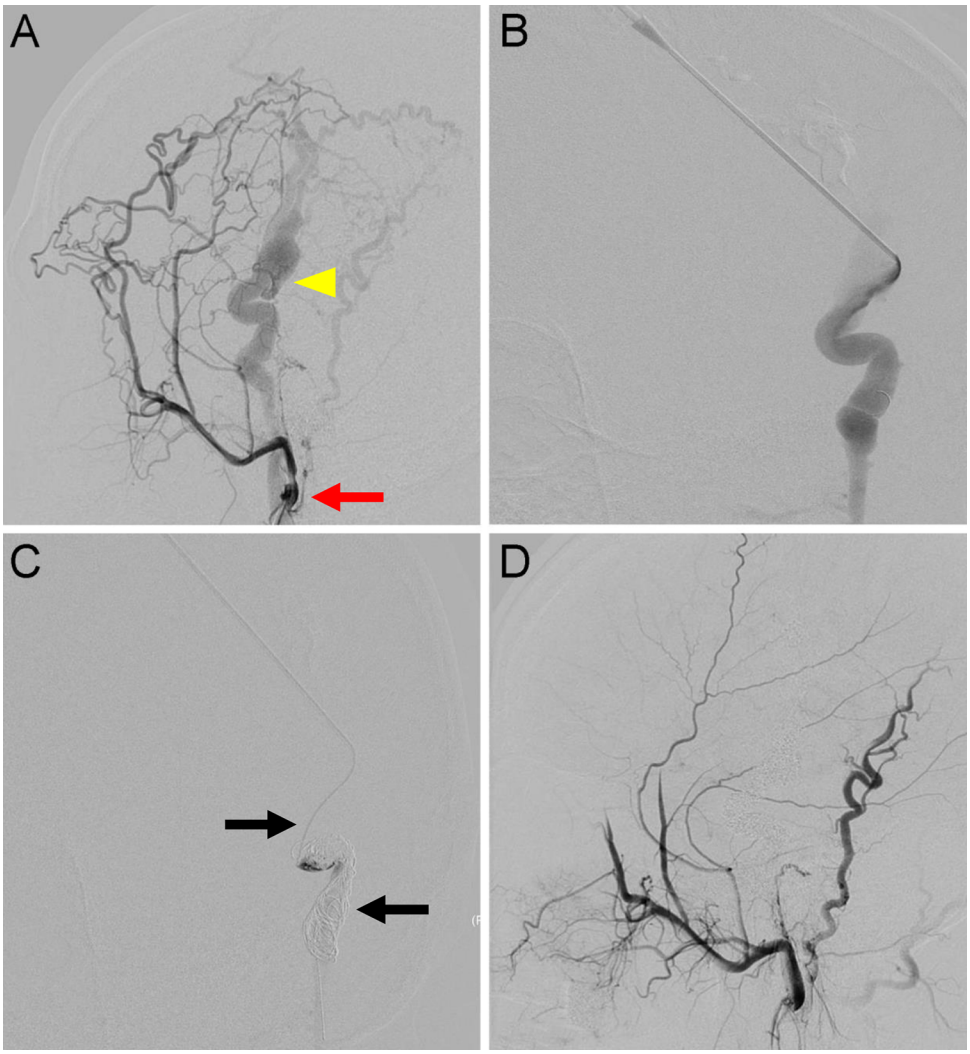

FIGURE 3
Traumatic arteriovenous fistulas located at the scalp. **(A)** Anteroposterior view of a left external carotid angiography showing AVFs (arrow) DOV (arrowhead) around the parietal area. **(B)** For high-flow lesions with DOVs, an 18-gauge needle was used to percutaneously puncture the DOV. **(C)** A 2.1-F microcatheter (upper arrow) was introduced through the needle into the dilated venous sac. The detachable coils (lower arrow) were then released after confirmation of no migration in the distal end of the draining veins. **(D)** Final angiography showing 100% devascularization.

Regular follow-up was achieved in all patients, with an average duration of 40.0 ± 25.9 months (range: 3–90 months) (Table 1).

Discussion

Managing TAVFs remains challenging, with limited available reports. This study demonstrates that ethanol embolization of TAVFs produces satisfactory clinical and radiographic results with few complications.

Congenital AVMs are characterized by a vascular developmental defect in the differentiation of the primitive capillary plexus during fetal angiogenesis, owing to genetic variations associated with *MAP2K1* and *GNA11* mutations (14, 15). Congenital AVFs are deemed as a simple form of AVMs (16). On the other hand, TAVFs are vascular anomalies usually secondary to trauma or invasive procedures, including biopsy, surgical intervention, and placement of intravenous catheters (17–19). We found that TAVFs were more frequently located in the head and neck, which is different from previous reports that TAVFs are more common in the extremities (20). The onset of initial symptoms varied from weeks to years, depending on the mode and degree of injury, indicating that the development of the lesions secondary to trauma is dissimilar (21).

Trauma promotes the formation of AVFs via direct and indirect potential approaches, establishing direct communication between the walls of veins and arteries in proximity by damaging their walls. During the healing process, small bridging vessels develop via proliferation of endothelial cells and angiogenesis, facilitated by a variety of secreted vascular growth factors (22). TAVFs usually result from deep penetrating injuries that cause damage to arterial and venous walls. This injury is thought to

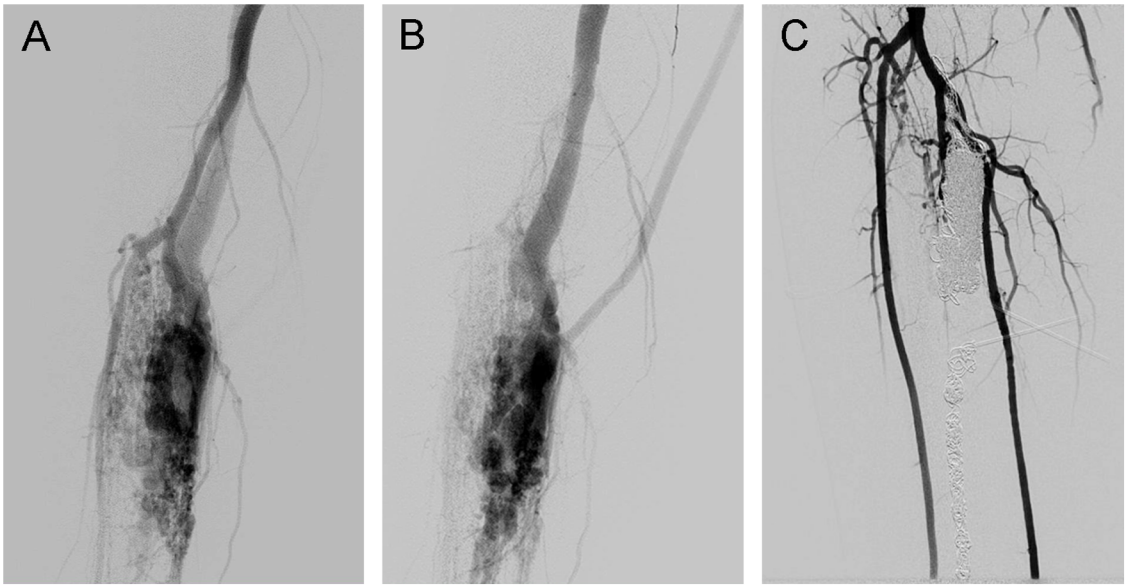

FIGURE 4
Traumatic arteriovenous fistulas located at the lower extremity. (A) Angiography in the arterial phase, (B) angiography in the venous phase, and (C) angiography showing 100% devascularization after coil deployment and ethanol injection.

initiate the growth of endothelial progenitor cells, known as angioblastic rest, and cause arterial recruitment in the affected area (22). TAVFs have been reported, but controversy exists about whether the trauma acts as an independent factor or merely a trigger for the disintegration of pre-existing fistulous embryonic connections (23). In addition, it remains unclear whether the variated gene lies in TAVFs, needing further investigation.

Treatment strategies for TAVFs include embolization, surgical resection, or a combination. Historically, surgical resection is the primary treatment for TAVFs, often at the expense of esthetics and function. However, the complexity of head and neck anatomy and potential massive blood loss during the operation hindered a complete resection, further accelerating lesion expansion and complicating future treatment. In comparison, endovascular therapy has gained popularity. Various embolic agents are available, such as coils, ethanol, n-Butyl cyanoacrylate (NBCA), Onyx, polyvinyl alcohol (PVA), etc. The insufficient destruction of the nidus is the disadvantage of NBCA or Onyx, leading to recanalization and recurrence (24, 25). Our previous reports have confirmed the potent efficacy of absolute ethanol in treating peripheral AVMs (26, 27). Unlike NBCA or Onyx, high-concentration ethanol exerts a unique denaturation effect on proteins. By destroying vascular endothelial cells, ethanol disrupts the angiogenesis engine, eliminating the possibility of recanalization (13). Nevertheless, ethanol embolization still confronts obstacles to popularization. One of the most notable reasons is radiolucency of ethanol. Clinicians have to make a "blind shot" when injecting ethanol under digital subtraction angiography (DSA), increasing the risk of ethanol reflux into normal vasculature and causing tissue necrosis. To solve this dilemma, our team has been researching and developing radiopaque ethanol injections (28).

During ethanol embolization of high-flow TAVFs, the embolic efficiency depends on adequate contact time with the nidus. In managing high-flow congenital AVMs with dilated draining

TABLE 2 Improvement of clinical manifestations and Schobinger stage after ethanol embolization.

Clinical manifestations	Preoperation		First-time follow-up	
	Patient No.	Schobinger stage[a] (No.,%)	Patient No.	Schobinger stage[a] (No.,%)
Pulsatile mass	41 (97.6%)	Stage Ⅱ (39, 92.9%) Stage Ⅲ (3, 7.1%)	12 (28.6%)	Stage Ⅰ or asymptomatic (29, 69.0%) Stage Ⅱ (12, 28.6%) Stage Ⅲ (1, 2.4%)
Secondary vasodilation	40 (95.2%)		0	
Thrill	28 (66.7%)		0	
Elevated skin temperature	20 (47.6%)		10 (23.8%)	
Persistent tinnitus	7 (9.7%)		0	
Pain	3 (7.1%)		1 (2.4%)	
Limb ulceration	2 (4.8%)		0	

[a]Stage I: quiescence—cutaneous blush, skin warmth, arteriovenous shunt on Doppler ultrasound; stage II: expansion—darkening blush, lesions show pulsation, thrill, and bruit; stage III: destruction—steal, distal ischemia, pain, dystrophic skin changes, ulceration, necrosis, soft tissue, and bony changes; stage IV: decompensation—high-output cardiac failure.

veins, previous reports have shown that coil placement can increase ethanol exposure to endothelial cells of the nidus by reducing the rate of arteriovenous shunting, yielding satisfactory therapeutic outcomes and decreasing the risk of complications, such as ethanol-related necrosis and cardiopulmonary collapse (29, 30). The results showed that the disappearance of signs and symptoms and satisfactory devascularization on angiogram achieved after coil embolization indicate that the treatment of congenital AVMs can be applied to TAVFs in the head and neck region. When we analyzed the treatment results, the complete and partial responses were better than those observed for congenital AVMs. The complete and partial response rates of 66.7% and 33.3%, respectively, were comparable to previous reports (10, 30, 31). Therefore, coil-assisted ethanol embolization therapy could be an effective treatment option for TAVFs.

This study has several limitations. First, this study presents a retrospective report. A prospective study is needed for a more precise assessment. Second, the location of the lesions and pathogenic factors differ among patients. At last, the sample size is relatively small. More patients with TAVFs are supposed to be included in our future research.

Conclusion

In conclusion, TAVFs are more common in the head and neck region than in other body parts. Coil-assisted ethanol embolization achieved safe and effective outcomes in treating TAVFs.

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 humans were approved by the Institutional Review Board of Shanghai Ninth People's Hospital. The studies were conducted in accordance with the local legislation and institutional requirements. Written informed consent for participation in this study was provided by the participants' legal guardians/next of kin. Written informed consent was obtained from the individual(s), and minor(s)' legal guardian/next of kin, for the publication of any potentially identifiable images or data included in this article.

Author contributions

YS: Validation, Writing – original draft. QH: Writing – review & editing. DW: Resources, Supervision, Writing – review & editing. LS: Methodology, Supervision, Writing – review & editing. MW: Data curation, Resources, Writing – review & editing. XF: Conceptualization, Project administration, Supervision, Writing – review & editing. XY: Formal Analysis, Investigation, Software, Visualization, Writing – original draft.

Funding

The authors declare financial support was received for the research, authorship, and/or publication of this article. This work was supported by the Transverse Research Project of Shanghai Ninth People's Hospital (No. JYHX2022007) and the Rare Disease Registration Platform of Shanghai Ninth People's Hospital, Shanghai Jiao Tong University School of Medicine (No. JYHJB202301).

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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frontiers | Frontiers in Neurology

TYPE Original Research
PUBLISHED 02 October 2024
DOI 10.3389/fneur.2024.1450102

OPEN ACCESS

EDITED BY
Deming Wang,
Shanghai Jiao Tong University, China

REVIEWED BY
Harsali Fransiscus Lampus,
Sam Ratulangi University, Indonesia
Wayne Yakes,
The Yakes Vascular Malformation Center, United States

*CORRESPONDENCE
Huaijie Wang
whj1324707188@hotmail.com

RECEIVED 16 June 2024
ACCEPTED 16 September 2024
PUBLISHED 02 October 2024

CITATION
Yang W, Wang H, Xie C, Lin W, Wang P and Guo Z (2024) Management for lymphatic malformations of head and neck.
Front. Neurol. 15:1450102.
doi: 10.3389/fneur.2024.1450102

Management for lymphatic malformations of head and neck

Weijia Yang, Huaijie Wang*, Chong Xie, Weilong Lin, Peihua Wang and Zhengtuan Guo

Department of Pediatric Surgery and Vascular Anomalies, Xi'an International Medical Center Hospital, Xi'an, China

Background: To explore the management of lymphatic malformation in head and neck.

Methods: This is a retrospective study at a single center. Data on demographic, surgery, sclerotherapy and follow-up information were collected from our Vascular Anomalies Center database. Patients with lymphatic malformation of head and neck who had undergone surgery and sclerotherapy between March 2020 and March 2024 were included.

Results: There were 94 patients in this study, the lesion sites included head ($n = 60$), tongue ($n = 7$), neck ($n = 41$), pharynx ($n = 7$), and head and neck ($n = 7$). Symptoms included bleeding ($n = 6$), infection ($n = 2$), dyspnea ($n = 2$), dysphonia ($n = 4$), and dysphagia ($n = 4$). Lymphatic malformation included macrocystic ($n = 61$), microcystic ($n = 12$) and mixed ($n = 21$). Surgeries for LM included radical resection, subtotal or partial resection and staged surgeries. Sclerotherapies included bleomycin monotherapy and combined sclerotherapy with ethanol and bleomycin, under ultrasound or fluoroscopy guidance. The follow-up period was from 3 months to 1 year. The therapeutic effect was evaluated according to the size of the treatment area. 55 patients, 21 patients, 11 patients and 7 patients were evaluated with excellent, good, moderate and no response, respectively.

Conclusion: Surgical resection, sclerotherapy and the combination of the two are efficacious treatment modalities for head and neck LM. Combined with oral drugs and other new therapies may be warranted in future for challenging conditions.

KEYWORDS

lymphatic malformations, neck, macroglossia, sclerotherapy, surgery, tracheotomy

Introduction

Lymphatic malformations (LM) are classified as a low-flow vascular malformation, which belongs to benign lesions, but its harm and treatment are related to the morphologic type, anatomic location and extent. Lymphatic malformations are divided into 3 types (1), macrocystic, microcystic and mixed cystic, which are lymphatic masses composed of cysts of varying sizes. LM are common in the head and neck, accounting for about 75 percent (2). The prognosis is worse when the lesion involves tongue, floor of mouth and pharynx (3).

Currently, management include conservative observation, surgery, sclerotherapy and oral medication. This paper reviewed the treatment of LM in head and neck at our center.

Material and method

A 3-year (March 2020 to March 2024) retrospective electronic chart review of all patients with LM admitted to Xi'an International Medical Center Hospital was performed. Keywords lymphatic malformation was used to identify patients in our electronic medical records system. Diagnosis was based on clinical history, photographs, physical examination, color Doppler ultrasound, and magnetic resonance imaging (MRI). Approval was obtained from Xi'an International Medical Center Hospital Institutional Review Board. Color Doppler ultrasound and MRI images were reviewed for morphological subtype of the LM, tissue involvement, therapeutic response evaluation.

Surgical resection

In patients with macrocystic LM, pre-sclerotherapy treatment of LM involving the airway may require tracheostomy, as the post-procedure swelling may cause airway obstruction. A preemptive tracheostomy may be required. For microcystic LM, the therapeutic response of sclerotherapy was often limited, and surgical debulking is needed, such as macroglossia, LM involving glottis and epiglottis. However, cosmetic concern following facial lesion surgery needs to be weighting. For mixed LM, surgery was considered if response was poor to sclerotherapy. Additional sclerotherapy for residua via drainage tube or intraoperative injection could be required in some cases.

Surgeries for LM included radical resection, subtotal or partial resection and staged surgeries. During some surgeries, the intercapsular separation can be removed to form a large cavity, creating conditions for intraoperative or postoperative sclerotherapy.

Sclerotherapy

All the children underwent preoperative routine examination after admission, and interventional therapy was performed after no contraindications were confirmed. Before operation, the lesions were marked on the body surface according to the imaging examination. Before puncture, bleomycin was dissolved in iodohexol contrast medium, and the concentration was between 0.5 mg/mL and 1 mg/mL according to the depth of the puncture site. A maximum of 0.5 mg/kg bleomycin was used per session. The puncture is under the guidance of ultrasound. Bleomycin alone was only used for treatment of microcystic or mixed LM (no obvious lymph fluid or a small amount of lymph fluid was extracted after puncture). Bleomycin was dissolved in contrast medium, and any lymphatic fluid (LM intracavity or suspected intracavity) was extracted from the lesion by puncture into the lesion, and the drug should be injected, mainly into the lesion intracavity and interstitial. According to the skin markings before surgery, multi-point injection can be performed to manage localized lesion. Postprocedural pressure bandage could help local adhesion and closing the capsule cavity. The response was evaluated 3 months after discharge, repeated injection may be needed. For macrocystic or mixed LM that can extract lymph fluid by puncture, rinse with anhydrous ethanol. If the cyst was large, double-needle technique could be used to reduce the risk of anhydrous ethanol exosmosis related necrosis. Then the mixture of contrast and bleomycin was injected. Multi-sites injection also can be used to maximize the sclerosant diffusing in the lesion area.

Clinical evaluation scale (4) was used to evaluate the treatment effect of patients with or without related symptoms and signs: mass regression ≥90%, no symptoms and signs (excellent); mass regression ≥50%, no obvious symptoms and signs (good); mass regression <50%, occasionally associated symptoms and signs (moderate); The mass did not significantly subside, and the symptoms and signs were not significantly improved; or larger mass or worse symptoms and signs than before treatment (no response). We used three senior physicians to independently evaluate follow-up patients based on Doppler ultrasound, MRI and appearance. If at least two physicians are the same rating, the patient is considered to have this rating.

Result

There were 94 patients in the retrospective study (Table 1), the lesions included head ($n=60$), tongue ($n=7$), neck ($n=41$), pharynx ($n=7$) and head and neck ($n=7$). Symptoms included bleeding ($n=6$), infection ($n=2$), dyspnea ($n=2$), dysphonia ($n=4$), and dysphagia ($n=4$). Morphological subtype included macrocystic ($n=61$), microcystic ($n=12$) and mixed ($n=21$).

Eighty-four patients underwent totally sclerotherapy and 10 underwent surgical resection. There were 39 females and 55 males, with an age ranging 1 to 11 years (median 2 years). Operative duration ranged 5–156 min (median 38 min). The follow-up period was 6 months to 1 year. The effect of sclerotherapy on 61 cases of large cystic LM in the head and neck was significantly improved, and the lesions were reduced by at least 50%, even >90% (Figure 1), without serious complications. In 5 patients with facial microcystic LM, for aesthetic considerations, parents preferred sclerotherapy to improve local enlarging, with poor short-term effect and only slight local improvement. In the long term, due to the stability of the lesions, the lesions may be relatively smaller with the growth and development of children. For patients with unsatisfactory effect of sclerotherapy, surgical treatment is combined with excision and sclerotherapy. Figure 1 shows the reduction of maxillofacial mixed cystic LM in a patient with a session of sclerotherapy. The therapeutic effect of a patient with a large microcystic lesion on the tongue is shown in Figure 2. Two patients had dyspnea due to pharyngeal involvement. One of the patients underwent endoscopic bleomycin injection and the other was treated with multiple sclerotherapy after tracheotomy (Figure 3), and the dyspnea was improved. There was only one complication in the excised patient, poor healing of the tongue wound resulted in a slight bifurcation of the tip of the tongue. The therapeutic effect was evaluated according to the size of the treatment area. There were 55 patients with excellent response, mainly sclerotherapy for macrocystic lesions and excision for localized microcystic or mixed lesions. A total of 21 patients were evaluated with good response, mainly with excision for macrocystic lesions and localized microcystic or mixed lesions which in order to protect skin blood transport without skin excess, and sclerotherapy for macrocystic or mixed lesions. There are 11 patients with moderate, mainly with sclerotherapy for microcystic and mixed lesions and excision for infiltrative microcystic or mixed lesions. There were 7 patients with no response, mainly sclerotherapy for microcystic or mixed lesions and excision therapy for microcystic lesions.

Discussion

The clinical symptoms of lymphatic malformations on patients mainly depends on the location of the disease, the extent of the lesion and the type of cystic lesions. The lesions may present with bleeding, infection, enlargement, etc., resulting in varying degrees of dysfunction or affect appearance, such as megaloglossia, facial deformities, breathing, swallowing, articulation difficulties, etc. (5), requiring intervention and treatment. Among them, the anatomical structure of the head and neck is complex, there are many vital tissues and organs, and the treatment is more difficult with increased risks. LM in the head and neck are mainly cystic, and can be divided into macrocystic, microcystic and mixed types according to the size of the cystic cavity. There is no strict standard for the size of the cystic LM (6), but some authors use 2 cm (7) or 1 cm (8) as a limit to distinguish macro-versus micro-cystic, the significance of which is whether the cyst can be successfully aspirated to achieve visible decompression. The midface and oral lesions were mainly microcystic, the parotid gland and submandibular region were mainly mixed, and the neck was mainly macrocystic and mixed (9). Microcystic lesions located on the hyoid bone and on both sides are factors predicting difficult treatment and poor prognosis, especially the lesions involving the tongue, floor of the mouth and pharynx (3, 10). The goal of treatment is to remove LM as much as possible to control symptoms, restore function, or improve the appearance of the affected organ (11). At present, the main management methods include conservative observation, surgery, sclerotherapy, oral drug therapy and combination therapy. This article focuses on the comprehensive treatment of lymphatic malformations of head and neck.

TABLE 1 Clinical characteristics of the study population.

Variable	Sclerotherapy (*N* = 84)	Surgical resection (*N* = 10)	Total (*N* = 94)
Sex (No.)			
Female	36	3	39
Male	48	7	55
Age (y)			
Median	2	2	2
Range	1–11	1–5	1–11
Location			
Head	52	8	60
Tongue	4	3	7
Neck	37	4	41
Pharyngeal	5	2	7
Head and Neck	5	2	7
Symptom			
Hemorrhage	5	1	6
Infection	2	0	2
Dyspnea	0	2	2
Cacoepy	1	3	4
Dysphagia	1	3	4
Morphological subtype			
Macrocystic	61	0	61
Microcystic	5	7	12
Mixed	18	3	21
Operative duration (min.)			
Median	35	87	38
Range	5–63	57–156	5–156
Follow-up evaluation			
Excellent	52	3	55
Good	18	3	21
Moderate	8	3	11
No response	6	1	7

At present, most scholars believe that not all LM needs treatment, that is, patients with mild appearance and no functional impairment can be followed up for observation (12). However, some scholars believe that LM is more likely to progress gradually, and the risk of progression of diffuse lesions is much higher than that of localized lesions, and early treatment is recommended (13). For less significant lesions, follow-up observation may be an option.

Surgical treatment has always been an important treatment for LM and is still widely used today (14). However, due to the complex anatomical structure of the head and neck, the aggregation of important organs, and the invasive growth of the lesions, there is no obvious boundary with the normal structure, which makes the operation difficult and the risk high, and the postoperative recurrence rate high, especially the microcystic lesions on the hyoid bone are more prone to recurrence (15). The lesions involved the mouth and face, and multiple anatomical sites (more than 2) suggested poor prognosis and high surgical complications (16). The principle of surgical treatment is to remove as many lesions as possible under the premise of protecting normal tissue and organ function. Surgical treatment is mostly used for microcystic and mixed LM. For macrocystic lesions, sclerotherapy can often achieve good results and is minimally invasive. However, it should be noted that sclerotherapy often cannot shrink the lesions in a short time. For serious emergency complications such as airway obstruction, surgery should be considered first. In recent years, compared with the traditional surgical treatment of LM, some new surgical techniques have emerged that deserve our attention and exploration, such as endoscopic resection (17), liposuction-like sclerotherapy technique (18), curettage and sclerotherapy technique (19), radiofrequency ablation (20), carbon dioxide laser (21), etc. It is important to note that the use of new techniques may cause severe swelling and may require a tracheotomy in advance.

In the past 20 years, sclerotherapy has gradually become another important method for the treatment of LM. At present, a variety of sclerosant have been clinically used, including OK-432, bleomycin, doxycycline, anhydrous ethanol, etc. (22). Double-needle technique is a safe and efficient technique (23). For larger macrocysts, suction drainage tube can be placed after sclerotherapy with multiple use of sclerosant (24). Most sclerosant have a good effect on large cystic lesions, followed by mixed lesions, and a limited effect on microcystic lesions (25). Anhydrous ethanol directly destroys endothelial cells, denatures proteins, and leads to thrombosis and fibrosis. The reasons for the use of anhydrous ethanol combined with bleomycin in the treatment of LM are as follows: (1) anhydrous ethanol can not only destroy lymphatic endothelial cells and cystic cavity, but also destroy

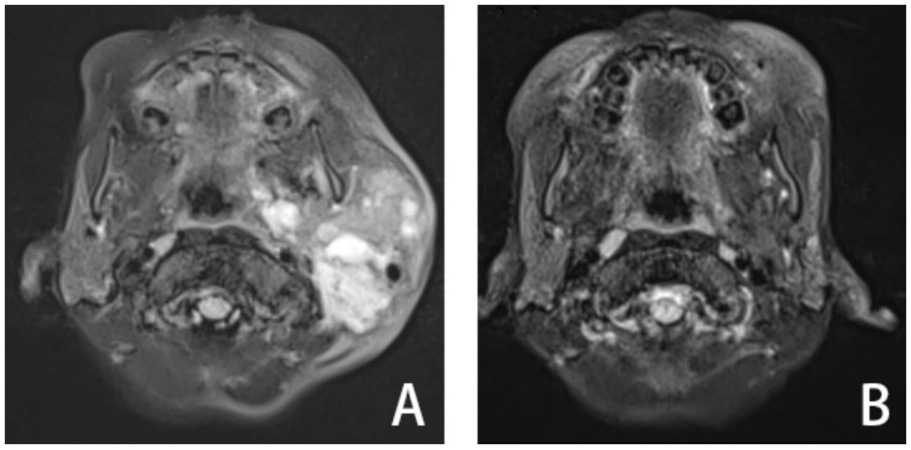

FIGURE 1
A patient with LM in maxillofacial region of T2-MRI axial scan: before treatment **(A)**, 1 year after treatment **(B)**.

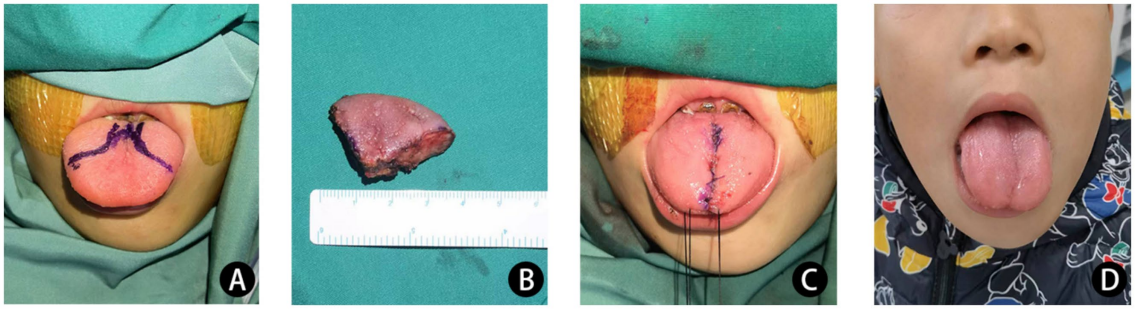

FIGURE 2
The patient had a large tongue, which affected mastication, swallowing and pronunciation, and there were lymphatic vesicles of different sizes on the surface of the tongue, some of which were accompanied by bleeding **(A)**. After partial removal of the tongue according to the marks, the tongue was thickened and tough **(B)**, and the tongue was reduced after surgery **(C)**. The 1-year postoperative follow-up showed improvement in mastication, swallowing and pronunciation **(D)**.

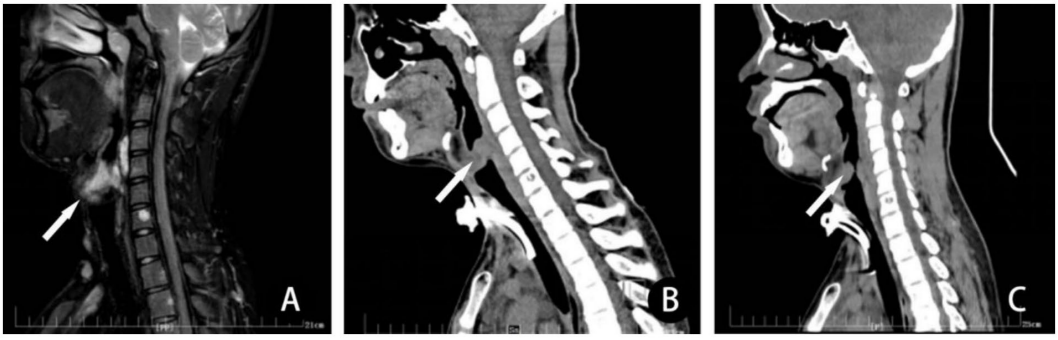

FIGURE 3
In a patient with LM involving the pharynx, **(A)** preoperative T2-MRI sagittal scan, revealed that the lesion involves and obstructs the airway (arrow) significantly. Three depressions sign was obvious when he walked fast. **(B)** He received a session of sclerotherapy with combination of ethanol and bleomycin after tracheotomy. Computerized tomography scan 1 month after treatment revealed severe obstruction of airway due to post-sclerotherapeutic reactive edema. **(C)** Computerized tomography scan 6 months after sclerotherapy demonstrated airway obstruction improved. Then, the tracheotomy tube was removed. There is a decrease in the size of the mass of the LM in the posterior subglottic LM lesion and little change in size of the mass in the anterior subglottic LM lesion. Despite this residual narrowing, the patient suffered no further sign or symptoms of airway obstruction.

small vessels that cause intracapsular bleeding, promote thrombosis and achieve hemostasis; (2) because the cyst cavity originally contained a large amount of lymph fluid, the irrigation process was a process of gradually increasing the concentration of ethanol, and the effect of destroying the cyst wall was better (3). The effect of anhydrous ethanol is strong but short, and the effect of bleomycin is mild but long lasting. The two complement each other to reduce the dose of bleomycin and reduce the side effects of pulmonary fibrosis. All kinds of sclerosant carry the risk of side effects, such as drug allergy, pulmonary fibrosis (unique to bleomycin), local pain, skin necrosis, nerve damage, generalized fever, skin pigmentation, and swelling (24). Compared with surgery, although sclerotherapy cannot remove the diseased tissue, it can still significantly reduce the lesions of some patients and even achieve the effect of "cure" on imaging, especially macrocystic lesions (26). Although there is also a high recurrence rate, the trauma ratio is significantly reduced by surgery, and the risk of nerve damage is lower than that of surgery.

At present, the oral drug commonly used in the non-surgical treatment of LM is sirolimus, which is an inhibitor of mTOR. It has achieved good results in the treatment of diffuse LM and is often used in patients with poor response to surgery and sclerotherapy. Although sirolimus cannot make the lesion disappear completely, it may improve the functional limitations, bleeding, pain, infection and exudation caused by the lesion (27). Oral ulcers, gastrointestinal discomfort, and bone marrow suppression are common side effects (28). Patients may need oral sirolimus lifelong, or have to be intermittently or permanently taken off sirolimus as complications and adverse events occur. Their symptoms will reappear when taking off sirolimus. In LM mouse models, both alpelisib and rapamycin improved mouse survival, but organ dysfunction was improved by only alpelisib, which is a p110α-specific PI3K inhibitor (29). This study implied that PI3K inhibitor may be superior to sirolimus in terms of LM treatment.

Conclusion

Surgical resection, sclerotherapy and the combination of the two are efficacious treatment modalities for head and neck LM. Combined with oral drugs and other new therapies may be warranted in future for challenging conditions.

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 humans were approved by Xi'an International Medical Center Hospital Institutional Review Board. The studies were conducted in accordance with the local legislation and institutional requirements. Written informed consent for participation in this study was provided by the participants' legal guardians/next of kin.

Author contributions

WY: Data curation, Formal analysis, Writing – original draft. HW: Conceptualization, Methodology, Writing – review & editing. CX: Data curation, Investigation, Writing – review & editing. WL: Data curation, Software, Writing – review & editing. PW: Data curation, Writing – review & editing. ZG: Conceptualization, Supervision, Writing – review & editing.

Funding

The author(s) declare that no financial support was received for the research, authorship, and/or publication of this article.

Acknowledgments

The authors thank all the physicians, patients, and families who provided clinical information.

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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frontiers | Frontiers in Neurology

TYPE Original Research
PUBLISHED 30 October 2024
DOI 10.3389/fneur.2024.1461341

OPEN ACCESS

EDITED BY
Xindong Fan,
Shanghai Jiaotong University School of Medicine, China

REVIEWED BY
Shancai Xu,
First Affiliated Hospital of Harbin Medical University, China
Wayne Yakes,
The Yakes Vascular Malformation Center, United States
Josue Ordaz,
Indiana University Hospital, United States
Abdulaziz Alghamdi,
King Saud bin Abdulaziz University for Health Sciences, Saudi Arabia

*CORRESPONDENCE
Ran Huo
huoran@medmail.com.cn
Lei Xu
xulei@sdfmu.edu.cn

†These authors have contributed equally to this work and share first authorship

RECEIVED 08 July 2024
ACCEPTED 22 October 2024
PUBLISHED 30 October 2024

CITATION
Han W, Yang K, Gao W, Wu X, Huo R and Xu L (2024) Retrospective clinical study on the efficacy and complications of interventional embolization in the treatment of scalp arteriovenous fistula.
Front. Neurol. 15:1461341.
doi: 10.3389/fneur.2024.1461341

Retrospective clinical study on the efficacy and complications of interventional embolization in the treatment of scalp arteriovenous fistula

Wenliang Han[1], Kexin Yang[2], Wei Gao[3], Xuejun Wu[2], Ran Huo[1*†] and Lei Xu[2*†]

[1]Department of Burn and Plastic Surgery, Shandong Provincial Hospital Affiliated to Shandong First Medical University, Jinan, Shandong, China, [2]Department of Vascular Surgery, Shandong Provincial Hospital Affiliated to Shandong First Medical University, Jinan, Shandong, China, [3]Department of Rehabilitation Medicine, Shandong Provincial Hospital Affiliated to Shandong First Medical University, Jinan, Shandong, China

Introduction: Scalp arteriovenous fistula (AVF) is a rare and intricate vascular anomaly characterized by a direct connection between an artery and a vein, without an intervening capillary system. This anomaly can induce significant local hemodynamic changes and is associated with various complications, such as pain, a pulsatile mass, increasing swelling, and venous hypertension skin ulcerations which may be non-healing. This study aimed to evaluate the efficacy and safety of interventional embolization treatments for scalp AVF at Shandong Provincial Hospital.

Methods: This retrospective clinical analysis assessed 21 patients who underwent interventional embolization between 2018 and 2024. Patients included were those treated in the vascular surgery department at Shandong Provincial Hospital, who had comprehensive medical records and follow-up data. Treatment methods, outcomes, and complications were thoroughly analyzed through patient medical records.

Results: Among the patients studied, direct puncture was the most prevalent treatment method, employed in 42.86% (9/21) of cases, followed by various combinations of arterial, venous, and direct approaches. Ethanol, used in 85.71% (18/21) of the cases, demonstrated its broad efficacy and application in clinical settings. Immediate imaging post-treatment confirmed a cure rate of 85.71% (18/21). The main postoperative complications included swelling, with some patients also experiencing nodules, scabbing, or hair loss.

Conclusion: Interventional embolization has proven to be a safe and effective method for managing scalp AVF, significantly minimizing complications. Future research should focus on further optimizing these treatment methods to enhance efficacy and improve patient quality of life.

KEYWORDS

scalp arteriovenous fistula, interventional embolization, clinical review, efficacy, safety

1 Introduction

Scalp Arteriovenous Fistula (AVF) is a rare vascular anomaly characterized by abnormal direct connections between arteries and veins, without an intervening capillary system. This condition often manifests as abnormal connections between the superficial scalp arteries and veins, involving any scalp blood vessels (1–3). These abnormal vascular structures can lead to local hemodynamic changes, producing pulsatile masses, and can cause severe clinical complications such as varying degrees of bleeding, pain, or skin ulcers (4). Scalp AVF, a rare and complex disease that can affect individuals of all ages, poses significant challenges in the fields of plastic surgery, neurosurgery, vascular surgery, interventional radiology, and interventional neuroradiology.

Currently, treatment options for scalp AVF include surgical resection, blood vessel ligation, vascular embolization, focal injection of sclerosing agents, and electrocoagulation thrombosis (5–9). These treatment modalities, either alone or in combination, yield different clinical outcomes. With advancements in medical technology, interventional embolization has emerged as a new and effective treatment option, offering advantages such as minimal invasiveness, high safety, and good efficacy (10–12).

Some patients with scalp arteriovenous fistulas (AVFs) have congenital spontaneous occurrence (generally developing from a red birthmark into a pulsatile mass), while others occur after trauma. These patients often have different degrees of bleeding as well as symptoms such as headache and tinnitus. Most of the reports in previous literature consist of individual case reports, but there is relatively little literature on systematic review studies regarding the effectiveness of injecting absolute ethanol for the treatment of scalp AVFs.

This study retrospectively analyzes the cases of scalp AVF treated with interventional embolization at Shandong Provincial Hospital's Department of Vascular Surgery between 2018 and 2024. The aim is to provide a detailed discussion of the clinical practice of interventional embolization, evaluate its efficacy and complications, and offer comprehensive insights into the treatment of scalp AVF.

2 Methods

2.1 Patient population

This retrospective clinical analysis evaluates the efficacy and safety of interventional embolization for scalp AVF at Shandong Provincial Hospital's Department of Vascular Surgery from 2018 to 2024. The inclusion criteria were patients treated at the hospital with complete medical records and follow-up data. Exclusion criteria included patients treated with non-interventional embolization methods or those with incomplete data. Patients with postoperative recurrent and residual arteriovenous fistulas were also included. These patients exhibited various signs and symptoms such as local erythema, scalp vasodilation, ulceration, and headaches. Written informed consent was obtained from each patient or their guardians to inform them of the benefits and risks of the surgery. The study was waived by the Ethics Committee due to the retrospective nature of the study, which did not require informed consent. The procedures for this study follow the Helsinki Declaration.

2.2 Data collection

Data were collected from the patients' medical records, including gender, age, predisposing factors, onset time, lesion location, whether internal carotid artery branches were involved in blood supply, treatment approaches (e.g., direct puncture, arterial approach, venous approach), embolization materials used (e.g., detachable coils and non-detachable coils, absolute ethanol, glue, microspheres), immediate imaging results, and post-treatment complications.

2.3 Statistical analysis

After screening, 21 patients (18 males, 3 females; aged 7–45 years, despite being a congenital vascular malformation, patients may initially be asymptomatic and later develop symptoms. Our patient population has had a more than one year duration of the various symptoms) were included in the study. The specific data analysis is presented in the Results section and in Tables 1, 2.

2.4 Treatment methods

Preoperative auxiliary examinations such as complete blood count, blood biochemical indices, coagulation function, and electrocardiogram were performed. Continuous monitoring of blood pressure, electrocardiogram, and blood oxygen saturation was conducted before and after treatment. All 21 embolization procedures were performed under general anesthesia with oral intubation. Serial digital subtraction angiography (DSA) was used to monitor the embolization process, providing detailed anatomical and hemodynamic information about the lesion. This allowed for timely evaluation of therapeutic effects and management of possible complications to achieve optimal outcomes and minimize risks.

Initially, patients underwent femoral artery puncture under anesthesia, with the catheter advanced to the carotid artery using radiographic image-guided technology. Contrast agent injection and arteriography provided detailed anatomical and hemodynamic information about the lesion, allowing for the determination of arterial and venous structures involved in the blood supply and drainage of the lesion. Based on the condition of the draining vessels, local puncture or continued access through the femoral vein was selected. For significant draining veins, 18G needles were used for direct puncture of the abnormal vascular mass and reflux veins, followed by micro catheter insertion through the needle. Peripheral non-detachable coils were first released, followed by detachable coils,. The coils are placed to partially obstruct and to slow AV shunting vascular flow to allow better ethanol intravascular contact, to denude the endothelial cells from the vascular wall (artery/vein) and precipitate their protoplasm and reduce the ethanol volumes required to achieve that goal. This then causes platelet aggregation on the denuded vascular wall by platelet accumulation peripherally to centrally to ultimately thrombose the vessel. This approach helped block abnormal blood flow, and improve the efficacy of absolute ethanol while minimizing its dosage. Absolute ethanol was injected after coil implantation. It should be noted that coil implantation does not damage vascular tissue. It causes and promotes intravascular thrombosis, not "damage." Ethanol DOES intravascular damage by

TABLE 1 Patients with scalp arteriovenous malformations (AVMs): patient and AVMs characteristics.

Patient no./Gender/ Age (y)	Cause	Duration of illness	Location of leision	Involvement of the internalcarotid arteryartery branches
1/M/45	No	10 years	RT	No
2/M/23	No	10 years	LO	No
3/M/45	Trau	2 months	LO	No
4/M/7	No	6 years	F	No
5/M/26	No	3 months	RT	No
6/F/16	No	10 days	P-O	No
7/M/38	Trau	7 years	LT	No
8/M/25	No	2 years	RF	No
9/M/3	IT	16 days	RFT	No
10/M/38	No	5 months	LT	No
11/M/12	No	18 days	F	No
12/F/33	No	10 months	F	No
13/M/18	No	17 years	LTP	Ophthalmic artery
14/F/22	No	3 years	RFT	No
15/F/39	No	2 years	T	No
16/M/16	No	10 years	LFT	No
17/M/19	No	16 years	RO	No
18/M/17	No	1 years	LF	No
19/M/45	Trau	5 months	LO	No
20/M/38	No	1 years	LT	No
21/M/19	No	16 years	RO	No

No., number; M, male; F, female; Trau, Cause Traumatism; IT, Iatrogenic Traumatism; RT, Location of leision Right temporal part; LO, Left occipital part; F, Frontal part; P-O, Parieto-occipital part; LT, Lefttemporal part; RF, Right frontal part; LTP, Left temporoparietal; RFT, Right frontotemporal; T, Temporal part; LFT, Left frontotemporal; RO, Right occipital part; LF, Left frontal part.

denuding the vascular wall of endothelial cells and precipitating their protoplasm, causing fractures of the vascular wall to the level of the internal elastic lamina, and the denuded/fractured wall that then has platelet aggregation that causes the thrombosis.

For patients without significant bulky draining veins, direct local puncture was chosen, supplemented by temporary occlusion of blood flow, extrinsic manual compression will limit vascular flow ("velocity"), but it increases the intravascular pressure proximal to the compression in the area desiring to be embolized. Distal and downstream to the manual compression it does decrease intravascular pressure due to the proximal occlusion limiting inflow, until collaterals distally replace that flow volume to this area. Superselective imaging assessed whether normal tissue-supplying vessels were present. If present, embolization through the venous route or local puncture was performed to avoid damaging normal tissue. For lesions with independent blood supply, where all vessels supplied only the lesion (Nidus), arterial route injection of absolute ethanol was chosen. Careful angiographic evaluation ensured that only the diseased tissue was affected. Intraoperative imaging monitored the distribution and efficacy of the embolization agent, ensuring complete closure of the lesions while maintaining blood flow integrity to surrounding normal tissues. Once confirmed, treatment was concluded, with continuous observation post-operation to ensure other complications, the original abnormal arteriolar characteristics have mostly disappeared, showing significantly fewer high-flow blood vessels and improved arteriovenous shunt, with arterial blood supply and venous drainage expansion and distortion significantly improved, and the blood flow distribution returning to a normal pattern (Figure 1).

3 Results

Several incident factors have been noticed that have initiated the patients' symptoms such as trauma (19.05%), however, in the majority of patients (80.95%) presenting with symptoms related to their AVFs no incident event was noted. This indicates that trauma is an important factor in the pathogenesis of acquired AVF (Table 1).

3.1 Onset time distribution

The onset of patients varied from days to years, indicating that scalp AVF can occur at any time without a specific morbidity peak (Table 1).

3.2 Lesion site analysis

The most common lesion site was the temporal region, accounting for 28.57% (6/21). The frontal, occipital, and multiple regions each accounted for 23.81% (5/21). This suggests that the richly vascularized

TABLE 2 Summary of interventional embolization with surgery in 21 patients with scalp AVMs.

Patient no./ Gender/ Age (y)	Approach	Controllable coils	Detachable coils	Alcohol	Glue	Microspheres	Immediate imaging results	Complications
1/M/45	DP	5	10	Yes	No	No	Cure	Swell
2/M/23	A, V, DP	2	8	Yes	Yes	No	Cure	Swell
3/M/45	A, V, DP	3	7	No	No	No	3	No
4/M/7	DP	2	3	Yes	No	No	Cure	Swell, gelosis
5/M/26	DP	0	4	Yes	No	No	Cure	Swell, gelosis
6/F/16	A, DP	0	0	Yes	Yes	No	Cure	swell, alopecia
7/M/38	A, DP	2	11	Yes	No	No	Cure	Swell
8/M/25	DP	0	5	Yes	No	No	Cure	Swell, gelosis
9/M/3	A	0	1	No	Yes	No	Cure	Scab
10/M/38	A, V	3	0	No	No	No	6	No
11/M/12	DP	0	0	Yes	Yes	No	Cure	Swell
12/F/33	DP	0	0	Yes	No	No	Cure	Swell, scab
13/M/18	V, DP	13	0	Yes	No	No	Cure	Swell, scab, alopecia
14/F/22	A, V, DP	1	2	Yes	Yes	No	Cure	Swell
15/F/39	A, DP	0	0	Yes	No	Yes	Improve	Swell
16/M/16	V, DP	5	35	Yes	No	No	Cure	Swell, gelosis
17/M/19	DP	6	0	Yes	No	No	Cure	Swell, alopecia
18/M/17	DP	2	0	Yes	No	No	Cure	Swell
19/M/45	A, DP	0	0	Yes	Yes	No	Cure	Swell
20/M/38	DP	3	16	Yes	Yes	No	Cure	Swell
21/M/19	A	0	0	Yes	No	No	Cure	Swell, scab, alopecia

AVMs, arteriovenous malformations. Approach Direct Puncture (DP), Arterial pathway (A), Venous pathway (V). Immediate imaging results Recurrence 3 months after surgery (3), Recurrence 6 months after surgery (6).

collateral network in the scalp area can cause lesions to appear in multiple locations on the scalp (Table 1).

3.3 Involvement of internal carotid artery branches

We observed that in most cases of scalp AVF, branches of the internal carotid artery were not involved in the blood supply. Only one case (4.76%) involved the ophthalmic artery. Fully evaluating the blood flow path allows for more accurate treatment strategies and more effective closure of abnormal blood flow, reducing complications (Table 1).

3.4 Treatment pathway analysis

Direct puncture was the most commonly used method, accounting for 42.86% (9/21) of all cases. This method is preferred due to its ease of operation and high efficiency in directly targeting the lesion area. Direct puncture allows precise delivery of embolic material to the abnormal Nidus, effectively reducing abnormal blood flow. Additionally, the combination of arterial and direct puncture methods and the combination of arterial, venous, and direct puncture methods accounted for 19.05% (4/21) and 14.29% (3/21) of all treatments, respectively. These combined methods, involving multiple vessels, enhance therapeutic effects, particularly for complex or extensive AVF. Other approaches, including combined arterial and venous methods, simple arterial methods, and venous combined with direct puncture, accounted for 4.76% (1/21), 9.52% (2/21), and 9.52% (2/21), respectively. These data reflect adjustments in treatment strategies based on clinical cases and demonstrate the applicability and potential of different approaches in specific scenarios. Although direct puncture is a major treatment option, the combined use of arterial and venous approaches also shows clinical value in complex cases. Comprehensive embolization using different methods can more fully close abnormal blood flow, especially important for complex structures or cases where previous treatments failed. This multi-route strategy improves treatment comprehensiveness, providing multiple options for achieving optimal clinical outcomes and enhancing patient quality of life (Table 2).

3.5 Embolization material usage

Absolute ethanol was used in 85.71% (18/21) of patients, reflecting its widespread clinical use and effectiveness. Absolute ethanol is reliable for quickly and effectively closing abnormal blood vessels by destroying endothelial cells and promoting thrombosis, effectively

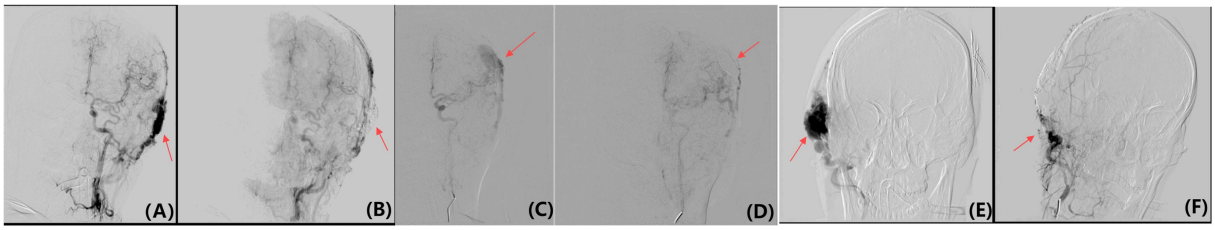

FIGURE 1
Pre-embolization DSAs and immediate post-embolization DSAs results of Yakes Type IIa AVM. (A) The head area shows obvious arteriovenous fistula, with a clearly visible abnormal blood vessel network, displaying vasodilation and circuitous characteristics, indicating a high flow of abnormal blood flow. This situation usually causes symptoms such as headache or skin ulcer and bleeding. (B) After embolization, the abnormal vascular network is significantly reduced. Vascular enhancement significantly diminishes, indicating that abnormal blood flow has been successfully blocked or reduced, and the vasodilation and circuitous characteristics have been relieved. (C) The head area shows obvious arteriovenous fistula, with a clearly visible abnormal blood vessel network, displaying vasodilation and circuitous characteristics. These abnormal blood vessels have remarkable enhancement, indicating a high flow of abnormal blood flow. (D) The abnormal vascular network is significantly reduced. Vascular enhancement significantly diminishes, indicating that abnormal blood flow has been successfully blocked or reduced. Vasodilation and circuitous characteristics have been relieved, showing that embolization materials effectively closed the arteriovenous fistula. (E) The left side of the head near the temporal area shows obvious abnormal arteriolar characteristics, indicating a high flow of arteriovenous shunt. The area indicated by the arrows shows a direct connection between the arterial and venous shunt, with some blood entering the Nidus and some draining from the Nidus through dilated veins. (F) DSAs was performed immediately after embolization.

controlling the condition. The novelty of this study lies in its evaluation of the efficacy of absolute ethanol in the treatment of AVF (arteriovenous fistula) based on a single-center retrospective analysis with a relatively large sample size. The results demonstrate that absolute ethanol is an effective treatment option, showing significant therapeutic outcomes. Detachable coils and non-detachable coils were also widely used, with a utilization rate of 71.5% (15/21). Coils physically block arterial or venous blood flow, providing long-term, stable embolization effects, particularly useful for complex vascular lesions. Glue embolization was used in 33.33% (7/21) of patients, demonstrating its advantages in precise embolization in certain cases. Glue materials rapidly solidify upon contact with blood, forming solid blocks suitable for precise vascular area occlusion. Microspheres were less commonly used, accounting for only 4.76% (1/21). Although effective for small vessel embolization, larger flow or diameter vessels may require more powerful materials to ensure efficacy (Table 2).

3.6 Analysis of real-time imaging results

To ensure accuracy and objectivity, international standard imaging results were used. Three senior doctors independently evaluated the images, each with extensive experience in scalp AVF analysis. They independently assessed post-treatment images for changes in blood flow, structural improvement, and potential anomalies. Their assessments were recorded separately and pooled. Consensus among the three radiologists was considered the final imaging result. In case of divided evaluations, they reviewed the images jointly and reached a consensus through discussion, consulting additional expertise if necessary. According to this standard, the majority of patients (85.71%) achieved a cured effect after treatment. One patient (4.76%) showed significant improvement in key clinical symptoms and quality of life but was not completely cured, necessitating continued follow-up. During postoperative follow-up, two patients relapsed at 3 and 6 months post-surgery, respectively. Despite embolization providing long-term effects for most patients, some may experience recanalization or incomplete thrombosis, requiring consideration of long-term follow-up and assessment in treatment planning (Table 2).

3.7 Complications

We conducted follow-ups at 1 month, 3 months, 6 months, and 1 year post-procedure. Postoperative complications primarily included swelling, with some patients experiencing lumps, scabbing, or hair loss. Only 9.52% (2/21) of patients had no obvious complications post-embolization, indicating that while interventional treatment effectively controls scalp AVF, it carries certain risks. Common issues such as postoperative swelling and lumps may result from local reactions and blood flow changes, while scabbing and hair loss may relate to skin damage in the operation area (Table 2).

4 Discussion

Scalp arteriovenous malformations (AVMs) are abnormal arteriovenous communications located within the subcutaneous fat layer of the scalp, forming a complex network of abnormal vessels and representing a rare and complex vascular disorder (13). There are two types of scalp AVFs: congenital and acquired. Congenital scalp AVF, also known as arteriovenous malformation, forms during early embryonic differentiation, with limited development leading to direct arteriovenous communication. This results in immature arteriovenous malformation with intertwined and dilated vessels, commonly located in the head and neck (14). Acquired scalp AVF often results from trauma or local piercing history (15, 16). In our study, eight congenital scalp AVM patients exhibited symptoms during adolescence, while the remaining nine showed symptoms in adulthood. Additionally, four cases (19%) developed secondary to scalp trauma.

Surgical resection is the classic treatment for scalp AVF (5), particularly indicated for bleeding prevention, cosmetic concerns,

and accompanying tinnitus and headache (7, 17). However, due to the difficulty of complete surgical eradication and frequent recurrence or progression, surgical treatment alone has become less common (6, 18, 19). With advancements in interventional radiology and interventional neuroradiology, endovascular embolization plays an increasingly important role in AVF treatment (10–12). Vascular embolization reduces or eliminates AVF blood supply by introducing embolic materials into abnormal vessels to block blood flow, reducing rupture risk and improving symptoms (20). Conventional embolic materials include metallic coils, calibrated microspheres, and bioglue (21). Due to the complexity of scalp AVF, selecting appropriate access and embolization materials is crucial.

The scalp's rich network of collateral vessels means that occluding major malformation nidus may not be sufficient, as blood may re-enter the diseased area through other routes. Therefore, treatment often involves venous embolization or blocking to directly address abnormal blood flow. In some cases, local direct puncture and precise embolization may be necessary, combining approaches to achieve optimal results (22–24). Half of the patients underwent embolization through two or more access routes. When it comes to the choice of embolic materials, liquid agents such as NBCA and Onyx polymerize and solidify quickly upon contact with blood, forming durable emboli that effectively occlude abnormal vessels. However, there remains a risk of recanalization over time (25). Particulate agents like polyvinyl alcohol (PVA) particles are capable of embolizing smaller vessels but may not completely block blood flow and carry the potential to migrate downstream with the blood flow (26). In recent years, the safety of absolute ethanol has been increasingly recognized. It causes direct damage to vascular endothelial cells and induces protein denaturation, leading to rapid and permanent vessel closure, making it an effective choice for treating arteriovenous malformations (AVMs) with minimal risk of recanalization (27–31). Dosage control is essential to prevent excessive embolization and tissue damage. High blood flow AVF may require combined embolization materials (e.g., coils) to physically reduce flow and enhance contact with embolic agents, preventing postoperative complications (32, 33).

4.1 Influence of approach and method

4.1.1 Arterial approach

Directly accessing the lesion core (Nidus) through the arterial route can be challenging due to arterial tortuosity and narrowing, resulting in a lower success rate and difficulty in achieving complete dense embolization (Figures 2A,B).

4.1.2 Venous reverse approach

Higher success rate due to relatively flat veins, but requires spanning multiple vascular branches, necessitating high skill and experience (Figures 2C,D). The thin walls of veins require caution to prevent rupture and other complications.

4.1.3 Direct puncture approach

Offers direct and convenient access but is challenging for finer venous drainage, with higher risk during catheter insertion and coil placement (Figures 2E,F). Consideration of vascular condition and risk–benefit balance is crucial (34).

4.1.4 Local compression and suture

Effective for small draining veins, providing temporary flow restriction but not long-lasting and may involve high radiation exposure (Figures 2G,H). Efficacy and potential risks must be weighed.

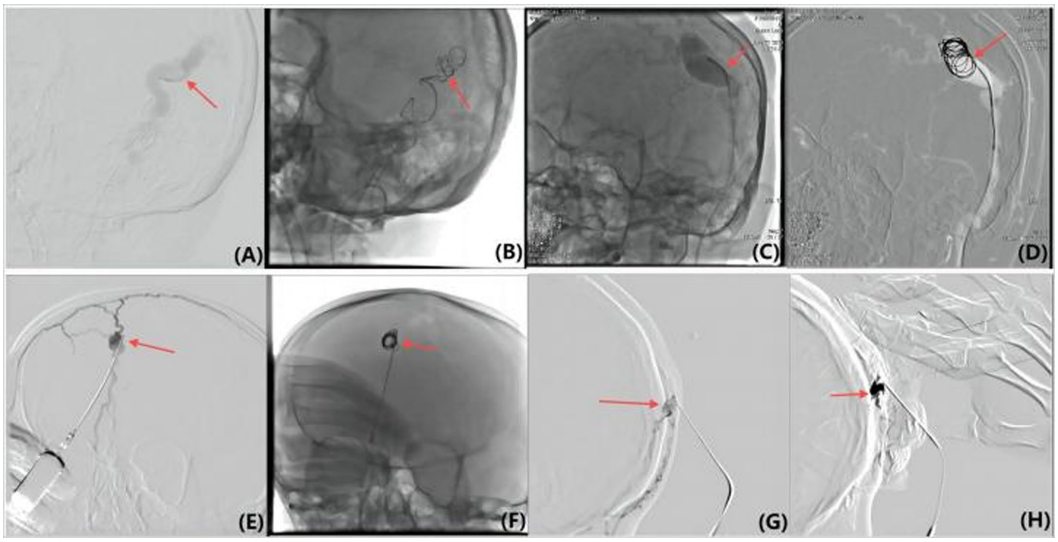

FIGURE 2
(A,B) Various methods were used to achieve flow control in the lesion, including arterial superselection into Nidus and coil insertion (C,D), reverse superselection through the external jugular vein and coil insertion (E,F), local lesion puncture and micro catheter implantation of the coil (G,H), and assisting finger compression to block the draining vein and reduce flow velocity.

4.2 Complications

4.2.1 Facial edema

Common during recovery, related to the distribution of draining veins from AVF. Postoperative swelling is often more pronounced on the affected side, particularly around the eyes. Acute swelling typically lasts about a week, with complete resolution taking 4–6 weeks. Semi-recumbent positioning and medications like Seven Ye Zao glycosides, flavonoids, and traditional Chinese medicine can help reduce swelling. The amount of absolute ethanol used also correlates with swelling severity. For patients experiencing postoperative swelling, it generally subsides on its own. The specific recovery time varies depending on individual differences, but most patients show noticeable reduction in swelling within 2 weeks.

4.2.2 Epidermal necrosis, scab, and scar

Closely related to factors like the degree of venous blockage, arterial reflux observed during local puncture angiography, the amount of absolute ethanol, and injection speed. Excessive ethanol can cause severe local reactions and extensive scarring. Complications occur from inadvertent non-target arterial embolization and occlusion of normal capillary beds supplying normal tissues. AVMs/AVFs supply NO tissues therefore occluding them causes no tissue injury issues. Despite not supplying tissues, extensive outflow vein occlusions can lead to venous injury/infarction, particularly in the skin/dermis. Four patients experienced post-procedural hair loss. While hair loss was not fully reversible in all cases, patients with unresolved localized hair loss managed it by changing hairstyles, undergoing hair transplants, or using wigs. Despite the hair loss, it did not significantly impact their quality of life. Three patients experienced scabbing post-procedure. The scabs required minimal intervention and resolved naturally as the wounds healed and the scabs fell off, allowing patients to return to normal life.

4.2.3 Coil occupancy and exposure

Correct placement of coils is crucial to blocking blood flow and minimizing risks. Improper placement can cause coil migration, partial blockage, or recanalization, while exposed coils can lead to vascular injury, infection, and thrombosis.

Congenital scalp AVM and acquired AVF may become difficult to distinguish on imaging angiography as the disease progresses. Both conditions involve abnormal arteriovenous connections, but their clinical presentation and treatment strategies can differ. AVMs may exhibit a more complex Nidus, while AVFs typically have a direct arteriovenous connection. Local skin erythema, often developing into pulsatile masses with bleeding, is common. Venous hypertension caused by AVFs leads to vein expansion and appearance distortion, with symptoms like tinnitus, headaches, and scalp ulceration. Trauma, partial excision, arterial blockage, and endocrine changes can cause rapid progression.

Coils combined with absolute ethanol effectively treat scalp AVF, reducing blood flow. However, complications are related to ethanol amount, injection route, and speed. Accurate calculation and control are essential to prevent treatment failure and complications. Detailed angiography ensures precise ethanol delivery. Injection speed must be controlled to avoid tissue damage and maximize embolization efficacy.

5 Conclusion

This study demonstrates that interventional embolization is an effective and relatively safe method for treating scalp AVF. Despite short-term complication risks, correct embolization material and technique choices can significantly improve treatment success and safety. Future research should optimize these treatments to enhance efficacy and patient quality of life.

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 humans were approved by Biomedical Research Ethic Committee of Shandong Provincial Hospital (SWYX:NO.2024-457). The studies were conducted in accordance with the local legislation and institutional requirements. Due to the retrospective nature of the study, the Biomedical Research Ethic Committee waived the requirement for written informed consent from the participants.

Author contributions

WH: Writing – original draft. KY: Writing – review & editing. WG: Data curation, Writing – original draft. XW: Writing – review & editing. RH: Conceptualization, Writing – review & editing. LX: Conceptualization, Writing – review & editing.

Funding

The author(s) declare that financial support was received for the research, authorship, and/or publication of this article. This study was supported by the National Natural Science Foundation of China (82372537).

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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frontiers | Frontiers in Cardiovascular Medicine

TYPE Brief Research Report
PUBLISHED 20 November 2024
DOI 10.3389/fcvm.2024.1439839

OPEN ACCESS

EDITED BY
Paul B. Yu,
Massachusetts General Hospital and Harvard Medical School, United States

REVIEWED BY
Xiaobing Liu,
Shanghai Jiao Tong University, China
Wayne Yakes,
The Yakes Vascular Malformation Center, United States
Chung Sim Lim,
Royal Free London NHS Foundation Trust, United Kingdom

*CORRESPONDENCE
Qingyang Li
✉ 18916111970@189.cn

†These authors have contributed equally to this work

RECEIVED 28 May 2024
ACCEPTED 24 October 2024
PUBLISHED 20 November 2024

CITATION
Su L, Zhao Y, Shen Y, Fan X, Wang Z, Wang D and Li Q (2024) Salvage of cardiopulmonary collapse caused by ethanol sclerotherapy for vascular malformations: clinical experience at a single center and literature review.
Front. Cardiovasc. Med. 11:1439839.
doi: 10.3389/fcvm.2024.1439839

Salvage of cardiopulmonary collapse caused by ethanol sclerotherapy for vascular malformations: clinical experience at a single center and literature review

Lixin Su[1,2†], Yan Zhao[3†], Yuchen Shen[2], Xindong Fan[2], Zhenfeng Wang[2], Deming Wang[2] and Qingyang Li[3*]

[1]Department of Vascular Anomaly, Fengcheng Hospital of Fengxian District, Shanghai, China, [2]Department of Interventional Therapy, Multidisciplinary Team of Vascular Anomalies, Shanghai Ninth People's Hospital, Shanghai Jiao Tong University, Shanghai, China, [3]Department of Anesthesiology, Fengcheng Hospital of Fengxian District, Shanghai, China

Objective: This review aims to summarize the salvage experience of cardiopulmonary collapse occurring as a result of absolute ethanol sclerotherapy for vascular malformations.

Methods: In total, we reviewed three cases of cardiopulmonary collapse induced by ethanol sclerotherapy for vascular malformations and described the details of the salvage procedure. Saturation of pulse oxygen (SpO_2), end-tidal CO_2, and invasive arterial pressure were the routine monitors for ethanol injection patients. Cardiopulmonary resuscitation, epinephrine, norepinephrine, and deoxyepinephrine were mainly used to correct circulation parameters. Manually ventilated via endotracheal intubation with 100% O_2, increased respiratory rate were mainly used to correct Respiratory parameters.

Results: All three cases were successfully salvaged without major complications. When cardiopulmonary collapse occurred, manual ventilation via endotracheal intubation with 100% O_2, increased ventilation frequency and external cardiac compression were the emergency treatments. Epinephrine, norepinephrine, deoxyepinephrine infusion solely or combined were crucial to maintaining the basic vital signs.

Conclusion: Despite the severity of cardiopulmonary collapse caused by ethanol sclerotherapy, it can be detected by close observation and reversed with timely treatment.

KEYWORDS

cardiopulmonary collapse, ethanol, vascular malformations, sclerotherapy, emergency

Introduction

Vascular malformations are clinically problematic and often difficult lesions to treat. They display unique heterogeneous manifestations and can occur anywhere in the body. In the past decades, embolotherapy has been a mainstay of treatment, with many clinical studies demonstrating its varying degrees of efficacy. Nonetheless, although methods and materials for sclerotherapy are extensively varied and heavily studied, there is no clear consensus on the suitable embolic agents for various malformations

(1–3). Yakes et al. first described the use of ethanol in malformation sclerotherapy in 1986 (4). Since then, ethanol has been increasingly used in high flows (AVMs) and lower flow venous, capillary, and lymphatic malformations (5).

Despite its high efficacy, ethanol is an extremely dangerous intravascular sclerotherapy agent, causing significant complications if it enters the systemic circulation. Ethanol sclerotherapy induces minor local complications including skin blistering, ulcerations, scar formation, and local nerve damage. Moreover, it may cause cardiopulmonary complications such as pulmonary embolism, pulmonary hypertension, and cardiac arrhythmias that potentially trigger cardiovascular collapse or even death (6–9). Thus, radiologists and anesthetists must be aware of the severity potential of these cardiopulmonary complications triggered by ethanol sclerotherapy, hence must be prepared to manage. Herein, we review three cases of cardiopulmonary collapse induced by ethanol sclerotherapy for vascular malformations and its periprocedural management.

Patients

The present work was approved by the Institutional Review Board of Shanghai Ninth People's Hospital, Shanghai Jiaotong University School of Medicine [No. SH9H-2019-T309-2]; All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Informed consent was obtained from all individual participants included in the study. Consent for publication was obtained for every individual person's data included in the study.

Case 1

A 32-year-old female patient with a height of 166 cm and weight of 58 kg was admitted to undergo ethanol sclerotherapy for a large venous malformation in the left waist. All preoperative examinations, laboratory tests, electrocardiography, and chest x-ray were normal. General anesthesia was intravenously induced using a bolus injection of 120 mg propofol and 40 mg rocuronium. Endotracheal intubation was inserted without difficulty and the patient was maintained using machine-controlled ventilation (tidal volume 300 ml, ventilation frequency 16 times per minute) on 68% nitrous oxide in oxygen with isoflurane at end-tidal concentrations of 1%–1.5%. Also, she was intravenously administered with 8 mg of atracurium benzenesulfonate. We applied routine patient monitors, including pulse oxygen saturation (SpO_2), three-lead electrocardiogram (ECG), end-tidal CO_2, and invasive arterial pressure. After venography from direct puncture, absolute ethanol injection was routinely performed (10). Immediately after ethanol injection, the blood pressure and heart rate of the patient slightly increased to 135/90 mmHg and 90 beats/min, respectively. Thereafter, blood pressure and heart rate became stable throughout the procedure. A 22 ml dose of 99.7% ethanol was injected into the lesion for over 15 min. Consequently, we noted an abrupt decrease in her invasive arterial pressure; 50–55 mmHg systolic and 20–22 mmHg diastolic blood pressure with a simultaneous decrease of heart rate to 35–38 beats/min; end-tidal CO_2 decrease to 19–21 mmHg; SpO_2 decrease to 55%. Within 60 s of onset, peripheral pulses were lost and invasive arterial pressure failed to yield a measurement. The ECG (lead II) showed that the heart rate first becomes slightly fast and then slows down, followed by severe sinus bradycardia with escape rhythm, and finally ventricular fibrillation until cardiac arrest. The anesthetic agents were discontinued then the oxygen concentration in ventilation was increased to under 100% and manually ventilated via endotracheal intubation 30 times per minute. External cardiac compression was started with resultant palpable femoral pulsation. Epinephrine 1 mg was given intravenously and chest compression continued for 3 min before the pulses were restored. Blood pressure increased to 50/30 mmHg, SpO_2 to 65%, heart rate to 55 beats/min. Subsequently, norepinephrine infusion was administered at 20 μg/2 min and repeated twice; as a result, blood pressure increased to 75/45 mmHg; SpO_2 to 86%; heart rate to 135 beats/min. Deoxyepinephrine infusion was administered at 10 μg/2 min and repeated twice; consequently, blood pressure increased to 93/55 mmHg; SpO_2 to 96%; heart rate decreased to 82 beats/min. After 50 min in the operating theater, the patient regained consciousness, began to spontaneously breathe, and obeyed commands. After removing the endotracheal tube, the patient was transferred to the intensive care unit. Echocardiography follow-up during the next day showed a normal heart with efficient biventricular function. After 3 days of observation, the patient completely recovered and was discharged.

Case 2

A 28-year-old male patient with a height of 175 cm and weight of 68 kg was admitted to undergo ethanol sclerotherapy for venous malformation in the left back. Preoperative examinations, including endotracheal intubation, general anesthesia, absolute ethanol injection was routinely performed.

The cardiopulmonary collapse occurred in a total dose of 25 ml of 99.7% ethanol was injected into the lesion over 20 min. We observed an abrupt decrease in her invasive arterial pressure, 50–60 mmHg systolic and 18–20 mmHg diastolic blood pressure with a simultaneous decrease in her heart rate to 22–36 beats/min, end-tidal CO_2 decrease to 20–23 mmHg, and SpO_2 decrease to 56%. The anesthetic agents were discontinued then under and manually ventilated via endotracheal intubation with 100% O_2 at 30 times per minute. Norepinephrine infusion was administered at 20 μg/2 min and repeated twice; consequently, the blood pressure increased to 94/65 mmHg, SpO_2 to 92%, and heart rate to 125 beats/min. Then, deoxyepinephrine infusion was administered at 10 μg/2 min and repeated once; consequently, blood pressure increased to 105/68 mmHg, SpO_2 to 98%, while heart rate decreased to 82 beats/min. After 35 min in the

operating theater, the patient regained consciousness, began to spontaneously breathe, and obeyed commands. The endotracheal tube was removed and the patient completely recovered.

Case 3

A 12-year-old female patient with a height of 152 cm and weight of 46 kg was admitted to undergo ethanol sclerotherapy for venous malformation in the lateral chest. Endotracheal intubation general anesthesia and absolute ethanol injection were routinely performed.

The cardiopulmonary collapse occurred in a total dose of 20 ml of 99.7% ethanol was injected into the lesion over 18 min. We observed an abrupt decrease in her invasive arterial pressure, 45–52 mmHg systolic and 16–20 mmHg diastolic blood pressure with a simultaneous decrease in her heart rate to 25–35 beats/min, end-tidal CO_2 decrease to 20–22 mmHg, and SpO_2 decrease to 55%. The anesthetic agents were discontinued then the patient was manually ventilated via endotracheal intubation with 100% O_2, 25 times per minute. Norepinephrine infusion was administered at 6 μg; consequently, blood pressure increased to 100/70 mmHg, SpO_2 to 91%, heart rate to 145 beats/min. Deoxyepinephrine infusion was administered at 6 μg/2 min and repeated once; consequently, blood pressure increased to 115/75 mmHg, SpO_2 to 96%, whereas heart rate decreased to 75 beats/min. After 45 min in the operating theater, the patient regained consciousness, began to spontaneously breathe, and obeyed commands. The endotracheal tube was removed and the patient completely recovered.

Clinical outcomes

All three cases were successfully salvaged without major complications. When cardiopulmonary collapse occurred, manual ventilation via endotracheal intubation with 100% O_2, increased ventilation frequency and external cardiac compression were the emergency treatments. Epinephrine, norepinephrine, deoxyepinephrine infusion solely or combined were crucial to maintaining the basic vital signs. The clinical data and results of 3 Patients with cardiopulmonary collapse were summarized in Table 1. The steps in salvage of cardiopulmonary collapse induced by ethanol sclerotherapy for vascular malformations was described in Figure 1.

Discussion

Numerous sclerosants have been developed for the treatment of vascular malformations. Among these, absolute ethanol is preferred to other embolic agents due to its relatively desired outcomes and minimal rate of recanalization. The injected ethanol in vascular malformations causes direct tissue toxicity leading to endothelial damage, severe vascular spasm, proteins denudation. Despite its benefits, ethanol sclerotherapy often produces minor local complications, such as tissue necrosis, peripheral nerve injuries, skin blistering, and ulcers. Besides, if absorbed into the systemic circulation, although rare, ethanol may cause fatal complications, including pulmonary embolism and pulmonary vasospasm. Because of changes in the cardiac conduction system, these complications may trigger right heart failure, cardiac arrhythmias, and even death in severe cases (7–9, 11, 12).

Systemic contamination with ethanol occurring during percutaneous sclerotherapy is directly related to the dose injected and independent of the vascular malformation morphology, venous drainage, or injection technique (13, 14). Theoretically, with the fast flow rate of arteriovenous malformations, absolute ethanol enters the systemic circulation more easily through the fistula compared to that of venous malformations, thereby increasing the incidence of cardiopulmonary accidents. This phenomenon has not been reported in clinical practice. All three cases in this work were venous malformations. The reasons were speculated as follows: First, doctors were more cautious about the speed of absolute ethanol injection in the treatment of arteriovenous malformations due to its high flow characters. Secondly, dominant outflow vein embolization with coils or compression was often used to control the flow speed of arteriovenous malformations. The rate of absolute ethanol entering the systemic circulation was highly decreased. Thirdly, doctors experienced in using absolute ethanol to treat vascular malformations should observe the fast flow rate of arteriovenous malformations. Absolute ethanol is more likely to be washed into the systemic circulation and diluted during the injection of absolute ethanol into arteriovenous malformations. it is not as easy to produce coagulation and hemolysis when treated venous malformations. Thus, micro-thrombosis and hemolysis may have less stimulation to pulmonary vessels.

Although the theory of pulmonary hypertension is not fully clear, acute pulmonary hypertension causes cardiopulmonary collapse. Based on previous studies, ethanol injection induces severe pulmonary vasospasm, acutely increases thin-walled right ventricular afterload, and decreases the right ventricular cardiac output. Besides, these effects can be further aggravated by systemic effects of alcohol affecting right atrial and ventricular contractility, including chronotropic and inotropic functions (15, 16). Pulmonary emboli due to ethanol-induced thrombosis may have also contributed but appeared less likely considering the rapid response of the patient to resuscitation. Ethanol and blood interaction produces embolic debris comprising denatured protein and cellular fragments described as “Sludge” by Yata (17). The thrombus produced by absolute ethanol injection is mostly micro-embolism, which will not produce pulmonary embolism as severe as deep venous thrombosis of the lower extremity. Nevertheless, the influence of micro-embolism may be cumulative. This may be the reason there is a dose limit in ethanol injection therapy.

Furthermore, ethanol-induced hemolysis releases erythrocyte arginase, which hydrolyses L-arginine to L-ornithine. Notably, L-Arginine is the precursor for nitric oxide (NO) production via NO synthase in the vascular endothelium. The combination of decreased production and increased inactivation of NO tips the vascular balance toward vasoconstriction (18). Kielstein et al.

10.3389/fcvm.2024.1439839

TABLE 1 Clinical data and results of salvage of 3 patients with cardiopulmonary collapse.

Patient No.	Sex	Age (year)	Height (cm)	Weight (Kg)	Ethanol (ml)	Cardiac arrest	Epinephrine	Norepinephrine	Deoxyepinephrine	Recover time (min)	Complications
1	Female	32	166	58	22	Yes	1.0 mg	20 μ g/2 min × 3	10 μg/2 min × 3	50	No
2	Male	28	175	68	25	No	No	20 μg/2 min × 3	10 μ g/2 min × 2	35	No
3	Female	12	152	46	20	No	No	12 μg × 1	8 μg/2 min × 2	45	No

investigated the relationship between percutaneous ethanol injection, pulmonary hypertension, and markers of altered NO metabolism. Specifically, ethanol, free hemoglobin, plasma nitrite, and L-arginine levels were analyzed before and after percutaneous ethanol injection treatment (19). NO is effective in both primary pulmonary hypertension and secondary pulmonary hypertension (SPH), of which ethanol-induced type is SPH (20). In Case #1, our anesthesiologist used 68% NO. The use of NO in anesthesia uses the secondary gas effect to increase the alveolar concentration of inhaled anesthetics and thus deepen the depth of anesthesia as quickly as possible. At the same time, NO can dilate pulmonary vessels and reduce pulmonary vascular resistance, so as to reduce pulmonary artery pressure, but has no effect on systemic pressure. However, if the concentration of NO in the inhaled gas is too high, it may lead to insufficient oxygen inhalation resulting in hypoxia, so the concentration of NO used clinically does not exceed 60%–70%. When rescuing patients, NO inhalation will be stopped, and 100% oxygen inhalation will be changed to improve the inhaled oxygen concentration and increase oxygen supply.

NO has little to zero effect on the peripheral vasculature and is very pulmonary specific so is the perfect agent in that cardiopulmonary collapse critical clinical situation and is administered quickly to act through the in-dwelling endotracheal tube.

In cardiopulmonary collapse the circulation is very sluggish (and may have zero cardiac output) and the circulatory system is severely compromised due to the significantly decreased left-heart filling and right heart overload. Also it could be stated that if any IV drugs are considered for vasodilation, the immediate placement of a catheter in the main Pulmonary Artery (PA) to administer drugs IV into the lungs would then facilitate drug placement to get where it was needed more expeditiously. However, placing a catheter in the main PA does take time to do and is a delay, whereas endotracheal NO is immediate without any additional catheter procedures. Further, placing a catheter in the main pulmonary artery can aggravate the cardiac conduction system and invoke an aggravating arrhythmia further complicating and adversely affecting this already critical situation.

Ethanol injection procedures are performed when the patient is intubated and under general anesthesia for numerous reasons, including severe pain during injection, the need for cessation of respiration during angiographic sequences, and the possibility of cardiovascular decompensation. Also, alcohol severely affects the heart. Studies have reported cardiopulmonary collapse among adults during ethanol sclerotherapy presumably related to the suppression of the myocardial conduction system with precapillary vasoconstriction and resultant elevation in pulmonary arterial pressures (21–24). In the present three cases, we observed an increase in airway resistance, a decrease in blood SpO_2, and an increase in end-tidal carbon dioxide during the early stages of cardiopulmonary collapse. This implies that pulmonary factors may cause impairment of cardiopulmonary circulation. The proposed physiologic sequence for cardiovascular collapse as following steps: (1) A bolus of ethanol flows into the pulmonary vasculature. (2) If enough of a bolus, it causes diffuse

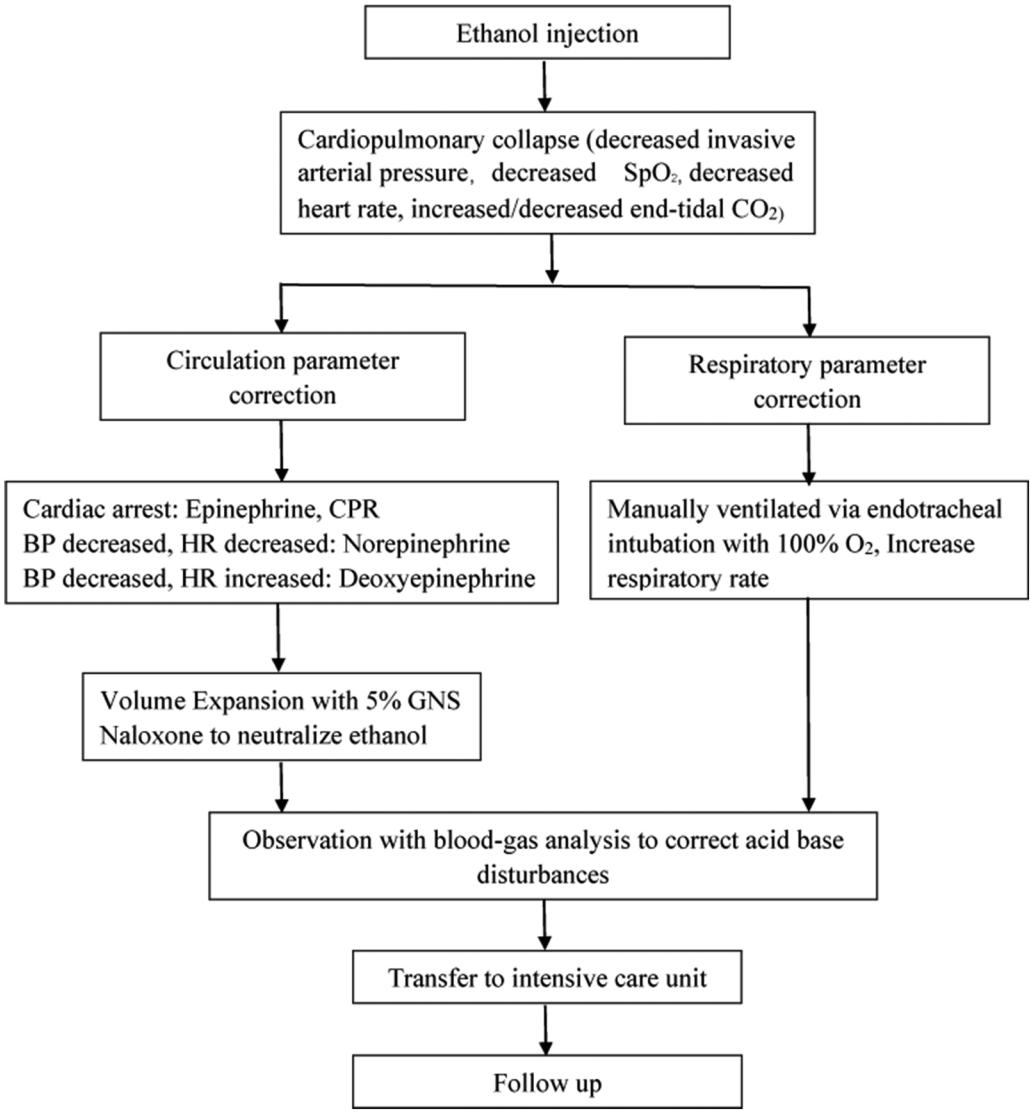

FIGURE 1
Steps in salvage of cardiopulmonary collapse induced by ethanol sclerotherapy for vascular malformations.

severe pulmonary artery spasm. (3) This then restricts right heart outflow to the left heart, leading to right heart overload, then right heart failure. (4) This then results in decreased left heart filling with oxygenated blood, leading to blood pressure dropping. (5) Significantly decreased left heart filling and collapsing blood pressure, leads to coronary artery hypoperfusion, then cardiac ischemia, and then resultant arrhythmias, usually Electro-Mechanical Dissociation (EMD) which is organized electrical depolarization of the heart without synchronous myocardial fiber shortening (no myocardial contractures), and then there is no cardiac output. A similar phenomenon was also reported by Naik (6).

Invasive arterial pressure monitor provides accurate, reliable, and continuous arterial pressure value, and establishes the status of the blood volume or the heart. The slight increase in blood pressure among patients during ethanol sclerotherapy related to pain caused by sympathetic stimulation, even when patients are under general anesthesia. For the prevention of cardiopulmonary accidents, the observation of the decrease of invasive arterial pressure has more clinical significance. A rapid decrease in blood pressure indicates the possibility of cardiopulmonary impairment. This should be timely corrected to avoid cardiac arrest accompanied by a further decrease in blood pressure.

In the ethanol injection cases monitored using the Swan-Ganz catheter, nimodipine is administered once the pulmonary artery pressure has increased. This can quickly relieve the pulmonary artery pressure (25). Due to the high cost and the technique reason, Swan-Ganz catheter was not regularly be used by absolute ethanol sclerotherapy, especially for low flow vascular malformation. In our study, the three patients had a significant decrease in blood SpO_2, peripheral blood pressure, and heart rate. Thus, the mechanisms of immediately improving the

ventilation exchange function and maintaining the stability of basic vital signs are vital for cardiopulmonary resuscitation. Absolute ethanol injection was immediately stopped once blood SpO_2 decreases and airway resistance increases. It should be noted that patients can be apneic during general anesthesia and minutes can pass before O_2 levels drop. The critical factor to monitor is CO_2 levels which are the very first to drop way before O_2 levels drop. CO_2 level is the first measurable parameter to drop physiologically because it measures the oxygen-carbon dioxide exchange at the alveolus and capillaries. O_2 goes into the red blood cells to oxygenate the blood. CO_2 is excreted into the alveolus and exhaled. The CO_2 monitor reveals the CO_2 level excreted. If there is no oxygen exchange occurring at the alveolus, there is no CO_2 released for excretion and for measurement. Thus, once CO_2 levels begin to fall, action must be taken then, not when O_2 levels later drop which may be harder to correct. Besides, the anesthetic agents were discontinued and the patient was placed under 100% O_2 and manually ventilated via endotracheal intubation to prevent further deterioration of cardiopulmonary impairment. Laryngeal Mask Airway was not recommended for general anesthesia for ethanol injection, which could not provide sufficient pressure when necessary.

Several types of drugs are used to increase blood pressure, including epinephrine, norepinephrine, deoxyepinephrine, dopamine, etc. Each drug has a different pharmacological effect and mechanism thus, requiring the guidance of professional anesthesiologists and physicians. Epinephrine is primarily used for the treatment of patients with acute allergy and cardiac arrest. On the other hand, norepinephrine is majorly used for the emergency treatment of patients with severe blood pressure reduction and heart rate reduction. Deoxyepinephrine is primarily used to raise blood pressure. Unlike norepinephrine, the effect of deoxyepinephrine in increasing heart rate is softer and used for blood pressure maintenance after the recovery of basic vital signs. A reasonable combination of various pressure-raising drugs to maintain the basic vital signs was crucial to the successful management of cardiopulmonary accidents caused by absolute ethanol sclerotherapy.

Conclusion

In conclusion, we reported three patients successfully salvaged from cardiovascular collapse potentially attributed to ethanol sclerotherapy. Despite its severity, the resulting complications can be reversed with timely treatment, which indicated our salvage techniques were effective in the adult and pediatric age groups. We recommend that anesthetists should continuously focus on the changes of airway pressure, SpO_2, tidal carbon dioxide, and invasive arterial pressure during the procedure and in the recovery room to prevent severe cardiovascular complications.

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 humans were approved by IRB of Shanghai Ninth People's Hospital. The studies were conducted in accordance with the local legislation and institutional requirements. The 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

LS: Conceptualization, Data curation, Investigation, Methodology, Writing – original draft, Writing – review & editing. YZ: Formal Analysis, Investigation, Resources, Writing – original draft. YS: Writing – review & editing. XF: Project administration, Supervision, Writing – review & editing. ZW: Validation, Visualization, Writing – review & editing. DW: Data curation, Methodology, Software, Writing – review & editing. QL: Conceptualization, Investigation, Methodology, Resources, Validation, Writing – review & editing.

Funding

The author(s) declare financial support was received for the research, authorship, and/or publication of this article. This study was supported by the Health Clinical Research Project of Shanghai Municipal Health Commission [No. 202140425].

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.

The reviewer XL declared a shared affiliation with the author(s) to the handling editor at the time of review.

Publisher's note

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frontiers | Frontiers in Neurology

TYPE Review
PUBLISHED 02 December 2024
DOI 10.3389/fneur.2024.1493873

OPEN ACCESS

EDITED BY
Deming Wang,
Shanghai Jiao Tong University, China

REVIEWED BY
Csaba Juhasz,
Wayne State University, United States
Anuruddha Padeniya,
Lady Ridgeway Hospital for Children,
Sri Lanka

*CORRESPONDENCE
Anne Comi
✉ comi@kennedykrieger.org

RECEIVED 09 September 2024
ACCEPTED 06 November 2024
PUBLISHED 02 December 2024

CITATION
Solomon C and Comi A (2024) Sturge–Weber syndrome: updates in translational neurology. *Front. Neurol.* 15:1493873.
doi: 10.3389/fneur.2024.1493873

Sturge–Weber syndrome: updates in translational neurology

Chase Solomon[1] and Anne Comi[1,2,3]*

[1]Neurology and Developmental Medicine, Kennedy Krieger Institute, Baltimore, MD, United States, [2]Department of Neurology, Johns Hopkins School of Medicine, Baltimore, MD, United States, [3]Department of Pediatrics, Johns Hopkins School of Medicine, Baltimore, MD, United States

Sturge–Weber syndrome (SWS) is a rare congenital neurovascular disorder that initially presents with a facial port-wine birthmark (PWB) and most commonly associated with a R183Q somatic mosaic mutation in the gene *GNAQ*. This mutation is enriched in endothelial cells. Contrast-enhanced magnetic resonance imaging (MRI) diagnoses brain abnormalities including leptomeningeal vascular malformation, an enlarged choroid plexus, and abnormal cortical and subcortical blood vessels. Mouse SWS models identify dysregulated proteins important for abnormal vasculogenesis and blood brain barrier permeability. Recent clinical research has focused on early diagnosis, biomarker development, presymptomatic treatment, and development of novel treatment strategies. Prospective pilot clinical drug trials with cannabidiol (Epidiolex) or with sirolimus, an mTOR inhibitor, indicate possible reductions in seizure frequency and improved cognitive outcome. This review connects the most recent molecular research in SWS cell culture and animal models to developing new treatment methods and identifies future areas of research.

KEYWORDS

Sturge–Weber syndrome, models, blood brain barrier, treatment, seizure, diagnosis

1 Introduction

Sturge–Weber syndrome (SWS) is a rare neurovascular disorder present at birth that is characterized by a facial port-wine birthmark (PWB), abnormal blood vessels in the brain and eyes, including leptomeningeal involvement. Historically, it is categorized with other phakomatoses; disorders in this classification include neurofibromatosis 1, tuberous sclerosis complex, and von Hippel–Lindau Disease (1). These disorders are characterized by cutaneous lesions, neuro-ophthalmic defects, and tumor formation (2, 3); however, it is now known that SWS is pathophysiologically more like other genetic neurovascular disorders, including Cerebral Cavernous Malformation and Hereditary Hemorrhagic Telangiectasia, except that bleeding is not a prominent part of the presentation at least in children. In addition, SWS is not hereditary and rather occurs sporadically during fetal development. The estimated incidence of SWS is 1 in 20,000 to 50,000 live births, with more recent population studies obtaining incidence rates of 0.19 per 100,000 people per year and 3.08 per 100,000 people per year (4, 5). Typical brain abnormalities of SWS patients include cortical and sub-cortical perivascular calcification, impaired venous drainage and perfusion, and brain atrophy of varying degree; tumors are not common. Individuals may present with seizures and stroke or stroke-like episodes; as a result, they can experience both cognitive and neurodevelopmental deficits.

SWS is caused primarily by a c.548G➔A (p. Arg183Gln) somatic mosaic mutation in *GNAQ*, hypothesized to be enriched in endothelial cells (6–8). *GNAQ* codes for the protein Gαq; when expressed in mutant form, Gαq demonstrates impaired deactivation resulting in hyperactivation of downstream pathways, including the Ras–Raf–MEK–ERK (also known as the MAPK/ERK pathway) and the mammalian target of rapamycin (mTOR) pathways (9, 10).

Human SWS brain tissue immunohistochemistry has indicated increased expression of phosphorylated ERK (p-ERK) and decreased expression of CD34 in endothelial cells from abnormal blood vessels in the leptomeninges (11). The presence of the R183Q *GNAQ* mutation in abnormal scleral tissue correlated with increased expression of p-ERK and p-JNK in endothelial cells that line blood vessels (12). When comparing lesioned brain tissue from SWS patients to epilepsy controls, researchers noted a greater likelihood of phosphorylated-S6 staining in the leptomeningeal endothelial cell layer of SWS brain tissue (13). Fibroblasts derived from SWS port-wine birthmark skin showed significantly higher levels of fibronectin gene expression compared to SWS normal skin (14). The R183Q mutation in *GNAQ* has also been identified as the primary mutation within blood vessels of PWBs (15). Upregulated vascular endothelial growth factor (VEGF)-A and VEGF receptor 2 (VEGFR2) are both found in PWB tissue and may contribute to abnormal MAPK/ERK pathway regulation (10, 16). Abnormal protein expression in human tissue and *in vitro* studies suggest that these pathways are targets to study with *in vivo* models and in clinical trials. Mouse models, using the R183Q mutation in *GNAQ,* have recently been developed to investigate abnormal molecular and vascular features of SWS and to promote preclinical drug and gene therapy research. The aim of this review is to highlight the clinical and genetic background of Sturge–Weber syndrome, provide an update on recent advances related to Sturge–Weber syndrome, and identify current gaps and potential future developments in molecular and clinical research.

2 Signs and symptoms

PWBs are commonly found in about 3 in 1,000 births. Only 6% of babies born with a facial PWB also have brain involvement and develop the common neurological deficits of SWS. A PWB on the forehead, temple region or upper eyelid yields a risk of 20 to 50% for disease brain involvement, and when a PWB covers both the upper and lower eyelid, the risk of eye involvement and glaucoma is 50% (17). Figure 1A depicts the typical phenotype of a high risk facial PWB. Figure 1B shows the patient's corresponding T1 post-contrast MRI image, which shows typical SWS leptomeningeal involvement and abnormal blood vessels. Previous research has established a positive correlation between the size of a facial PWB, the degree of SWS brain involvement, and severity of SWS-related neurological outcomes (18). Facial PWB size may be used as a predictor of the extent of neurological disability for an individual with SWS. Analyses of pattern distribution of a facial PWB are useful in determining SWS diagnosis. Commonly seen patterns of PWB include linear, frontotemporal, isolated cheek and canthus, combined linear and cheek, hemifacial, and median; hemifacial and median patterns are strongly associated with an increased risk of SWS (19, 20). Facial PWB often respond well to laser treatment and can safely be initiated in young infants (21).

Elevated eye pressure and glaucoma is seen in 30 to 70% of patients with a PWB that covers both the upper and lower eyelid. Glaucoma can present at birth with eye enlargement (bupthalmus), however increased eye pressure may also develop in infancy or later into adolescence. Because of this, it is suggested that an ophthalmological exam be performed as soon as possible, and that patients be regularly monitored for life. Untreated glaucoma can ultimately result in ischemic ocular injuries and permanent vision loss (22). Treatment includes eye drops, which lower eye pressure, and when unsuccessful, various surgical techniques may be implemented to accomplish this (23–25). Thickening of the choroid and retinal detachment are complications which occur in a subset of patients; treatment of retinal detachment can help recover vision in some of these patients (26).

The most common presenting neurologic symptom for children with SWS are seizures, which are exhibited in 75% of children with SWS within 1 year post-birth and 90% within 2 years post-birth (27). Seizures, in babies and young children, can further impair blood flow to the brain and can accelerate neurological deterioration. Patients with bilateral brain involvement are more susceptible to seizures than patients with unilateral involvement; the age of onset in patients with bilateral involvement also tends to be earlier than those with unilateral involvement (28). 75% of patients with unilateral involvement experience seizures; this increases to 95% for patients with bilateral involvement (28, 29). Seizures are most commonly focal motor seizures with or without impaired consciousness; less commonly seen seizure types include myoclonic epilepsy or infantile spasms (30, 31). It is important for a parent or guardian to be educated on typical seizure semiology in order to recognize the possible ways these children can present with seizures.

Seizures can trigger other symptoms such as stroke-like episodes and migraines. Conversely, migraines have the potential to trigger seizures and stroke-like episodes (22, 32). Status epilepticus is a classification of seizure which either lasts for at least 5 minutes or involves multiple seizures without returning to a base level of consciousness between episodes. It is common for SWS patients and is associated with stroke-like episodes, which can be defined as transient unilateral weakness with or without prior seizure activity (33). Stroke-like episodes may be accompanied by resulting neurologic deficits; these can also be acquired over time without a stroke-like episode or seizure as a trigger (34). Because toddlers and children with SWS are more susceptible to stroke-like episodes from minor head injury, it is advisable for children to avoid contact-heavy recreational activities that involve constant physical use or involvement of the head (22).

Cognitive impairments and deficits are common in SWS patients; these can include learning disabilities, attention problems, or other behavioral deficits. Bilateral brain involvement and an earlier age of onset of seizures both potentially contribute towards severe cognitive impairment (29). One retrospective study suggests that the combination of stroke-like episodes and seizures in SWS patients is a driving factor behind the development of hemiparesis and intellectual disorders as well as an increased risk in developing drug-refractory epilepsy, or DRE (35). See Mesraoua et al. for a comprehensive review on DRE, which is first identified in a patient when they are given two separates, tolerated antiepileptic drug schedules and fail to experience seizure control (36). While DRE presents increasing medical challenges for SWS patients, it has been shown to be attenuated through more aggressive initial therapy (37).

3 Genetics

In 2013, cause of SWS was discovered to be a single nonsynonymous mutation: the c.548G → A (p.Arg183Gln) mutation

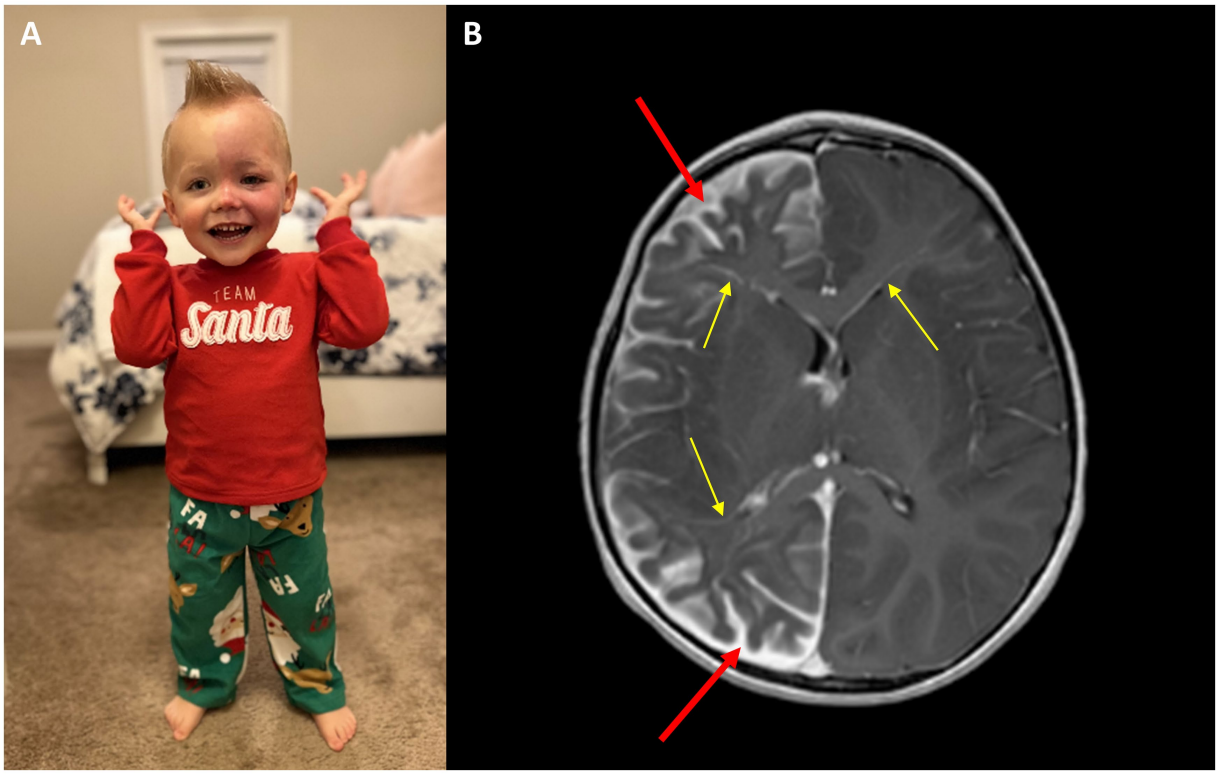

FIGURE 1
(A) Image of a SWS patient with a left facial port-wine birthmark and **(B)** corresponding T1 post-contrast MRI indicating leptomeningeal involvement and abnormal blood vessels, indicated by red arrows. Yellow arrows indicate enlarged deep veins that flow into the cortex.

in the gene *GNAQ* present in roughly 90% of patients (6) in affected brain, skin and eye tissue. The R183Q mutation has also been reported to be enriched in endothelial cells (8). It is hypothesized that this somatic mutation occurs during the early stages of embryonic development (38); however, the exact timing in which the mutation occurs in fetal development may vary and mutations that occur later on into development will have a local effect. Mutations that occur early on likely involve more cell types and have a greater chance to cause disease brain involvement (39).

GNAQ codes for the protein Gαq, which is a component of the trimeric G protein complex and associates with G protein coupled receptors (GPCRs). GPCRs associated with Gαq include glutamate, histamine, angiotensin, and vasopressin receptors and generally impact cellular processes affecting protein activity and phosphorylation regulating cellular proliferation and differentiation (40–43). The R183Q mutation in *GNAQ* results in the hyperactivation of Gαq due to impaired auto-hydrolysis, and thus a decreased rate of dissociation of Gαq from GTP and re-association with GDP. In the case of R183Q in *GNAQ*, hyperactive Gαq leads to hyperactivation of downstream pathways in endothelial cells, resulting in capillary malformations (7). Downstream hyperactive pathways such as the Ras–Raf–MEK–ERK pathway and the mTOR pathway are shown in Figure 2. The abnormal regulation of such pathways and their role in vascular malformation in SWS is highlighted in previous studies and a focus of studies currently taking place (8, 11).

While the R183Q *GNAQ* mutation is found most commonly in SWS patients, other somatic and germ line mutations have been reported to induce SWS brain involvement. *GNA11* is a paralogue gene of *GNAQ*; mutations of *GNA11* have been reported in individuals with SWS in two separate studies (44, 45). Hyperpigmentation is commonly seen in *GNA11*-related SWS cases, while SWS patients with the *GNAQ* mutation, are more likely to experience significant hemispheric brain atrophy and have seizures (46). The aforementioned differences between individuals with SWS with the R183Q *GNAQ* and the R183C *GNA11* mutation are important to consider in developing future treatment applications. Another study reported a novel somatic mutation (p.K78E) in the gene *GNB2*, which encodes for the β subunit of the G-protein complex in a skin biopsy from a patient with SWS. The mutation, which occurs via the substitution of lysine to glutamic acid results in the loss of the cationic ammonium from Lys78 and disrupts the salt bridge. The loss of an ammonium creates a charge repulsion and impairs the binding affinity of the β subunit to the α subunit. Functional studies with cells with the *GNB2* mutation demonstrated no downstream effect on MAPK signaling. However, both the *GNB2* and R183Q *GNAQ* mutation have direct influence on Yes-associated protein (YAP) expression, as endothelial cell YAP is reduced in both cases (47). The similarities in YAP expression between the *GNB2* and *GNAQ* mutation suggest that YAP expression levels through the Hippo pathway may play a role in the pathogenesis of SWS, although further evidence of this is needed.

Recent research suggests that genetic testing should be performed when atypical features are present in an individual with a facial port-wine birthmark (48). Other somatic variants in individuals with atypical features of SWS include G48V in *GNAQ*, R183C in *GNA11*, M1043I in *PIK3CA*, and a mosaic deletion involving *PTPRD* and *PTPRD-AS2*. Germ line mutations were detected in the *RASA1*, *EPHB4*, and *KIT*

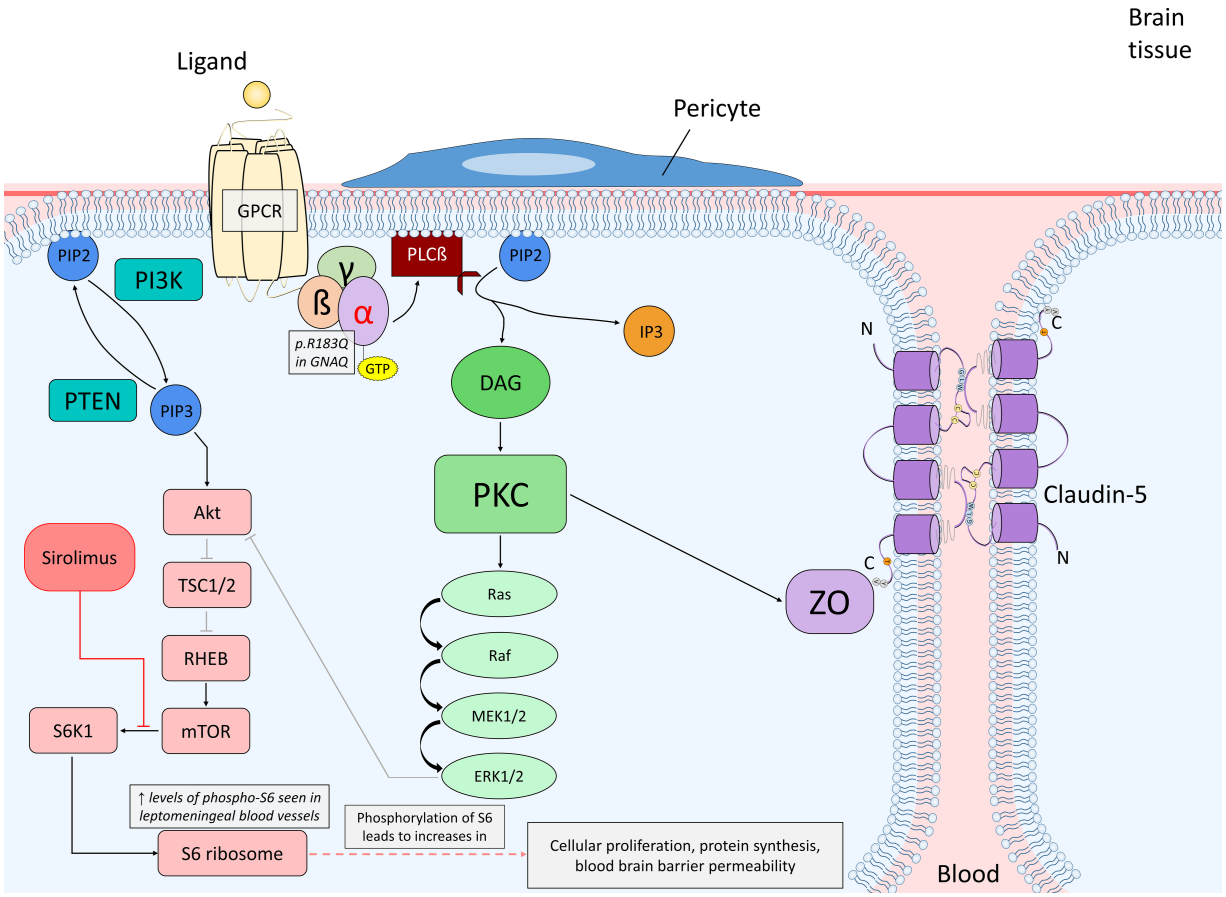

FIGURE 2
Diagram of endothelial cell mutant Gαq signaling (p.R183Q in *GNAQ*) and the primary affected downstream pathways, the Ras–Raf–MEK–ERK and mTOR pathways, within the context of the blood brain barrier. The alpha subunit becomes active when bound to GTP, which promotes PLCß to cleave PIP_2 into DAG and IP_3. DAG is able to activate PKC, which can then phosphorylate a variety of proteins. In this case, PKC can initiate the activation of the Ras–Raf–MEK–ERK pathway or phosphorylate ZO, which interacts with claudin-5 to maintain the integrity of endothelial tight junctions. ERK may stimulate cellular proliferation or also play a role in PI3K/Akt inhibition. PIP_2 may also be converted into PIP_3 by PI3K; PTEN dephosphorylates PIP_3 back to PIP_2. PIP_3 activates the Akt signaling pathway once bound to Akt, which can inhibit TSC1/2 via phosphorylation. TSC1/2 are negative regulators of mTOR due to their inhibitory mechanism on RHEB, an activator of mTOR. The inhibition of TSC1/2 by Akt allows for RHEB to activate mTOR. Proper expression of mTOR activates S6K1, which then phosphorylates the 40S ribosomal subunit S6 protein (phosphorylated-S6). Increased levels of phosphorylated-S6 result in increased cellular proliferation, protein synthesis and blood brain barrier permeability. Sirolimus acts as an inhibitor of mTOR by causing rapid inactivation of S6K1, and as a result, preventing phosphorylation of the S6 protein and further cellular proliferation as well as vascular growth. A. Abbreviations: phospholipase C ß (PLCß); phosphatidylinositol 3,4,5-bisphophate (PIP_2); diacylglycerol (DAG); inositol 1,4,5-trisphosphoate (IP_3); protein kinase C (PKC); zonula occludens (ZO); phosphatidylinositol 3,4,5-trisphophate (PIP_3); phosphoinositide 3-kinase (PI3K); phosphatase and tensin homolog (PTEN); tuberous sclerosis proteins 1 and 2 (TSC1/2); Ras homolog enriched in brain (RHEB); p70 ribosomal S6 kinase (S6K1).

genes of patients with atypical SWS features. *RASA1* and *EPHB4* germ line mutations are generally associated with capillary malformation-arteriovenous malformation syndrome, a disorder that increases the risk of fast-flow malformations and pleural effusion as well as other lymphatic anomalies (49, 50). Patients with reported mutations in either *RASA1* or *EPHB4* had family histories of capillary malformation. It is important to consider other genetic causes when atypical phenotypes are seen in skin presentation, MRI abnormalities, family history, or in other symptoms and features that deviate from typical SWS phenotype. Work is ongoing to better understand genotype–phenotype associations.

4 Updates on models for SWS

Accurate representation of SWS through models is necessary to continuously elucidate the impact of the R183Q *GNAQ* mutation on vascular development and for testing of new therapies and drug targets in the pre-clinical setting. It is important to differentiate models with the Q209L *GNAQ* mutation (51–53) from models with the R183Q *GNAQ* mutation (54, 55). While both are understood to be hyperactivating mutations, the Q209L mutation results in much greater hyperactivation (56, 57). The Q209L *GNAQ* mutation has never been reported with SWS or facial PWB; rather the Q209L mutation has been associated with vascular tumors (58–60). The PWBs seen in SWS are vascular malformations rather than vascular tumors (61, 62).

4.1 R183Q GNAQ *in vitro* models

Modeling the R183Q *GNAQ* mutation *in vitro* began initially with transient transfection of cells and has progressed to stable

transfection of cells from mice or humans, obtained from tissue, and studied continuously through cell culture (6, 47, 52). Multiple models isolating endothelial cells for variants in *GNAQ* mutations have been generated recently. Skin samples from mice injected with mutant R183Q GNAQ endothelial cells combined with bone marrow mesenchymal progenitor cells had a greater percentage of enlarged vessels compared to skin samples injected with wild type endothelial cells (63). The R183Q *GNAQ* mutation, when expressed in endothelial cells, resulted in constitutive activation of phospholipase Cβ (PLCβ), which plays a major role in cell signaling through the G-protein cycle. PLCβ generates other active molecules such as inositol 1,4,5-triphosphate (IP_3) and diacylglycerol (DAG). DAG, in particular, activates protein kinase C, which when activated, phosphorylates various proteins that can regulate membrane permeability, cellular proliferation, and control metabolic pathways. Angiopoietin-2 (Ang2) levels were increased in the abnormally large blood vessels of mice injected with mutant endothelial cells, and when treated with higher concentrations of AEB071, an inhibitor of PKC, levels of Ang2 were reduced to a normal, non-SWS phenotypic level (63), suggesting that constitutive activation of PLCβ plays a role in the phenotype of enlarged blood vessels.

A recent brain tissue study in 4 samples from patients with SWS indicated the presence of cells with multiple macrophage-associated molecules such as MRC1, CD163, CD68, and LYVE1 that were absent in the human control brain tissue from 2 patients. ICAM1, an endothelial cell-specific protein that promotes leukocyte adhesion and regulates cellular responses in inflammation, was also expressed at higher levels in the human SWS brain tissue (64). ICAM1 was also identified in the endothelial layer of some blood vessels. This work suggests that macrophages are potentially recruited to leaky perivascular areas where ICAM1 is expressed and play a role in the regulation of angiogenesis.

A common outcome of SWS seen in patients is brain calcification, likely due to the interactions of venous hypertension, brain ischemia, and seizures that worsen blood flow, with the R183Q *GNAQ* mutation in impacted cells. When IP_3 is produced from phosphatidylinositol 4,5-bisphosphate (PIP_2) being cleaved by PLCβ, it triggers an influx of calcium from the endoplasmic reticulum into the cell. Mutant R183Q HEK293 cells show increased production levels of IP_3 than wild-type cells, suggesting that the mutation results in a greater influx of calcium in the cytoplasm (65). Hyperactivated calcium signaling has been identified in mutant R183Q telomerase-immortalized microvascular endothelial (TIME) cells, accompanied by increased inositol monophosphate, which indicates the presence of IP_3 before initiating the release of calcium into the cell and degrading (66). This however, was attenuated by inhibition of the calcium-release-activated channel. While inhibition in this case does not reverse previous calcification found in blood vessels, the dynamic of regulating calcium within cells is worth understanding further in the context of mutant Gαq and its affected pathways.

4.2 R183Q GNAQ *in vivo* models

A mouse model using cre-drivers to express the R183Q *GNAQ* mutation during embryonic development was created to investigate the impact of the mutation in different cell types during fetal development (54). In *Gnaq*$RQ^{wt/wt}$;*β*-actin-Cre + x *Gnaq*$RQ^{fl/wt}$ transgenic mice, which express the R183Q *GNAQ* mutation globally, no mice were born containing both the Cre driver and the conditional *GNAQ* allele, suggesting that the mutation results in complete embryonic lethality when expressed during very early stages of development. When the R183Q *GNAQ* mutation was expressed in endothelial cells in a mosaic manner (mutation is present in only some cells), the transgenic mice that survived after birth did not exhibit any notable vascular defects.

A tetO-*GNAQ**R183Q X *Tie2-rtTA/TRE-βGal* (R183Q *GNAQ* mice) transgenic mouse model was recently created using doxycycline induced expression of the mutation in endothelial cells in mutant mice at age P15 (55). When perfused following injections with Evans Blue dye, a significantly higher percentage of mutant mice brains had severe Evans Blue staining in their brain; no littermate control mice exhibited severe Evans Blue staining. Phosphorylated-S6, which is an indicator of increased mTOR activity (67), was found at increased expression levels in leptomeningeal blood vessels of mutant mice, compared to littermate control mice, a finding similar to that reported in human brain tissue (13). Microvessels in the region of the retrosplenial cortex showed irregular and discontinuous expression patterns of both phosphorylated-S6 and claudin-5. Claudin-5 is a tight junction protein that contributes significantly to the integrity of the blood brain barrier (68). These results suggest that the blood brain barrier of mutant, R183Q *GNAQ* mice are significantly more permeable than that of their littermate controls, and that mTOR is likely to be found at elevated levels in the leptomeninges, suggesting involvement of this pathway as well. Other studies link mTOR inhibition and PI3K/Akt pathway inhibition to restoring blood brain barrier integrity through increased expression of tight junction proteins and decreased autophagy (69, 70). This suggests that mTOR inhibition may act in a similar manner for SWS, in which models already indicate increased phosphorylated-S6 and a compromised blood brain barrier (13, 55).

Angiopoietin-2, which acts as an antagonist towards angiopoietin-1, promotes vessel instability and leakiness by causing pericyte detachment (71). Ang2 plays a large role in the permeability of the blood brain barrier during angiogenesis (63, 72, 73). Together, the recent data from the mouse model and human tissue to date supports that the R183Q mutation in *GNAQ* plays a role in both blood vessel overgrowth via constitutive activation of PLCβ3, which results in irregular downstream pathway activity in the MAPK/ERK and mTOR pathways, resulting in abnormally high Ang2 expression, and breakdown of the blood brain barrier (see Figure 2) as well as abnormal macrophage invasion of the involved cortex.

5 Advances in outcome measurements

The SWS-Neurological Rating Score (SWS-NRS), or Neuroscore, is used as a cumulative assessment of the extent of neurological impairment in SWS patients (74). It is a metric that is comprised based off observed visual defects, seizure frequency, extent of hemiparesis, and degree of cognitive function. SWS Neuroscore has been used in various studies in comparison with MRI imaging and EEG evaluations and may serve as an important measurement when administering a certain treatment or therapy (75–77). The NIH Quality of Life in Neurological Disorders (Neuro-QoL) measures the physical, mental,

and social effects of neurological conditions in both children and adults. The extent of skin, total eyelid port-wine birthmark, eye, and overall SWS involvement were negatively correlated with cognitive function Neuro-QoL; as the involvement of SWS becomes more diffuse, patients typically see a drop in quality of life (78). Previous research has also shed light on linking SWS to increased suicidality compared to other neurological disorders (79). Continued research is necessary to understand whether this is due the disease pathology of SWS, facial port-wine birthmark, epilepsy or other factors.

5.1 Updates in treatment

5.1.1 Low dose aspirin

Multicenter studies for SWS have recently been conducted on individuals with SWS to understand current treatment patterns (77, 80). Studies show that low-dose aspirin is often recommended and used for management of seizures and stroke-like episodes (81, 82). However, adverse effects to aspirin for Sturge–Weber patients have been reported previously as well (83, 84). Lance et al. reports other side effects from SWS patients taking aspirin, however it is notable that only a small percentage of SWS patients with brain involvement in this study experienced side effects (81). It is recommended to treat hemiparetic stroke-like episodes with aspirin, in hopes of abating ischemia due to vascular malformation (85). Aspirin has also been taken along with levetiracetam in patients both pre-symptomatically and after the onset of symptoms (86, 87). When determining whether low-dose aspirin is an option for a SWS patient, one must consider the severity and degree of brain involvement as well as any symptoms that the patient already exhibits.

5.1.2 Presymptomatic treatment

If SWS diagnosis is obtained prior to the onset of symptoms, presymptomatic treatment with aspirin and antiepileptic drugs in low doses may aid in delaying the onset of seizures (84). Screening for brain abnormalities (calcification, blood vessel abnormalities) prior to the onset of symptoms may help in calculating the risk of future brain involvement as well as encourage presymptomatic treatment (88). Early MRI with gadolinium enhancement, when possible, aids in accurate determination of SWS brain involvement and allows for the potential for presymptomatic treatment (89). Recent studies suggest that rapid "feed & wrap" non-contrast MRIs can be obtained in young infants, and show various vascular and parenchymal (indirect) signs of SWS that could be used to detect presymptomatic SWS brain involvement (90). The argument against this, however, presents that in infants, MRI requires anesthesia and can potentially show false-negative results that are more difficult to elucidate early on into postnatal development (91). Conversely, especially for high-risk patients, early detection of SWS brain involvement leading to presymptomatic treatment may be beneficial; this of course should be discussed and implemented on a case-by-case basis. Shortened MRI may be useful and effective in infants that are not sedated (92). Further prospective study of non-sedated, non-contrast MRI is being used by various centers, along with neurological examination and EEG to screen for brain involvement. This strategy may prove useful in future presymptomatic drug trials that would require pre-treatment verification of brain involvement (90). The potential drawbacks of sedation in infants requiring MRI as well as different approaches to mitigate the risks of sedation have been previously described (93). Retrospective analyses show that presymptomatic treatment results in a noticeable delay in age of seizure onset as well as a lower (improved) hemiparesis Neuroscore (94). In this study, it is notable that the presymptomatic treatment group had a higher percentage of both bilateral brain involvement and skin involvement. Delaying the onset of seizures in infants with presymptomatic treatment allows for more normal neurological development with a lower likelihood of future brain injury and cognitive impairment (95).

5.2 mTOR inhibition

5.2.1 Mouse studies

Increased expression of phosphorylated-S6, which is a downstream target of the mammalian target of rapamycin (mTOR) pathway, is observed in multiple models with the R183Q *GNAQ* mutation (13, 55, 96). Another animal model that used leukosomes to package rapamycin as a biomimetic drug delivery system showed that mice, when given rapamycin in encapsulated form, showed suppressed endothelial cell proliferation and recovery of normal vessel structure from an inflamed state (97). It is hypothesized that somatic mutations in *GNAQ* that cause hyperactivation of the Ras–Raf–MEK–ERK pathway, and specifically ERK expression, also result in increased activation of mTOR in mutated endothelial cells lining blood vessels. Elevated mTOR pathway activity is commonly known to increase transcription rates, enhance nucleotide, protein, and lipid synthesis, and promote cellular proliferation, which can lead to tumor growth (98). In SWS patients, the increased cellular proliferation is seen through dysregulated angiogenesis primarily in the brain, eye, and facial regions. Patients with SWS, therefore, could potentially receive effective treatment from an mTOR inhibitor.

Growth factors mediate the activation of mTOR and influence rates of protein synthesis. Sirolimus, also known as rapamycin, is able to inhibit the mTOR pathway, and thus protein synthesis, by causing rapid inactivation of S6K1, which is a downstream target of mTOR and essential for the phosphorylation of the ribosomal S6 protein, a protein directly involved in protein synthesis (99, 100). S6K1, when active, facilitates the activation of CREMτ, which belongs to the cAMP-response-element-binding family of transcription factors, and induces further gene transcription and transcription of proliferating cell nuclear antigen (PCNA), which plays an important role in cellular proliferation and DNA synthesis in the S-phase of the cell cycle (101, 102). Through inactivating S6K1, sirolimus is able to inhibit these downstream events. Figure 2 describes the application of sirolimus in mTOR inhibition in the context of G protein-coupled receptor signaling. Previously, sirolimus has been used in multiple mouse models to treat vascular malformation disorders (103, 104). Sirolimus may also minimize the risk of stroke or stroke-like episodes and can potentially better stabilize seizures in mice (105). A clinical trial using topical rapamycin combined with pulsed dye laser (PDL) on the lateral areas of a PWB showed decreased skin pigmentation and a reduced frequency of blood vessels throughout the brain tissue (106).

5.2.2 Human studies

More recently, oral sirolimus has been proposed as another delivery mechanism for SWS patients. In an open-label prospective study with ten subjects with SWS brain involvement and cognitive impairments, patients were given oral sirolimus for 6 months, which resulted in a consensus of improvements in quality of life, cognitive function, and improvements in processing speed (107). The adverse effects of sirolimus for these ten patients were mild, concluding that sirolimus is generally safe for SWS patients and may contribute to benefits in cognitive ability specifically for patients that have previously experienced stroke-like episodes. For a group of patients with DRE, oral sirolimus controlled epileptic symptoms in all patients and resulted in improvements in hypertrophy of pathological tissue (108). Oral sirolimus administered for a SWS patient with left facial hemihypertrophy resulted in depigmentation of their port-wine birthmark as well as decreased soft tissue overgrowth (109). Notably, PDL was not used for this patient. Another case with diffuse choroidal hemangioma has been reported to be treated with oral sirolimus as an adjuvant therapy for PDL of the port-wine birthmark (110). There is a wider range of clinical application of mTOR inhibition in other mTOR pathway-linked diseases, especially tuberous sclerosis (111). A phase III trial of sirolimus for vascular malformations also indicates that side effects such as stomatitis are clinically manageable (112). More extensive research on the application of sirolimus for SWS patients is necessary, especially when treating patients with histories of stroke and stroke-like episodes.

5.3 Cannabidiol

5.3.1 Mouse studies

Cannabidiol (CBD) has emerged as a novel therapeutic for many facets of health such as anxiety, depression, insomnia, PTSD, and schizophrenia amongst other diseases. There is growing literature on CBD and its potential application and benefits regarding epilepsy and seizure disorders (113–115). In order to make the case for preclinical drug trials with CBD, animal models must be established proving clear improvements in seizure activity. Two models using CBD to attenuate seizure activity as part of Dravet syndrome each achieve seizure reduction by inhibiting GPR55 (116, 117). CBD has also produced anti-inflammatory effects in a mouse model for Parkinson's that also suggests GPR55 as a viable target (118). GPR55 is a G protein-coupled receptor that functions as a cannabinoid receptor and is involved in regulating blood pressure as well as cytoskeletal modulation (119). Future clinical work may target GPR55 and other receptors associated with epilepsy and seizure reduction. Multiple mouse models for epilepsy have been produced, further demonstrating the beneficial effects CBD has on seizure reduction and prevention as well as improving social behavior (120–122). In another model looking at chronic CBD treatment, there was no apparent change to the frequency of seizures, and no delay to the onset of seizures (123). There may be differences in outcome between short-term versus chronic administration of CBD that have yet to be explored. In mice given kainate injections to induce seizures, pharmaceutical CBD at the highest dose of 240 mg/kg significantly decreased the severity and frequency of seizures, whereas chronic administration of artisanal CBD did not reduce seizure severity to the same degree as pharmaceutical CBD (124). CBD has yet to be applied to a mouse model specifically for SWS and could potentially be explored in the future.

5.3.2 Human studies

In 2018, the FDA approved Epidiolex, also known as cannabidiol (CBD), for the treatment of seizures for two separate pediatric disorders, Lennox–Gastaut syndrome and Dravet syndrome, which both involve epilepsy (125). Since then, Epidiolex has expanded towards treatment with other disorders relating to seizures and epilepsy, including SWS. A recent multicenter study which treated patients with epilepsy and myoclonic-atonic seizures as well as SWS patients with CBD allowed for reduced seizure frequency in all patients; over half of all patients saw a seizure reduction of at least 50% (126). Epidiolex has also been used in clinical trials only involving SWS patients. The first, which aimed to abate seizure intensity as well as reduce the frequency of seizures in SWS patients, resulted in improved quality of life, significant seizure reduction, and other improvements such as cognitive function, speech and communication, and physical capability (127). Another clinical trial with Epidiolex for ten SWS patients reported no seizures after 6 months of administering oral CBD (128). This was also accompanied by noticeable improvements in SWS Neuroscore and patient-reported quality of life. CBD is suggested to have neuroprotective abilities by inhibiting the mTOR pathway indirectly through JNK inhibition (129). It is a cannabinoid without the psychoactive properties, and administration has proven to be safe and effective for patients with treatment-resistant epilepsy (126, 130). Further investigation into CBD use for SWS patients as well as the potential role that CBD plays in the molecular inhibition of SWS-related abnormally regulated pathways is needed.

6 Discussion

Aggressive seizure management has been the mainstay of neurologic management in SWS for the last 25 years. In the last eleven years since the discovery of the p.R183Q mutation in *GNAQ*, the focus of research has shifted towards constructing transgenic animal models, whether *in vivo* or *in vitro*, to further understand the mutation and the downstream pathways and proteins it affects. Through the evidence presented in these models, we can start to implement known inhibitors (such as sirolimus) in prospective pilot trials. The way in which the clinical field has assessed diagnosis and treatment over the past decade has changed as well. MRI with and without contrast has become the gold standard for proper SWS identification. Patients and their families are encouraged to opt for presymptomatic treatment with low-dose aspirin or other anti-epileptic drugs in attempt to delay seizure onset and ameliorate neurocognitive function. Treatment focusing on mTOR inhibition, specifically with sirolimus, has become increasingly more common in the clinical setting. Further research is still necessary regarding the effects of sirolimus on SWS patients and the potential role it may play in management of symptoms for those who experience stroke or stroke-like episodes. Continued research with cannabidiol regarding managing SWS patients' symptoms as well

as its context in an animal model for SWS will be important to reinforce its potential clinical use. It is important that research conducted in the clinical setting runs parallel to that in the bench-laboratory research setting; by modeling SWS through the R183Q mutation in *GNAQ* via cell culture and animal models, we can achieve a more lucid understanding of disease manifestation and progression.

Author contributions

CS: Conceptualization, Writing – original draft, Writing – review & editing. AC: Conceptualization, Supervision, Writing – review & editing.

Funding

The author(s) declare that financial support was received for the research, authorship, and/or publication of this article. This work was supported by the Faneca 66 Foundation and Celebrate Hope Foundation.

Acknowledgments

We would like to thank the patient and their family for providing consent for their photograph and neuroimaging.

Conflict of interest

AC is an inventor on a patent involving cannabidiol for the treatment of Sturge-Weber syndrome.

The remaining author declares 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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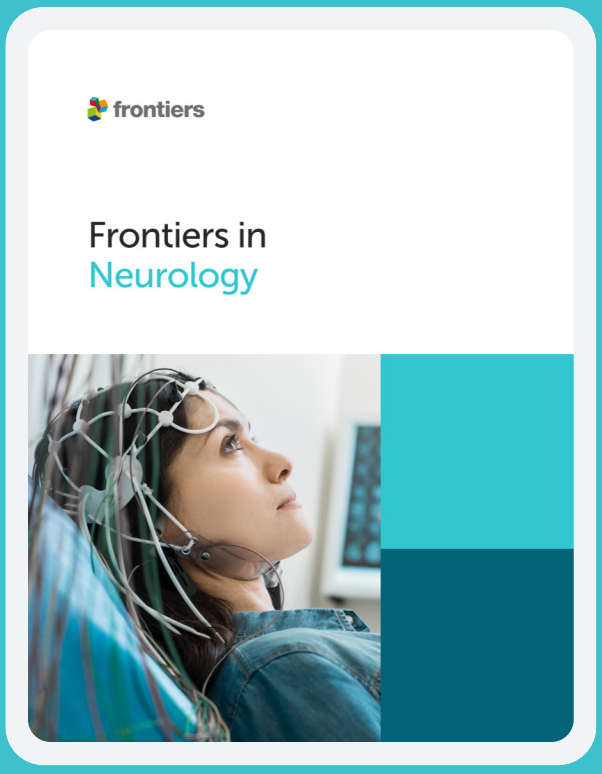

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