

Interim results of bleomycin-polidocanol foam sclerotherapy as a highly efficient technique for venous malformations



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ABSTRACT

Objective: The objective of this study was to retrospectively review the clinical and radiographic outcomes of patients with venous malformations (VMs) treated with bleomycin-polidocanol foam (BPF) sclerotherapy.

Methods: The Institutional Review Board waived ethical approval for this retrospective review in which 55 patients (31 female and 24 male patients; mean age, 18.8 years; range, 2-60 years) were treated with BPF sclerotherapy. The stability (half-life) of BPF compared with polidocanol foam was studied. Standard sclerotherapy techniques were used. A total of 111 sclerotherapy sessions were performed, with a mean of 2.0 treatments per patient (range, 1-6). An average of 10 mL of BPF was used per procedure, with the total amount ranging from 2.5 to 30 mL. Symptoms before and after treatment, follow-up time, complications, and volume reduction on magnetic resonance imaging were recorded.

Results: The median half-lives of the BPF and polidocanol foam were 238.25 ± 3.86 seconds and 194.33 ± 3.5 seconds, respectively. A *t*-test indicated significant differences between the groups ($P < .01$). The mean follow-up was 14 months (range, 6-24 months). All 55 patients (100%) reported improvement in symptoms. The total excellent and good response rate was 94.6%. An excellent response was achieved in 32 cases (58.2% [32/55]), a good response in 20 cases (36.4% [20/55]), and a poor response in 3 cases (5.4% [3/55]). Postprocedural magnetic resonance imaging demonstrated volume reduction of treated lesions in 54 of 55 patients (98%), with a mean lesion volume reduction of 84.6%. Postprocedure complications were minor in 13 of 111 procedures (12%) that were performed on 10 of 55 patients (18.2%), and no major complications occurred.

Conclusions: BPF sclerotherapy of VMs is safe and effective. BPF sclerotherapy can be a promising first-line treatment of VMs. (*J Vasc Surg: Venous and Lym Dis* 2020;8:1066-73.)

Keywords: Venous malformation; Sclerotherapy; Bleomycin; Polidocanol foam; Foam stability

Venous malformations (VMs) are the most common type of vascular malformation, occurring in up to 1 in 5000 births.^{1,2} The current mainstay for treatment of a VM that requires active treatment is percutaneous sclerotherapy when it is not surgically accessible.³⁻⁶

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In sclerotherapy, intralesional injections with sclerosing agents cause destruction of the endothelium lining of the VM, followed by inflammation, thrombotic vascular occlusion, and sclerosis and decrease in the size of the lesion.⁷ A variety of sclerosing agents have been used to treat VMs, and there is a wide variation in their use among clinical practices. Absolute ethanol is accepted to be the most effective and has the lowest recurrence rate but a higher rate of complications.⁸ Milder sclerosants with decreased complication rates, such as polidocanol, sodium tetradecyl sulfate, and bleomycin, have also been used to treat VMs.⁹⁻¹²

Bleomycin is reported to have a lower complication rate than other sclerosants.^{12,13} The most frequent adverse events of bleomycin are minimal, transient, and mostly localized pain and swelling.¹⁴ Bleomycin can damage the endothelial cells by inciting an inflammatory response and causing vascular fibrosis, but compared with ethanol, vascular fibrosis occurs at a slower rate, and there is a greater probability that VMs will recanalize after administration.¹⁵⁻¹⁷ In the study by Horbach et al,¹⁸ monotherapy with bleomycin resulted

in only little to moderate improvement of health in most patients with low-flow vascular malformations, and further treatment was required. There is also a concern that bleomycin may result in pulmonary fibrosis if the cumulative lifetime dose exceeds 350 to 450 units.¹⁹

Bleomycin foam has been proposed by Mitchell et al²⁰ to allow treatment of larger lesions while minimizing the total dose of bleomycin. They created bleomycin foam by resuspending bleomycin in 25% human serum albumin to increase efficacy by slowing the rate of sclerosant washout from the VM and increasing the endothelial surface area in contact with the sclerosant.²¹ In our study, we created bleomycin foam by dissolving bleomycin powder in liquid polidocanol and then mixing with air. As polidocanol is a detergent sclerosant widely used for foam sclerotherapy of VMs, we presumed that it not only can be a surfactant to create foam but also has a synergistic effect with bleomycin in sclerotherapy.²²

There are currently no studies of bleomycin-polidocanol foam (BPF) sclerotherapy for VMs. The purpose of this study was to report clinical and radiographic outcomes in patients with VMs treated with BPF sclerotherapy.

METHODS

We conducted a retrospective study from November 2016 to June 2018. The protocol and informed consent were approved by the Institutional Review Board, and all patients gave informed consent. The patients agreed to publication of images that identify them.

Patients. Fifty patients who came to our center from July 2016 to June 2018 were enrolled in this study. All patients had been diagnosed with common sporadic VMs by the referring center and had magnetic resonance imaging (MRI) before sclerotherapy to confirm the diagnosis and to assess the extent of the lesion. Patients with VMs due to Bean syndrome, glomuvenous malformation, Maffucci syndrome, and Klippel-Trénaunay syndrome were not included in the series. VM patients with symptoms such as swelling, pain, and enlargement were offered sclerotherapy. Patients treated by sclerotherapy with other sclerosants during the study or within 6 months before the study began were excluded from this study. The patients who received sclerotherapy with other sclerosants >6 months before the study were included. All the patients with or without pain in this study underwent coagulation studies consisting of a full blood count, prothrombin time, activated partial thromboplastin time, and D-dimer and fibrinogen levels. Localized intravascular coagulation was found in 75% of the patients.

Sclerosant foam. Fifteen milligrams of bleomycin powder (15,000 IU; Nippon Kayaku, Tokyo, Japan)

ARTICLE HIGHLIGHTS

- **Type of Research:** Single-center, retrospective cohort study
- **Key Findings:** Bleomycin-polidocanol foam sclerotherapy was used to treat venous malformations in 55 patients with a mean follow-up of 14 months, resulting in 94.6% total excellent and good response, 84.6% mean lesion volume reduction, and 12% minor complications.
- **Take Home Message:** Bleomycin-polidocanol foam sclerotherapy has high efficiency and few complications.

was dissolved in 4 mL 3% polidocanol (Aethoxysklerol; Kreussler Pharma, Wiesbaden, Germany). Sclerosing foams were produced by the Tessari method using two 5-mL syringes connected by a three-way valve to generate an air (room air)-liquid sclerosant with a ratio of 4:1, and the plungers of the syringes were moved back and forth 20 times for each foam preparation.²³

Foam stability. Once the BPF and polidocanol foam were prepared by the Tessari method, the filled syringe was immediately disconnected from a three-way valve and placed vertically with the piston beneath. The destruction of the foam in the syringe was observed, and the liquid detergent was found to gradually re-form at the bottom. When half the volume (2.5 mL) of the liquid detergent drained, the time was recorded as the half-life, which served as the indicator of foam stability.²⁴ Five tests of half-lives in both BPF and polidocanol foam groups were measured.

Treatment techniques. The treatment procedures were guided by ultrasound for initial needle access for the deep lesions, and direct vision was preferred in superficial locations. Direct puncture was performed using 21-gauge needles. At each session, two to six injection sites were needed according to the size of the lesions. A double-needle technique was used to avoid extravasation.²⁵ Once the blood returned, 0.25% lidocaine was injected to fill the venous space until the lidocaine flowed out from the other needle.²⁶ Then, the architecture, distribution, volume, flow rate, and type of venous drainage were confirmed by phlebography. BPF was injected soon thereafter, with the maximum dose in a single procedure being 30 mL (Fig 1). Blood pressure, heart rate, and oxygen saturation were monitored during the procedure, and no tourniquet was used during the procedure. Sclerosing foam was injected until the lesion had been fully filled under visual or ultrasound observation. The amount of sclerosant foam injected was recorded.

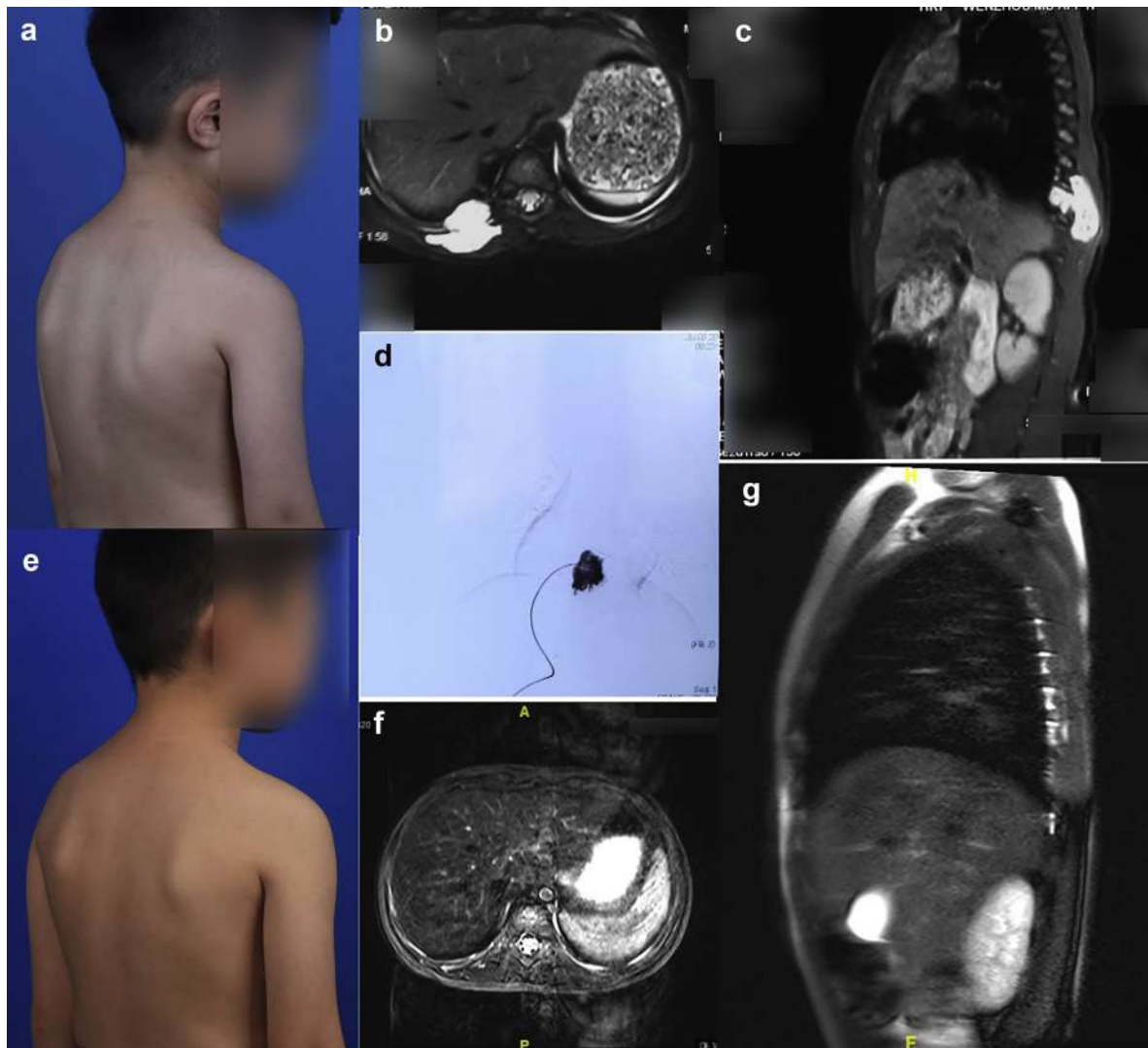


Fig 1. A 4-year-old boy with localized venous malformation (VM) of the back treated by bleomycin-polidocanol foam (BPF) sclerotherapy. **a**, Clinical appearance before treatment showing a mass on the right side of the back. **b** and **c**, Pretreatment T2-weighted magnetic resonance imaging (MRI) showing a hyperintense mass of the right side of the back involving the thoracic cavity. BPF sclerotherapy was performed under digital subtraction angiography. **d**, Phlebography showed that the lesion was localized, and no outflow vein was observed. **e**, After one session of BPF sclerotherapy, significant improvement of VM lesions was achieved. **f** and **g**, Post-treatment T2-weighted MRI 3 months after treatment showing complete disappearance of VM lesions.

Postoperative follow-up. Patients were scheduled to return to our outpatient clinic 1 month after treatment. Clinical response and whether repeated sessions were necessary were evaluated for each patient at clinical follow-up on the basis of physical examination and postprocedural MRI. Complications were also evaluated and recorded by questionnaire and physical examination and classified as major or minor according to the Society of Interventional Radiology reporting standards.²⁷ The end point was the disappearance of symptoms or the disappearance of lesions. Patients were followed up for 1 month, 3 months, 6 months, 12 months, and 24 months after the final treatment. MRI

examination was performed at the end point and at the 12-month follow-up. Five patients were lost to follow-up in this study, and those patients were excluded from this study.

Clinical evaluation. The following patient data were collected: sex, location of lesions, volume of sclerosant foam, treatment session number, treatment response, and complications. Clinical results were graded as follows: poor, little or no improvement; good, significant decrease in size (50%-95% reduction) and symptoms; and excellent, clinical obliteration or >95% reduction in size. To assess treatment response on MRI, the treated

portion of the VM was measured in three dimensions on preprocedural and postprocedural T2-weighted MRI by three radiologists. Each lesion was assumed to be ellipsoid and was calculated by the ellipsoid volume formula $(4/3)\pi abc$, where a is the anteroposterior axis, b is the transverse axis, and c is the craniocaudal axis.

Statistical analysis. Data analysis was performed using SPSS 19.0 (IBM Corp, Armonk, NY). The t -test was applied to estimate the variance of the half-lives between BPF and polidocanol foam. $P < .01$ was considered significant.

RESULTS

Foam stability. The median half-lives of the BPF and polidocanol foam were 238.25 ± 3.86 seconds and 194.33 ± 3.5 seconds, respectively. The t -test indicated significant differences between the groups ($P < .01$).

Patients' characteristics. Fifty patients (31 female and 24 male patients; mean age, 18.8 years; range, 2-60 years) were treated with BPF sclerotherapy. Lesions were located in the head and neck in 38 patients (69.1%), extremities in 15 patients (27.3%), and trunk in 2 patients (3.6%). A total of 111 embolizations were performed with a mean of 2 and a range of 1 to 6 treatments per patient. An average of 10 mL of BPF (7.5 mg of bleomycin, 2 mL of 3% polidocanol, and 8 mL of air) was used per procedure, with the total amount ranging from 2.5 to 30 mL. The summary for the main clinical data is presented in Table I.

Clinical efficacy and complications. The mean follow-up was 14 months (range, 6-24 months). All 55 patients (100%) reported improvement in their symptoms. The total excellent and good response rate was 94.6%. An excellent response was achieved in 32 cases (58.2% [32/55]), a good response in 20 cases (36.4% [20/55]), and a poor response in 3 cases (5.4% [3/55]). The mean pre-treatment VM volume on MRI was 53.3 ± 79.9 mL, and mean post-treatment VM volume on MRI was 8.8 ± 14.9 mL. Postprocedural MRI demonstrated volume reduction of treated lesions in 54 of 55 patients (98%), with a mean lesion volume reduction of 84.6% (Figs 2 and 3).

Postprocedure complications were minor in 13 of 111 procedures (12%) and in 10 of 55 patients (18.2%). No major complications occurred. Swelling and pain after treatment were observed in all 55 patients, which resolved within 1 to 2 weeks and were not regarded as complications. Complications included skin hyperpigmentation (4.5% [5/111]), blisters (2.7% [3/111]), hair loss (1.8% [2/111]), nausea (1% [1/111]), fever (1% [1/111]), and abdominal pain (1% [1/111]). These adverse effects were self-limited and minor. No major complications, such as cutaneous necrosis, anaphylactic shock, deep venous thrombosis, pulmonary embolism, and stroke, occurred in our study. A summary of the clinical efficacy and complication data is presented in Table II.

Table I. Clinical characteristics

Clinical data	No. or mean (range)
Sex	
Female	31
Male	24
Age, years	18.8 (2-60)
Location	
Head and neck	38
Extremity	15
Trunk	2
Treatment sessions	2.0 (1-6)
Foam volume per session, mL	10 (2.5-30)
Previous treatment	
Ethanol sclerotherapy	15
Surgery	1
Polidocanol foam	1

DISCUSSION

This retrospective study was designed to assess the efficacy and safety of a novel sclerotherapy strategy for VMs using BPF. In this study, we observed a total excellent and good response rate in 94.6% of patients after a mean of two sessions, with a 58.2% excellent and a 36.4% good response rate; the mean lesion volume reduction was 84.6% on MRI. No major complications occurred. Most complications completely resolved within 1 month, with the exception of skin hyperpigmentation.

Historically, multiple sclerosants were used in performing percutaneous sclerotherapy, and no sclerosant was proved to be superior to other sclerosants in clinical practice. Absolute ethanol is accepted to be the strongest sclerosant, with a remission rate ranging between 75% and 96%, and has the lowest recurrence rate. It can result in immediate denaturing of endothelial cell membrane proteins with subsequent denuding of the endothelium, rapid thrombosis, and inflammation leading to fibrosis. It used to be the most commonly used agent. However, its use is limited by the high complication rate and severe complications, such as skin necrosis, nerve injury, and cardiovascular collapse, which can occur in 12% to 30% of patients.²⁸ Bleomycin liquid and polidocanol have a better tolerance but are less effective than absolute ethanol.²⁹⁻³¹ Bleomycin and polidocanol have different mechanisms in sclerotherapy. Bleomycin, a glycopeptide antibiotic that incites a robust inflammatory response after administration, results in endothelial cell loss and thrombosis.³⁰ Polidocanol, a detergent agent that can solubilize endothelial membrane proteins, results in endothelial cell membrane instability that progresses to thrombosis and fibrosis.³¹ However, unlike with absolute ethanol, the thrombosis occurs at a slower rate,

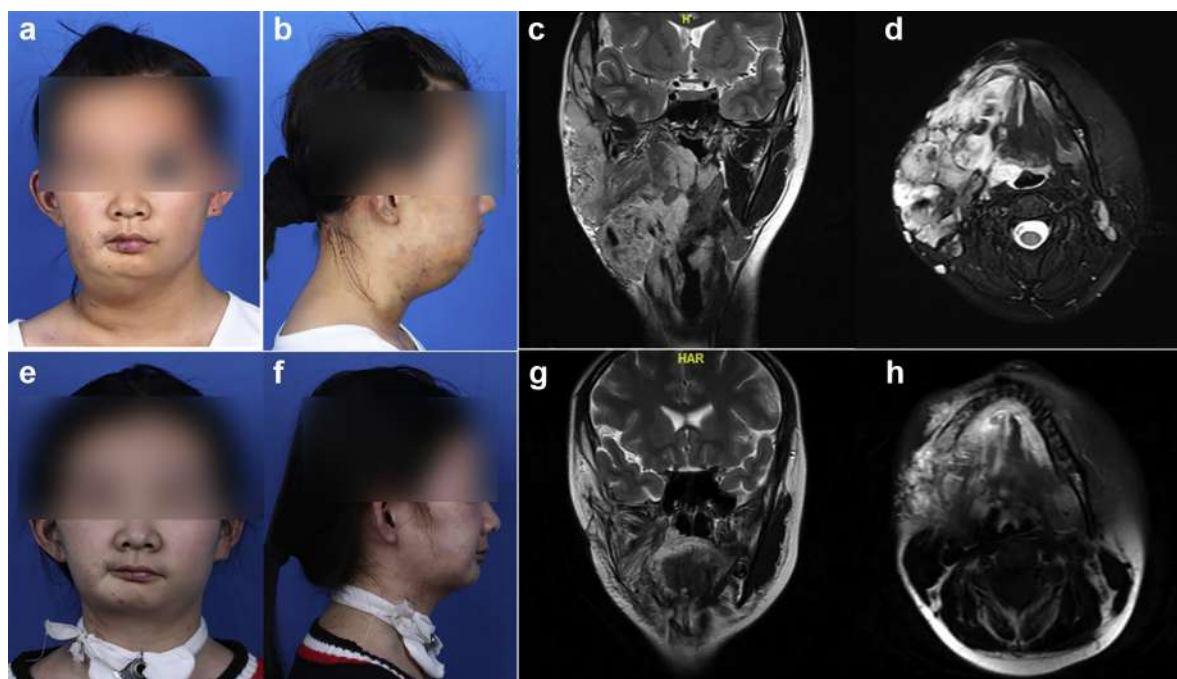


Fig 2. A 16-year-old girl with extensive venous malformation (VM) of the face and neck treated by bleomycin-polidocanol foam (BPF) sclerotherapy. **a** and **b**, Clinical appearance before treatment showing extensive lesion and severe deformity. **c** and **d**, Pretreatment T2-weighted magnetic resonance imaging (MRI) showing an extensive hyperintense mass of the right facial and neck region. **e** and **f**, After tracheotomy followed by six sessions of BPF sclerotherapy, significant improvement of VM lesions was obtained. **g** and **h**, Post-treatment T2-weighted MRI 12 months after treatment showing almost complete resolution of VM lesions.

and there is a greater probability that the VMs will recanalize.³² That is why we presumed that the combination of polidocanol and bleomycin can enhance the effect of sclerotherapy.

Various attempts were made to enhance the efficacy of sclerosants without increasing the complication rate. The efficacy of sclerotherapy depends on the strength of the sclerosing agent and its contact time and contact surface area with the endothelium.³³ The strength of the sclerosant is determined by its chemical properties. Foam sclerotherapy is a common technique to increase the contact time and contact surface area of sclerosant. Foams can mechanically displace the blood in the vessels, maximizing the contact between the sclerosant and the endothelial wall and reducing the deactivation of the sclerosant caused by blood components. A prospective randomized study evaluated 1% polidocanol sclerotherapy in the form of either liquid or foam and found better rates of total disappearance with foam sclerotherapy.³⁴ Ul-Haq et al²⁰ and Azene et al²¹ prepared bleomycin foam by using a ratio of 6 units of bleomycin suspended in 1 mL of normal saline solution plus 1 mL of human 25% serum albumin. Their studies also proved that bleomycin foam is more effective with a mean lesion volume reduction on MRI of 66%. In our study, the mean lesion volume reduction on MRI was 84.6%. Therefore, BPF seems to be more effective than bleomycin foam. We assume that

the strength of the BPF is enhanced by the synergistic effect of polidocanol and bleomycin, which makes BPF sclerotherapy more effective.

Foam stability is the primary factor for the contact time and contact surface area of the foam with the endothelium that determines its performance during clinical treatment. Foam half-life (the time until half of the liquid used to produce the foam reverts to the liquid state) was commonly used as the parameter to quantify foam stability. Improving foam stability allows the use of a smaller total dose to achieve a better therapeutic outcome and to reduce the complication rate.³⁵ Foam stability can be improved by increasing the viscosity or reducing the surface tension of the foam.³⁶ Chen et al³⁷ successfully prolonged polidocanol foam stability by dissolving hyaluronic acid in the polidocanol solution before foams were manually produced. The clinical study by the same authors also showed more efficacious sclerotherapy results in hyaluronic acid-polidocanol foam sclerotherapy for treating head and neck VMs.³⁸ In our study, the half-life of the BPF (238.25 ± 3.86 seconds) was longer than that of the polidocanol foam (194.33 ± 3.5 seconds). The foam stability was improved by mixing the bleomycin with polidocanol solution before the foams were manually produced, which means that the distribution, contact time, and contact surface area of the BPF with the endothelium were improved. This is also one of the

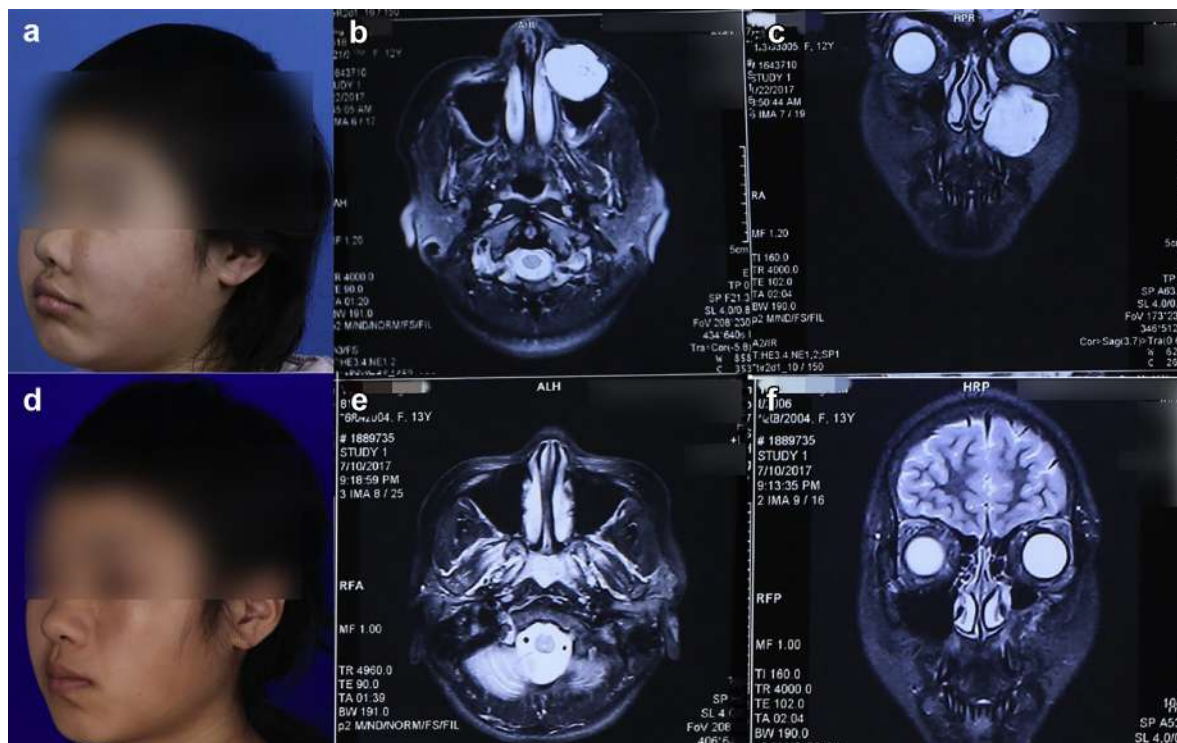


Fig 3. A 13-year-old girl with localized venous malformation (VM) of the face treated by bleomycin-polidocanol foam (BPF) sclerotherapy. **a**, Clinical appearance before treatment showing a mass on the left side of the face. **b** and **c**, Pretreatment T2-weighted magnetic resonance imaging (MRI) showing a hyperintense mass of the right facial region. **d**, After one session of BPF sclerotherapy, significant improvement of VM lesions was obtained. **e** and **f**, Post-treatment T2-weighted MRI 6 months after treatment showing complete resolution of VM lesions.

reasons that BPF sclerotherapy is highly effective. The reason that BPF stability was improved still needs further research.

Table II. Clinical efficacy and complication

Clinical data	No.
Follow-up, months	14 (6-24)
Clinical response	
Excellent	32 (58.2)
Good	20 (36.4)
Poor	3 (5.4)
Pretreatment VM volume on MRI, mL	53.3 ± 79.9
Post-treatment VM volume on MRI, mL	8.8 ± 14.9
Size reduction on MRI, %	84.6
Complication	
Skin hyperpigmentation	5 (4.5)
Blister	3 (2.7)
Hair loss	2 (1.8)
Nausea	1 (1.0)
Fever	1 (1.0)
Abdominal pain	1 (1.0)

MRI, Magnetic resonance imaging; VM, venous malformation. Categorical variables are presented as number (%). Continuous variables are presented as mean ± standard deviation.

In our study, postprocedure complications were all minor in 10 of 55 patients (18.2%), and no major complications occurred. The complication rate of BPF sclerotherapy (18.2%) appears to be higher than that of polidocanol foam sclerotherapy (15.9%) and lower than that of ethanol sclerotherapy (24.9%).³¹ We believe it is necessary to perform phlebography before injecting BPF to avoid misinjection into the arteries, and the foam can also be tracked under the “roadmap” function of digital subtraction angiography.

There were multiple limitations in this study. First, the sample size was small because only 55 patients were included in this study. Second, this was a retrospective study without a control group. The evaluation approach we used was mostly from other publications, and the outcome measures differed in various studies. The comparison with other studies was not sufficiently accurate. We are now conducting a controlled randomized clinical trial to enable further confirmation of the efficacy and safety of this treatment. Third, a longer follow-up period is needed.

CONCLUSIONS

We introduce BPF sclerotherapy as a feasible technique to treat VMs, and our results show that it is safe and effective. BPF sclerotherapy is a promising first-line treatment of VMs.

AUTHOR CONTRIBUTIONS

Conception and design: XY, HC, XL

Analysis and interpretation: XY, HC, HG, CH

Data collection: XY, HC, HG, YJ, LH, YW, YS, WY

Writing the article: XY, YS

Critical revision of the article: XY, HC, HG, YJ, LH, CH, YW, WY, XL

Final approval of the article: XY, CH, HG, YJ, LH, CH, YW, YS, WY, XL

Statistical analysis: XY, HC

Obtained funding: XL

Overall responsibility: XL

XY and HC contributed equally to this article and share co-first authorship.

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