DSA-guided percutaneous sclerotherapy for children with oropharyngeal low-flow venous malformation

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Abstract. The present study investigated the efficacy and safety of digital subtraction angiography-guided 3% polidocanol foam sclerosing agent, as well as the combination of pingyangmycin and dexamethasone, for the treatment of children with oropharyngeal low-flow venous malformation. A total of 27 children with 35 lesions with oropharyngeal low-flow venous malformation were included. The subjects were randomly divided into Groups A (13 patients with 16 lesions, treated with 3% polidocanol foam sclerosing agent) and B (14 patients with 19 lesions, treated with pingyangmycin + dexamethasone), respectively. The clinical efficacies and adverse reactions were analyzed and compared between these two groups. The average number of treatment times for Group A was 2.45±0.6, with an efficacy rate of 87.50%, while the average number of treatment times for Group B was 2.07±0.4, with an efficacy rate of 84.21%. No significant difference was found in the average treatment times or efficacy rates between Groups A and B. In addition, the adverse reaction incidence for Groups A and B were 38.46 and 14.29%, respectively, with statistically significant differences between these two groups. The combination of pingyangmycin and dexamethasone was safe and effective in treating children with oropharyngeal low-flow venous malformation, with fewer adverse reactions and is worthy of clinical promotion.

Introduction

Venous malformation is one of the most common types of congenital vascular dysplasia, mainly caused by venous system stagnation at different stages during embryo development (1). The oropharynx represents the common site for venous malformation in children, where not only the appearance and function would be influenced, but also the psychological development (due to the affected appearance and organ dysfunction). Due to the complex and specific anatomical structure and physiological function of the oropharynx, the inappropriate choice or dosage of sclerosing agent may lead to tissue necrosis and dysfunction, dysphagia, sleep apnea and respiratory obstruction caused by lesion swelling. Therefore, the oropharyngeal venous malformation is difficult to treat.

At present, interventional sclerotherapy is the treatment recommended by the International Association of Veins (2,3). Interventional sclerotherapy is characterized by easy surgical procedures, limited trauma and satisfactory curative effects (4). In traditional sclerotherapies, sclerosing agents are usually injected under digital subtraction angiography (DSA) guidance, which can lead to complications such as local tissue necrosis, ulceration and ectopic embolism (5). The most commonly used interventional sclerosing agents include pingyangmycin, bleomycin, polyglycerol, polidocanol and ethanol (3). Sclerosing agents may cause local vascular endothelium damage, which may be followed by thrombosis, endothelial exfoliation, collagen fiber shrinkage and blood vessel occlusion. However, there is still disagreement on the application of sclerosing agents for venous malformation (6-8).

Clinicians generally opt for different sclerosing agents with varying dosages based on experience. The efficacy and adverse reactions to the sclerosing agents still need to be fully elucidated (7-10). This is of importance for the improvement of treatment efficacy for oropharyngeal venous malformation in children, by reducing postoperative adverse reactions and improving quality of life. In the present study, the efficacy and safety of DSA-guided polidocanol foam and the combination of bleomycin A5 and dexamethasone in the treatment of oropharyngeal low-flow venous malformation in children were investigated and analyzed. Both pingyangmycin and polidocanol have effects, with different efficacies and complications. The present study aimed to determine an effective treatment plan with lesser side effects for oropharyngeal venous malformation in children.

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Materials and methods

Study subjects. A total of 27 children with oropharyngeal low-flow venous malformation who were admitted to Qilu Children's Hospital of Shandong University from January 2016 to June 2017 were included in this study. The subjects comprised 11 males and 16 females, with an average age of 2.5±0.7 years, and the age of onset ranged between 4 months and 7 years old. The diagnostic criteria were consistent with the treatment guidelines for Oral and Maxillofacial Hemangioma and Vascular Malformations (11). Inclusion criteria for the study were as follows: i) Children with complete data and follow-up records; ii) children receiving no previous interventional sclerotherapy; iii) according to clinical history, physical examination and imaging data, cases diagnosed by direct puncturing diagnosis under DSA fluoroscopy, with angiographic results indicating low-flow venous malformation, with a slender reflux vein and slow reflux speed, in which there was still obvious contrast agent residue in the tumor after 5 mins of angiography (12); and iv) cases having normal liver and kidney function, without sepsis, coagulopathy or cardiopulmonary insufficiency, nor a history of allergies for iodine angiography and anhydrous ethanol. The exclusion criteria were as follows: i) Cases with incomplete data; ii) cases with lesions that had been previously treated with sclerotherapy; iii) cases with high-flow venous malformations; and iv) cases with other vascular diseases such as arteriovenous malformations and lymphatic malformations. The present study was approved by the ethics committee of Qilu Hospital of Shandong University. The guardians of all parents provided written informed consents and were informed of the possible risks and complications of interventional sclerotherapy for oropharyngeal venous malformation. All 27 children underwent an MRI examination, which showed round or irregular long T1 and T2 signals, with clear boundaries. Enhanced scanning showed varying degrees of enhancement. The ultrasound examination showed uneven echoes within the lesions, with a tubular echo signal inside. Study subjects were randomly divided into the following groups: Group A, which included 13 cases, with 16 lesions, subjected to treatment with polidocanol foam sclerosing agent; and Group B, which included 14 cases with 19 lesions, subjected to the combination treatment of pingyangmycin + dexamethasone (Table I). Among the patients, the smallest lesion size was 0.5x0.5x1.2 cm, while the largest lesion size was 3.1x2.7x3.8 cm. All subjects were unaware of the grouping process.

Table I. Clinical data of included cases.

Characteristics	Group A (n=13)	Group B (n=14)
Sex, n		
Males	5	6
Females	8	8
Age at initiation of treatment, years	2.7±1.2	2.1±5.7
Location of IH, n		
Lip	4	3
Pharynx	2	2
Tongue	5	6
Multiple	2	3
Average no. of treatments, frequency	2.45±0.6	2.07±0.4

IH, infantile hemangioma.

Preparation of sclerosing agents. Polidocanol foam sclerosing agent was prepared according to the Tessari method (13). Two 2.5-ml screw syringes were briefly connected with a three-way valve. A total of 0.5 ml polidocanol (3%; Chemische Fabrik Kreussler & Co. GmbH) in one syringe was mixed with 2 ml CO_2 in another syringe by pumping the syringes 20 times. The valve was switched down as much as possible, and the syringes were rapidly pumped another 10 times to obtain the foam agent. A volume of <10 ml of 3% polidocanol was injected each time. For the preparation of pingyangmycin + dexamethasone, 8 mg pingyangmycin (Jilin Aodong Pharmaceutical Group Co., Ltd.) was dissolved in 4 ml contrast agent (Iodixanol injection; Beijing Beilu Pharmaceutical Co., Ltd.). The dosage was determined according to the body surface area (10 mg/m^2), which was subsequently mixed with 1-2 mg dexamethasone.

Treatment methods. Sclerotherapy was performed using DSA equipment (Artis zee; Siemens Healthineers). Prior to surgery, the lesions were marked on the surface according to the results of the MRI examination. Following general anesthesia, the child was placed in a relaxed position. The skin of the lesion area was routinely disinfected. A 4.5-scalp needle was used to puncture the lesion, and the injection depth was determined based on the MRI imaging. A venous malformation that could be observed under radiography was defined as a successful puncture. Local angiography was performed under DSA fluoroscopy. The shape, extent, and venous drainage of the tumor nests were determined. For Group A, 3% polidocanol foam was injected under the path diagram mode. The sclerosing agent was shown as a negative shadow, until the reflux vein was filled with the sclerosing agent. For Group B, DSA fluoroscopy indicated that the pingyangmycin dilution was directly injected into the venous malformation vascular mass. The original contrast in the tumor nest was displaced, and the injection was stopped when the tumor nest was filled or the venous drainage was observed. Thereafter, multi-point and multi-angle puncture and angiography were performed in the lesion area to determine whether there were any residual or new lesions. Subsequently, the treatment was continued according to the above protocol. Following treatment, routine DSA fluoroscopy was performed to confirm the sclerosing agent within the lesion without subcutaneous exudation or abnormal reflux. The patients were then carefully observed. For cases with disappearing or partial remission of clinical symptoms, but with the MRI examination showing a residual lesion >10%, or those suffering from recurrence following stabilized symptoms, the interventional therapy was repeated (with time intervals of >1 month). Treatment endpoints were as follows: i) When clinical symptoms disappeared, and the imaging examination showed residual lesions of <10%; ii) cases reporting no symptom relief or even aggravation,

Table II. Analysis of number of treatments between Groups A and B.

Characteristics	Group A (n=16)	Group B (n=19)	t	P-value
Number of treatment times (range)	2-3	1-3	10.985	0.072
Average number of treatment times, X±SD	2.45±0.6	2.07±0.4		

after three sequential treatments; and iii) parents who ended treatment.

Evaluation of drug efficacy and adverse reaction to drugs. Post-operative adverse reactions including fever, skin swelling, ulceration, digestive tract reaction, hemorrhage, and abnormal function of surrounding tissues and organs were observed. Follow-up observation was performed at 1, 3, 6 and 12 months after surgery. Therapeutic efficacy was evaluated based on clinical symptoms and MRI examination. The efficacy criteria were as follows (14): i) Cured, the symptoms completely disappeared after interventional treatment, with normal surface color and without recurrence; ii) basic remission, the lesion generally disappeared (reduced by >80%), with no dysfunction, mild skin pigmentation, and further treatment needed; iii) effective (improved situation), the tumor was significantly reduced (to <80%), and further treatment would be needed and iv) invalidation, the tumor was not reduced, remained unchanged or continued to develop. The therapeutic efficiency was calculated according to the following formula: Efficiency=(cured cases + basic remission cases + effective cases)/total cases x100. Minor complications mainly included self-limiting symptoms requiring no clinical intervention, and permanent residual functional damage after clinical treatment such as fever, local swelling, skin ulceration and pain. Major complications included permanent nerve damage, extensive tissue necrosis, cerebral embolism and death.

Statistical analysis. Statistical analysis was performed using SPSS 18.0 software (SPSS, Inc.). The count data was compared using the χ^2 test, while the measurement data were analyzed with a Student's t-test. Data are presented as the mean ± SD. $P<0.05$ was considered to indicate a statistically significant difference.

Results

Analysis of number of injections of sclerosing agents. The number of injections of sclerosing agents were analyzed and compared between Groups A and B. The results showed that Group A subjects (polydoxan foam sclerotherapy), who underwent treatment 2-3 times, had an average number of treatments of 2.45±0.6. Group B subjects (pingyangmycin and dexamethasone combination), underwent treatment 1-3 times, with an average number of treatments of 2.07±0.4. No significant difference was observed in the number of injections between these two groups ($P>0.05$; Table II).

Analysis of therapeutic efficacy. The therapeutic efficacies of the drugs were analyzed and compared between Groups A and B. The results showed that the efficacy rate of Group A was 87.50%, which was not significantly declined in Group B (84.21%; Table III; Figs. 1 and 2). The results suggested that both methods resulted in the satisfactory treatment of children with oropharyngeal low-flow venous malformation.

Analysis of postoperative adverse reactions. Postoperative adverse reactions were analyzed and compared between Groups A and B. The results showed that one fever case, three cases of swelling in the lesion area and one case of necrosis with rupture were found in Group A subjects, with an adverse reaction incidence of 38.46%. One case of fever and one case of vomiting was found in Group B subjects, with an adverse reaction incidence of 14.29%. A significant difference was measured in the adverse reaction incidence between these groups ($P<0.05$; Table IV). These results suggested that the combination of pingyangmycin and dexamethasone is safer for the treatment of children with oropharyngeal low-flow venous malformation.

Discussion

Venous malformation mainly results from abnormal development of the embryonic vascular plexus, rather than abnormal proliferation of vascular endothelial cells (15). Direct puncture venography represents the gold standard for the diagnosis of venous malformation, which could contribute to the evaluation of morphological and blood flow characteristics (16). According to puncture angiography, venous malformation can be divided into low- and high-flow types, based on the thickness, number and flow speed of the reflux veins (16-18). At present, sclerotherapy has become the first choice for the treatment of venous malformation, especially under DSA guidance (19). Sclerotherapy can clearly define the size, extent and drainage of the lesions, and reduce the extravasation of sclerosing agents, reducing the number of treatments required as well as the ensuing complications (20). Polidocanol is widely used in Europe and the United States, although its clinical application is still in its infancy in China (7). Polidocanol has certain anesthetic effects, causing less pain and better pain tolerance (21). The main side effects of polidoclanol treatment include liver and kidney function damage, ulcer, necrosis, fever, dizziness, chest tightness, nausea and visual impairment (21). Cabrera *et al* (22) used 0.5-3% polidocanol foam sclerosing agent under ultrasound guidance to treat venous malformations, with an efficacy rate of 92%, and no serious complications were observed. Foam sclerosing agents have been gradually developed for the sclerotherapy for venous malformations (10). The effects of pingyangmycin in the treatment of venous malformation are based on the fact that it may damage and destroy the vascular endothelial cells (by inducing cell degeneration and atrophy),

Table III. Analysis of therapeutic efficacy between Groups A and B.

Therapeutic efficacy	Group A (n=16) (%)	Group B (n=19) (%)	χ^2	P-value
Cured	7 (43.75)	9 (47.37)	2.132	0.242[a]
Basic remission	5 (31.25)	4 (21.05)		
Effective	2 (12.50)	2 (10.52)		
Invalidation	2 (12.50)	3 (15.79)		
Effective rate	87.50	84.21		

[a]P<0.05.

Table IV. Analysis of postoperative adverse reactions between Groups A and B.

Complication	Group A (n=16) (%)	Group B (n=19) (%)	χ^2	P-value
Fever	1 (7.69)	1 (7.14)	5.286	<0.001[a]
Pain	0 (0)	0 (0)		
Digestive tract reaction	0 (0)	1 (7.14)		
Local swelling	3 (23.08)	0 (0)		
Necrosis/ulceration	1 (7.69)	0 (0)		
Adverse reaction rate	5 (38.46)	2 (14.29)		

[a]P<0.05.

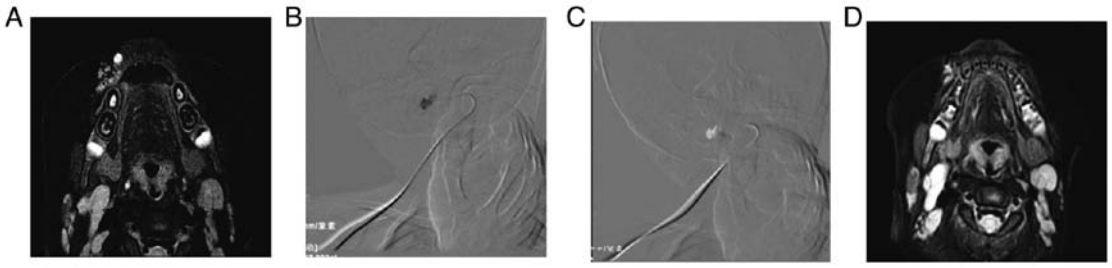

Figure 1. Therapeutic efficacy of polidocanol foam sclerosing agent. (A) Pre-operative MRI (T2WI fat-suppressed images) showing abnormal signals in the lips. DSA orthotopic images of DSA-guided interventional sclerotherapy for lip venous malformation are presented. (B) DSA orthotopic image showing the lesion. (C) Under the path diagram mode, polidocanol foam sclerosing agent was injected into the lesion vessels through a puncture. (D) MRI data at 3 weeks after interventional sclerotherapy, indicating significantly reduced original lesion signals. DSA, digital subtraction angiography.

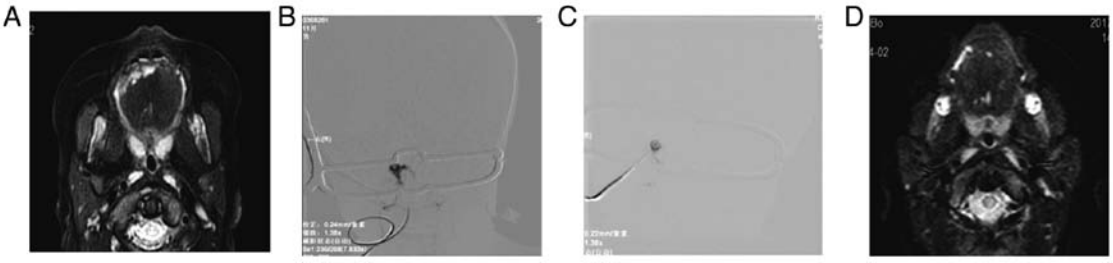

Figure 2. Therapeutic efficacy of pingyangmycin and dexamethasone combination treatment. (A) Pre-operative MRI (T2WI fat-suppressed images) showing abnormal signals in the tongue. (B) DSA orthotopic images of DSA-guided interventional sclerotherapy for lip venous malformation are presented. (C) A combination of pingyangmycin and dexamethasone was injected into the lesion vessels through a puncture. (D) MRI data at 2 weeks after interventional sclerotherapy, indicating significantly reduced original lesion signals. DSA, digital subtraction angiography.

leading to the regression of venous malformation (23). Since pingyangmycin injection treatment does not cause damage to peripheral nerves, blood vessels or other tissue structures, it is suitable for the treatment of oropharyngeal venous malformations, especially for children (24). The main adverse reactions to pingyangmycin treatment include fever, gastrointestinal

reactions, pulmonary fibrosis, local pain and stomatitis (25). Dexamethasone has an inhibitory effect on the angiogenesis of vascular endothelial cells and anti-inflammatory effects, which can reduce adverse reactions such as fever (2). The combination of dexamethasone and pingyangmycin has been shown to not only improve the curative effect and shorten treatment duration, but also significantly reduce local swelling and fever and prevent the release of excessive heat in the body, caused by pingyangmycin and related allergic reactions (26).

The results of the present study showed that there was no significant difference in the number of treatments and therapeutic efficiency between polidocanol treatment and the combination treatment of dexamethasone and pingyangmycin. The efficacy rate for polidocanol foam sclerosing agent was at 87.50%, with an average number of treatments of 2.45±0.6. Moreover, 3% polidocanol foam sclerosing agent was used to treat low-flow venous malformation. The foam agent demonstrates unique adhesiveness and compactness and is injected into the vein to form a mass. This prevents blood from diluting the drug, enlarges the contact area with the vascular endothelium, prolongs contact time and improves hardening efficiency (27). Moreover, the curative effect was clear, with reduced treatment numbers, thereby effectively reducing the risk of adverse reactions (28-30). In the present study, 19 lesions were treated with a pingyangmycin and dexamethasone combination. The results showed that the efficacy rate for the combination treatment was 84.21%, with an average number of treatments of 2.07±0.4, indicating satisfactory therapeutic efficiency, consistent with previous findings (31). The main adverse reactions in these two groups included fever, digestive tract reaction, local soft tissue swelling and ulceration. No patients had life-threatening complications such as cardiopulmonary and cerebrovascular accidents. The adverse reaction incidences for Groups A and B were 38.46% and 14.29%, respectively, suggesting that the therapeutic efficacy of pingyangmycin and dexamethasone combination was better compared with polidocanol treatment. The post-operative adverse reaction incidence for polidocanol foam sclerosing agent was 38.46%, including fever, local soft tissue swelling and ulceration. In three cases, swollen lesions were observed, which generally disappeared 2-5 days after surgery. After injection with polidocanol foam sclerosing agent, the drug may accumulate to induce local necrotic ulcers. In the present study, one case reported local tissue ulceration after polidocanol foam sclerosing agent injection, which was cured by local anti-infection treatment. In addition, among the 14 patients subjected to the combination treatment of pingyangmycin and dexamethasone, two of the cases displayed adverse reactions (fever and digestive tract reactions), with an incidence rate of 14.29%, which returned to normal after treatment. Compared with the treatment of polidocanol foam sclerosing agent, the adverse reactions to the combination treatment were significantly reduced, making the combination treatment a safe and reliable treatment method, with few adverse reactions, as well as satisfactory appearance and functional recovery.

The current study had several limitations. Firstly, the sample size of children with low-flow oropharyngeal venous malformation was limited. The sample size should be increased in future research, which will improve the accuracy and reliability of the data obtained. Secondly, the long-term efficacy of the treatments remains to be further observed.

In conclusion, polidocanol foam sclerosing agent, as well as the combination of pingyangmycin and dexamethasone, represent effective treatment methods for children with oropharyngeal low-flow venous malformations. Compared with the polidocanol foam sclerosing agent, the combination of pingyangmycin and dexamethasone was safer with fewer complications, and is worthy of clinical promotion. Collectively, DSA-guided therapy is a visualization technique that monitors the treatment process and increases treatment safety.

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Availability of data and materials

All data generated or analyzed during the present study are included in this published article.

Authors' contributions

DS, LG, HS, JL, LW, CWa, CWu, YN and QZ designed the current study, performed the experiments, collected and analyzed the data, and prepared the manuscript. All authors read and approved the final manuscript.

Ethics approval and consent to participate

The present study was approved by the Ethics Committee of Qilu Hospital of Shandong University. The guardians of all patients provided written informed consent.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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