

Clinical efficacy of absolute ethanol combined with n-butyl cyanoacrylate sclerotherapy in the treatment of Puig's classified advanced venous malformation in children

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Abstract. The aim of the present retrospective study was to investigate the clinical safety and efficacy of absolute ethanol combined with n-butyl cyanoacrylate sclerotherapy in the treatment of Puig's classified advanced venous malformation. Sclerotherapy was performed in 121 children (52 males and 69 females; age range, 5 months to 16 years) with venous malformations under general anesthesia between April 2009 and October 2014 at the Department of Interventional Radiology and Vascular Anomalies, Guangzhou Women and Children's Medical Center, Guangzhou, China. The patients with venous malformations were diagnosed and classified according to the diagnostic criteria of the International Society for the Study of Vascular Anomalies. According to the characteristics of intraoperative percutaneous angiography, 21 patient cases (9 males and 12 females; age range, 6 months to 14 years) were classified as advanced Puig's venous malformation. These 21 patients were treated with absolute ethanol combined with n-butyl cyanoacrylate. The patients were followed-up for 6-24 months (average, 15 months) after treatment. Following treatment with absolute ethanol combined with n-butyl cyanoacrylate, 15 cases were controlled and the total effective rate was 71% (15/21). However, 1 patient developed skin ulcerations, which was classed as a minor complication, 1 patient developed ectopic embolism caused by n-butyl cyanoacrylate reflux, and 1 patient developed transient pulmonary hypertension, the latter two complications were

classified as major. Notably, the incidence rate of minor and major complications were 14.3%. To conclude, the present findings indicated that absolute ethanol combined with n-butyl cyanoacrylate sclerotherapy was a safe and effective method with a low complication rate in the treatment of Puig's classified advanced venous malformation in patients.

Introduction

Venous malformation is the most common type of vascular malformation (1,2). Typically, venous malformations are present at birth and develop gradually throughout life. The lesions grow in proportion to the body over time, and unlike hemangioma, do not spontaneously regress (3). The pathological feature of venous malformation is the absence of endothelial cell mitotic activity, which is the most fundamental difference from hemangioma (4). Venous malformation may be characterized by thin vascular walls, a reduced number of smooth muscle cells and a larger than normal ratio of vascular wall radius to vascular wall thickness. Also, veins are typically small and/or medium-sized (5). Additionally, the vein wall only has one or no layer of smooth muscle cells and is therefore abnormally expanded. Due to the lack of valves in venous malformations, blood readily flows backward and stops when it accumulates in the cavity. As a result, a thrombus can form after coming into contact with endothelial cells. This state is defined as local intravascular coagulation, which is the leading cause of pain in venous malformation. The incidence of venous malformations is low, without predisposition for sex. Unlike hemangioma, venous malformation is not associated with endothelial cell proliferation. Furthermore, the malformations can vary according to the location of malformed lesions. If the surface is violaceous with a protuberant subcutaneous mass, which can be reduced by pressing. Currently, interventional sclerotherapy is recommended as the first choice treatment by the International Union of Phlebology (6,7). However, due to rapid reflux rate following the injection and the short half-life of the sclerosing agent, the efficacy of this method is typically unsatisfactory (8). Furthermore, postoperative recurrence in

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Puig's classified advanced venous malformation is common (9). In the current study, a total of 121 patients with venous malformations who underwent interventional sclerotherapy between April 2009 and October 2014 were retrospectively analyzed. A total of 21 patients with Puig's classified advanced venous malformations were successfully treated with absolute ethanol combined with n-butyl cyanoacrylate.

Materials and methods

Clinical data. A total of 121 patients with venous malformations, who underwent interventional sclerotherapy under general anesthesia between April 2009 and October 2014 at the Department of Interventional Radiology and Vascular Anomalies, Guangzhou Women and Children's Medical Center, Guangzhou, China were retrospectively enrolled in the present study. This retrospective study was approved by the Ethics Committee of Guangzhou Women and Children's Medical Center, Guangzhou, China.

All patients (52 males and 69 females; age range, 5 months to 16 years) met the International Society for the Study of Vascular Anomalies diagnostic criteria for venous malformations (10,11). Most lesions were present since birth and had grown proportionally with the patients. The superficial foci appeared blue, the masses were compressible and the texture was soft. The skin temperatures in the lesion areas were not higher compared with the surrounding area (a key point for hemangioma identification) and the lesions tested positive in the posture experiment. During this experiment, changing the position or pressing the proximal part of lesion increased the local venous pressure and mass swelling. In addition, when venous draining was unimpeded, the venous malformation could be partly or largely retracted. All patients underwent magnetic resonance imaging (MRI) examinations (Philips Achieva 3.0 T dual gradient MRI imager). The lesions exhibited equal or low signals on T₁WI and high signals on T₂WI. Ultrasound examinations revealed that the lesions were expressed as uneven internal echoes with irregular sharp and pipe-like echoes. Venous blood flow was probed using the Doppler test.

A total of 121 patients with venous malformations were initially selected on the basis of admission time. The venous malformations were classified according to Puig's classification (12) using the angiography of venous malformations, for which 21 cases met the inclusion criteria. The inclusion criteria were as follows: Complete follow-up records; no previous intervention sclerotherapy; diagnosis was confirmed by direct puncture angiography under digital subtraction angiography (DSA) guidance and belonged to type III or type IV, according to Puig's classification; and the patient/guardian provided informed consent for treatment. Exclusion criteria consisted of the following: Incomplete data; the effective lesion had been previously treated with sclerotherapy; and other vascular diseases were also present, including venolymphatic malformation and/or arteriovenous malformations.

Among the 21/121 selected patients (9 males and 12 females; age range, 6 months to 14 years), the lesion in 9 patients occurred at birth and gradually increased with age, and the lesion in 12 cases occurred 3-24 months after birth.

With regard to the lesion distribution, the lesions were located in the maxillofacial region in 8 patients (38%), in the limbs in 6 patients (29%), in the trunk in 4 patients (19%) and in the gluteal region in 3 cases (14%). A total of 7 patients had superficial venous malformations and the foci were subcutaneously located in 5 patients but in the mucous membrane in 2 patients. A total of 14 cases had intramuscular venous malformations; the foci were located in the deep muscle tissue and the mass was only palpable when painful. Foci involving the skin or mucous surface were bluish-violet in color and elevated from the skin surface or mucous membrane; the foci located in deep muscle tissue were expressed as a mass in MRI imaging, the texture of which was soft and tested positive in the posture experiment. A total of 9 patients exhibited a single localized lesion, whereas 12 patients exhibited multiple diffuse lesions (≥ 2). The lesion sizes ranged from 1.5x2.2x1.0 to 14.0x11.0x7.0 cm. There were 14 patients who had chief complaints of irregular pain at the lesion site, which could be relieved without further treatment.

Angiography and classification of venous malformations. All 121 patients underwent local puncture angiography of the lesion prior to treatment. With regard to the angiography method applied, the most protuberant part of the venous malformation or the most painful site was labeled according to the child's complaint and punctured directly using a 6.5 disposable venous transfusion needle. When the lesion was successfully punctured, venous blood was smoothly pumped back. If there was no venous blood or the pumping was not smooth, the puncture was performed again. Subsequently, iohexol contrast agent (30% iodine content) was slowly injected under fluoroscopy until the lesion was fully opacified. A small quantity of contrast agent was injected to observe any draining vein and its diameter. Furthermore, it was observed whether vascular malformations could be fully filled. In addition, the size, whether there was definite drainage, the vein development and the direction of vein drainage was recorded. Based on lesion morphology and the characteristics of draining veins, the venous malformations were classified as type I-IV according to Puig's classification as follows: Type I, isolated malformation without peripheral drainage; Type II, malformation that drains into normal veins; Type III, malformation that drains into dilated veins; and Type IV, malformation that represents dysplastic venous ectasia. The draining rate was slow in the type I and II malformations, and the sclerosing agent worked more effectively. By contrast, the draining rate was fast in type III and IV malformations and the injected sclerosing agent did not have adequate contact with the blood vessel wall, and thus the effect was poor, leading to ready recurrence of the lesions. Of the selected patients, 13 were diagnosed with type III and 8 with type IV venous malformations.

Drug allocation. All operations were performed under the guidance of Innova 3100 (American GE Corp., Fairfield, CT, USA). The drugs used during the operation included absolute ethanol, n-butyl cyanoacrylate (NBCA glue, 0.5 ml; B. Braun Melsungen AG, Melsungen, Germany), lipiodol injection (10 ml/tube; Guerbet, Roissy, France) and iohexol injection (120 mg/ml; GE Pharmaceutical Co., Ltd., Shanghai, China). The ratio of absolute ethanol to lipiodol in the sclerosing agent

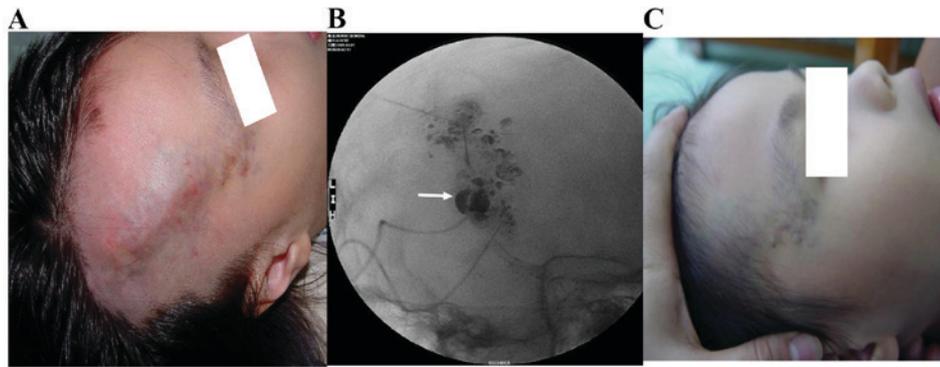


Figure 1. Representative follow-up by angiography imaging. (A) A 9-year-old child, with a mass on the left maxillofacial region that was discovered at birth. The lesion gradually increased in size, and was diagnosed as venous malformation. (B) Percutaneous interventional sclerotherapy was guided by digital subtraction angiography; 0.5 ml of n-butyl cyanoacrylate glue and 2 ml ultra-liquefied lipiodol were used (arrow), and then 8 ml absolute ethanol and 1.6 ml ultra-liquefied lipiodol suspension were injected at another needle puncture point (not shown). (C) The child was treated with interventional sclerotherapy twice, and reviewed 6 months after the operation, by which time the lesion size had markedly reduced.

was 5:1 (v/v). The maximum dosage of absolute ethanol was 1 ml/kg, with a total dosage of ≤ 50 ml. When the dosage of absolute ethanol exceeded 0.5 ml/kg, the pulmonary artery pressure was monitored. The ratio of NBCA glue to lipiodol was 1:3 to 1:5 (v/v).

Treatment method. All interventional sclerotherapies were performed on patients under general anesthesia as the patients were children. The surgical sites were labeled according to the description given by the parents. Following successful anesthesia, the most protuberant part of the venous malformation was directly punctured using a 6.5 disposable venous transfusion needle containing the contrast agent. When the lesion was successfully punctured, venous blood was smoothly pumped back. If there was no venous blood or the pumping was not smooth, the puncture was performed again. Following this, iohexol contrast agent (30% iodine content) was injected under fluoroscopy and the filling of venous malformation was continuously observed. Prior to treatment with sclerosing agent, the patients were intramuscularly injected with 0.3 mg/kg dexamethasone and the proximal-end draining veins of the venous malformation were pressed using a tourniquet to expand lesions. The NBCA glue was slowly injected into the lesion under fluoroscopy via a venous transfusion needle, which was used for injecting the contrast agent. The ratio of glue and lipiodol mixture used was 1:4. During the injection process, NBCA glue was observed under fluoroscopy to monitor whether it entered into the draining veins and to assess the filling of the vessel mass. In addition, 5% glucose water was used prior to and following injection to avoid solidification of the NBCA glue. The use of salt water was prohibited as NBCA glue solidifies quickly following ion exposure. When angiography exhibited a marked reduction in the draining velocity of lesions, absolute ethanol was injected. When the draining vein was embolized completely, injection of the sclerosing agent was stopped. If the lesion could not be completely filled via one injection point, another puncture site was used to inject the embolization agent. Subsequently, a second needle was used next to the original puncture point. All patients were followed-up 2 months after treatment. If the symptoms persisted, the treatment was continued. The time interval between treatments was 2 months. The patients were

followed-up for 6-24 months (average, 15 months) following treatment.

Efficacy criteria and follow-up. All patients were reviewed 2 months after treatment and efficacy of the treatment was evaluated. If the lesions were reduced by $< 80\%$ or if the symptoms persisted, the treatment was continued and the aforementioned therapeutic method was used. The efficacy of treatment was evaluated by MRI examination. The final efficacy was determined by an MRI performed 6 months after the final treatment. The treatment efficacy was classified into three levels (11,13): i) Controlled, the majority of lesions disappeared after injection (lesions were reduced by $> 50\%$) and the pain symptoms were relieved; ii) no change, the lesions were reduced by $< 50\%$ and the pain symptoms persisted; and iii) failed, lesions remained unchanged or continued to increase. The following calculation was used to determine the effective rate: Effective rate = the number of controlled cases/the number of total cases $\times 100\%$. Additionally, the systemic and local adverse reactions in patients were recorded. Since all patients demonstrated local swelling and pain following the operation, which was relieved without treatment 3-7 days after operation, and the swelling was due to the sclerotherapy mechanism, swelling and pain were not classified as adverse reactions.

Statistical analysis. The data are presented as the mean \pm standard error of the mean. SPSS 13.0 statistical software (SPSS, Inc., Chicago, IL, USA) was used to calculate the efficacy and adverse reaction rates in the study. The comparison of effective rates and incidence of adverse reactions between the two groups were tested using the χ^2 test. $P < 0.05$ was considered to indicate a statistically significant difference.

Results

Efficacy. Telephone follow-ups (for patients who resided far from the treatment center) and questionnaire follow-ups were performed for 6/21 patients (29%); office visits, imaging and questionnaire follow-ups were performed for 11/21 patients (52%); and office visits and imaging follow-ups with no questionnaire were performed for 4/21 patients (19%). Imaging

Table I. Patient demographic and clinical characteristics.

Patient no.	Age (years)	Sex	Lesion location	Number of procedures for each patient	Follow-up result
1	3.0	F	Maxillofacial region	2	Controlled
2	1.5	F	Upper limbs	2	Controlled
3	6.0	M	Maxillofacial region	3	Controlled
4	5.0	F	Trunk	1	No change
5 ^a	7.0	M	Lower limbs	3	Controlled
6	3.6	M	Maxillofacial region	2	Controlled
7	11.0	F	Trunk	4	Controlled
8	6.0	F	Lower limbs	2	Controlled
9 ^b	8.0	M	Maxillofacial region	3	No change
10	3.0	F	Lower limbs	2	Controlled
11	14.0	M	Trunk	1	No change
12	7.0	M	Maxillofacial region	3	Controlled
13	5.0	F	Gluteal region	2	Failed
14	8.0	F	Trunk	1	Controlled
15	0.5	F	Upper limbs	1	Controlled
16 ^c	5.0	M	Maxillofacial region	2	Controlled
17	4.0	M	Gluteal region	2	Controlled
18	3.0	F	Maxillofacial region	3	Failed
19	9.0	F	Upper limbs	2	Controlled
20	2.0	M	Gluteal region	1	No change
21	10.0	F	Maxillofacial region	2	Controlled

M, male; F, female. Certain patients exhibited adverse reactions, including ^askin ulcerations, ^bectopic embolism and ^ctransient pulmonary hypertension.

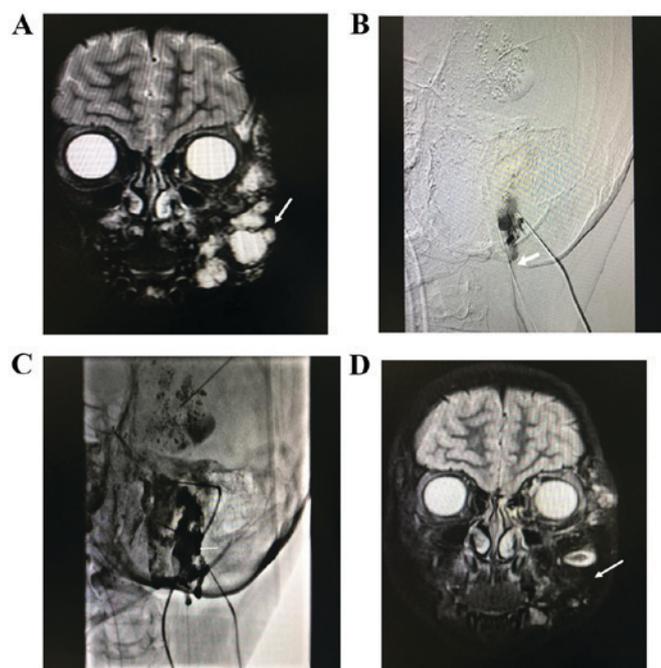


Figure 2 (A) A 6-year-old child with right temporal venous malformation. (B) The refractory lesion can be seen. Percutaneous interventional sclerotherapy was guided by digital subtraction angiography; (C) 0.5 ml n-butyl cyanoacrylate glue with 2 ml ultra-liquefied lipiodol and then 10 ml absolute ethanol with 2 ml ultra-liquefied lipiodol suspension were used. (D) The child was treated once, and was reviewed 5 months after the operation, by which time the lesion size had markedly reduced.

follow-ups consisted of MRI imaging in 16 patients and angiography in 5 patients (Figs. 1 and 2).

Treatment outcome and adverse events. A total of 21 patients with Puig's classified advanced venous malformations were treated with absolute ethanol combined with n-butyl cyanoacrylate, of whom in 15 patients the syndrome was controlled and the symptoms disappeared; thus the total effective rate was 71% (15/21). Notably, 1 patient developed skin ulcerations, which classified as a minor complication, 1 patient developed ectopic embolism caused by n-butyl cyanoacrylate reflux and 1 patient developed transient pulmonary hypertension. The incidence rate of adverse reactions was 14.3% (Table I).

Discussion

Puig's classified advanced venous malformation is difficult to treat clinically. Extensive lesions cannot be surgically removed and the efficacy of sclerosing embolization is poor since large draining veins cannot be embolized by liquid embolic agents (14-16) or foam embolic agents (17,18). Furthermore, the contact time between the sclerosing agent and vein endothelial cells is short, and thus proper treatment of vascular malformation sclerosis cannot be achieved (19). It has also been indicated that notable sclerosing agent reflux causes serious complications. The effective rate of absolute ethanol treatment for low draining venous malformations has

been reported as 75-95% (14,15,20); however, the efficacy of interventional therapy for Puig's classified advanced venous malformations has been unsatisfactory, which was reported to be at only 41% (21). To the best of our knowledge, this is the first study to report the use of absolute ethanol combined with n-butyl cyanoacrylate sclerotherapy in patients for the treatment of Puig's classified advanced venous malformation. The present findings indicated that the effective rate was 70%, which was higher compared with rates described in a previous study, which was 55% (15).

NBCA is an acrylic adhesive. In the blood, it rapidly polymerizes with free hydroxide in plasma and causes blood clots (22). As the acrylic adhesive is in liquid form, it can be evenly dispersed throughout the lesions and can promote embolic effects (23). Furthermore, NBCA is spongy following polymerization and does not easily form lumps (24). Lipiodol can delay the polymerization of NBCA and also the NBCA can be monitored under DSA (25). Hence, NBCA is considered safe and accurate for embolizing lesions. Previously, NBCA glue has been predominantly used in the treatment of encephalic angioma, carotid body lesions and arteriovenous fistulas (22,26). It is less aggressive than absolute ethanol, instantly polymerizes in the blood and is considered non-toxic and non-carcinogenic. In the current study, NBCA glue was used to embolize venous drainage such that blood flow was substantially reduced in Puig's classified advanced venous malformations, and the reported efficacy was ~70% in combination with absolute ethanol. NBCA and lipiodol are commonly mixed at a 1:3-5 ratio for intraoperative use. In the present study, when the proportion of lipiodol was low, NBCA could easily solidify, therefore, it could not fully reach the distal end of the draining vein. If the proportion of lipiodol was high, the concentration of NBCA decreased and NBCA was easily refluxed, therefore, it failed to fully embolize the draining vein. Notably, injection of an appropriate volume was crucial. If the quantity of sclerosing agent injected was too low, the efficacy was limited; if too high, the sclerosing agent refluxed, which can lead to serious consequences. According to the present results, the sclerosing agent injection should be stopped in any of the following cases: If the injection pressure increased, if the sclerosing agent diffused into the interstitial space outside the lesions or if the skin color changed. In the present study, all injection procedures followed the above principles.

It was critical to accurately determine the endpoint for the application of sclerotherapy in the treatment of venous malformations. It was difficult to cure large venous malformations, and therefore the other objective of the treatment used in the present study was to control the development of the lesion, decrease the volume and improve the appearance, rather than radically attempt to cure the lesion (7,27-29). In a clinical setting, it was determined that the lesions could not be removed in certain patients with venous malformations who had undergone sclerotherapy >10 times. Therefore, the concept of 'cure' for venous malformation was not the removal of the lesion but the disappearance of symptoms. In addition, sclerotherapy may be unable to prevent the continued progression of remaining lesions according to previous reports (30). For Puig's classified advanced venous malformations, the indications for treatment must be

carefully considered. There is no consensus on the selection of sclerosing agent in the clinical practice and large randomized clinical trials are insufficient. Most clinicians select the sclerosing agent according to their own familiarity with sclerosing agents and the focus size (8,31,32). To the best of our knowledge, this is the first study to report the use of NBCA glue combined with absolute ethanol in the treatment of Puig's classified advanced venous malformations. The findings in the present study provide a novel option for the sclerotherapy of venous malformations.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

HBL and CQN acquired data. LGL and JZ designed the present study. XML, ZYL and SYZ interpreted of data. The final version of the manuscript has been read and approved by all authors, and each author believes that the manuscript represents honest work.

Ethics approval and consent to participate

Ethical approval was granted by the Ethics Committee of Guangzhou Women and Children's Medical Center, Guangzhou, China. All procedures performed involving human participants were in accordance with the ethical standards of the Ethics Committee of Guangzhou Women and Children's Medical Center and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Patient consent for publication

Informed consent, which included agreement to the publication of patient data and accompanying images (following anonymization), was obtained from the parents or guardians of participants included in the present study.

Competing interests

The authors declare that they have no competing interests.

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