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Efficacy and safety of DSA-guided percutaneous sclerotherapy for venous malformations of penile region in children

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ABSTRACT

Objective: To describe the effectiveness and security of DSA-guided percutaneous sclerotherapy for venous malformations of penile region in children.
Methods: A total of 9 cases children with penile venous malformations treated by DSA-guided percutaneous sclerotherapy from January 2017 to June 2018 were enrolled in this study. Local angiography was performed under DSA fluoroscopy, and the shape, extent and venous drainage of the tumor nest were judged. Then sclerosing agents (Pingyangmycin and Polidocanol) were selected according to the flow rate of angiography and treated by percutaneous injection under DSA monitoring. Imaging examination (MRI) was performed to evaluate clinical improvement.
Results: A total of 26 interventional sclerotherapy sessions were performed in 9 children, with an average of (2.3 ± 0.5) sessions per case. After a mean follow-up of 7.3 months, 6 cases were cured, and 3 cases were in basic remission. There were 9 cases of temporary edema secondary to the treatment site and 3 cases of mild pain. No serious complications such as ulceration, hemorrhage, infection and dysfunction occurred in any patients.
Conclusion: DSA-guided percutaneous sclerotherapy for venous malformations of penile region in children is safe and effective, does not affect the appearance and function of penis, and is worthy of clinical promotion.
Type of study: Treatment Study.
Level of evidence: Level IV, Case series with no comparison group.

Venous malformation (VMs) is one of the most common types of congenital vascular dysplasia, and can occur in any tissue of the body [1,2]. The usual clinical presentation is a faint blue patch or a soft blue vascular mass. Venous malformations located on the penis are thought to be quite rare, which may give rise to psychological discomfort and cosmetic disfigurement rather than pain, swelling, or thrombosis [3], and their treatment is still controversial. Conventional treatment options include surgery [4], sclerotherapy [5], laser treatment [6,7]. Currently, parents and their relatives prefer conservative treatment for children rather than surgical excision, usually due to concern about scarring. Sclerotherapy has been described as another therapeutic approach for the management of VMs in children [8–10].

At present, interventional sclerotherapy is the treatment recommended by the International Society for the Study of Vascular Anomalies [11]. Interventional sclerotherapy is characterized by easy surgical procedures, limited trauma and satisfactory curative effects [12]. The aim of this article was to present and discuss the management and outcomes of a series of cases of VMs of penis.

1. Materials and methods

1.1. Study subjects

A total of 9 children with venous malformation of penis who were admitted to Qilu Children's Hospital of Shandong University from January 2017 to June 2018 were included in this study. The patients ranged in age from 10 months to 7 years (mean age 2.4 ± 2.0 years). Six lesions were found on the glans penis and three on the trunk of the penis. A faint blue patch or a soft blue vascular mass was presented as main clinical manifestation in all patients. All patients presented for aesthetic reasons and/or anxiety in the parents. In addition, two patients presented with mild discomfort when urinating. The diagnostic criteria were consistent with ISSVA classification for vascular anomalies [13]. 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 puncture under DSA

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fluoroscopy; 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 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 venous malformation of penis.

1.2. Preparation of sclerosing agents

Polidocanol foam sclerosing agent was prepared according to the Tessari method [14]. 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. Polidocanol foam itself can be a visual medium under DSA in fluoroscopic application, and therefore an additional contrast agent was not used with polidocanol foam. 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 surface area (10 mg/m^2), and the injectant subsequently mixed with 1-2 mg dexamethasone.

1.3. Treatment methods

Sclerotherapy was performed in an operating room with general anesthesia using DSA equipment (Artiszee; Siemens Healthineers). The penis was prepared and draped in a sterile manner. A 4.5-scalp needle connected to a syringe containing contrast agents was inserted into the venous space, and the intraluminal position of its tip was confirmed by blood aspiration. Local angiography was performed under DSA fluoroscopy to further confirm the intraluminal position of the tip of the needle, and appraise the shape, extent, and venous drainage of the tumor nests simultaneously. Sclerotherapy with a liquid sclerosant (such as pingyangmycin) has been used with various radiographic-guided techniques for several decades. The efficacy and safety of intralesional injection of pingyangmycin for treatment of low-flow lesions has been described [15]. 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. The superiority of foam sclerotherapy over liquid sclerotherapy has been demonstrated [16,17]. Therefore, for high-flow venous malformations, polidocanol foam was injected into the lesion until the contrast medium in the target lesion administered at the initial venogram was displaced by the air in the foam sclerosant as negative contrast. For low-flow venous malformation, the pingyangmycin dilution was directly injected into the venous malformation vascular mass under DSA in fluoroscopic application. Multipoint and multi-angle puncture and angiography were performed in the lesion area to discover new lesions, and then continue the treatment according to the above protocol.

1.4. Follow-up and evaluation of treatment response

All cases in our study were followed up one month later after the initial treatment. Therapeutic efficacy was evaluated based on clinical symptoms and MRI examination. The efficacy criteria were as follows [18]: 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 $>75\%$), with no dysfunction, mild skin pigmentation, and further treatment needed; iii) effective (improved situation), the tumor was significantly reduced (to $<50\%$), and further treatment would be needed and iv) ineffective, the tumor was not reduced, remained unchanged or continued to develop.

2. Results

In all patients, the correct diagnosis was obtained by careful history taking and physical examination and confirmed by MRI evaluation. The venous malformation was located on the glans penis in six patients, and on the trunk of penis in three patients. All patients underwent treatment 2-3 times, with an average number of treatments of 2.3 ± 0.5. There were 12 foci in 9 patients with 26 sclerotherapy injections, including 19 times using pingyangmycin and 7 times with polidocanol. All patients experienced marked swelling after the injection, and three developed cutaneous blistering, which subsided without treatment. Transient pain was observed in 3 patients. Allergic reactions, cutaneous necrosis, transient hemoglobinuria, and pigmentary changes were not observed. No urethral retraction was observed.

At a mean follow-up of 7.3 months (range 4 to 13 months), 6 patients were cured (Fig. 1-2) and 3 had a basic remission. The cosmetic results were satisfactory for patients and also considered satisfactory by physicians. No patients had signs of recurrence.

3. Discussion

Venous malformations (VM), formerly known as cavernous hemangioma, are composed of abnormal veins that show variable luminal diameter and wall thickness [19]. According to the International Society for the Study of Vascular Anomalies (ISSVA) classification, they can be subdivided into common VM, familial VM cutaneo–mucosal (VMCM), blue rubber bleb nevus syndrome and others [20].

Venous malformations are usually present at birth and slowly progress. Clinically the typical lesions are characterized by bluish, soft, easily compressible, non-pulsatile masses that increase in size with maneuvers to increase venous pressure. Histologically, the common VMs are characterized by enlarged venous channels lined by a single flattened layer of endothelial cells surrounded by sparse, irregularly distributed smooth muscle cells [21]. They usually occur in the head and neck, and penile venous malformations are rare. Penile VMs usually present for aesthetic reasons without symptoms in children, rather than sudden pain when spontaneous localized thromboses within the malformation occur. Pain during erection and bleeding during sexual intercourse have also been reported in adults [6]. In our series, only 2 had with mild discomfort when urinating.

Careful history taking and physical examination may be helpful in the diagnosis of venous malformation. Direct injection venography represents the gold standard for the diagnosis of venous malformation, which could contribute to the evaluation of morphological and blood flow characteristics. In 2003, Dr. Puig proposed modified a phlebographic classification system, according to the type of venous drainage: type I was isolated VM without peripheral venous drainage; type II was VM that drains into normal veins; Type III was VM that drains into dysplastic veins; Type IV was VM that represents a venous dysplasia [10]. They can also be divided into low- and high-flow types based on the thickness, number and flow speed of the reflux veins from a rheologic standpoint [22].

Sclerotherapy is the targeted chemical ablation of VMs by intravenous injection of a liquid or foamed sclerosing drug, which has become the first choice for the treatment of venous malformation, especially under DSA guidance [23]. There are a number of different sclerosing agents have been used, such as ethanol, polidocanol, pingyangmycin

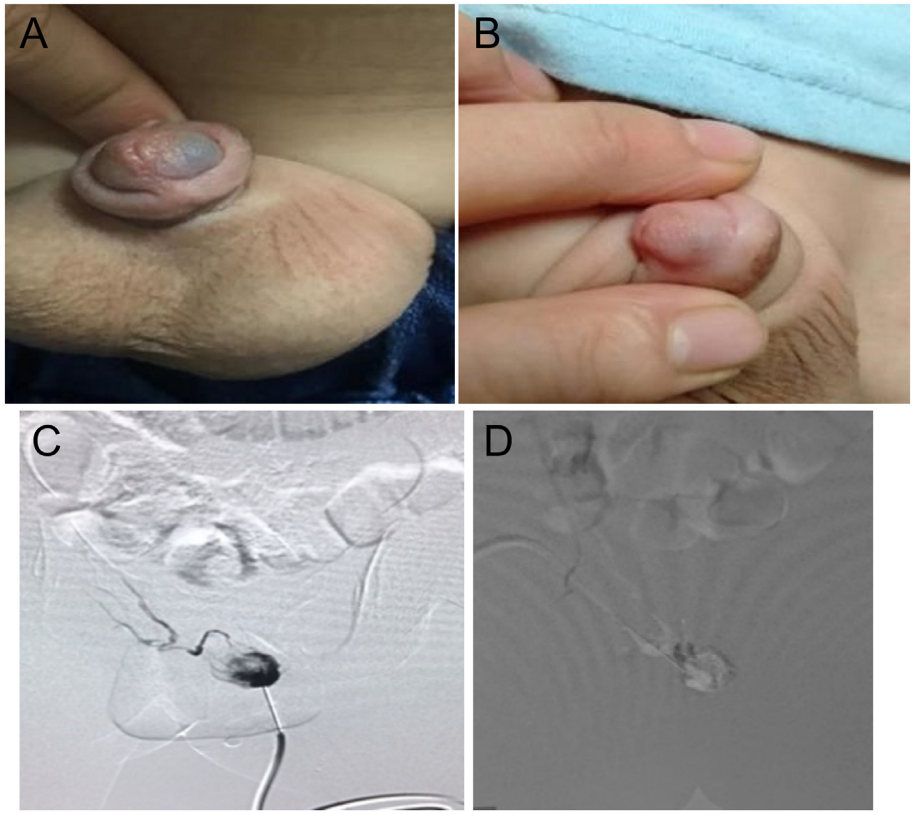

Fig. 1. Venous malformation of penile present as a bluish, soft, easily compressible, non-pulsatile mass. (A) Baseline before sclerotherapy; (B) Complete regression after 2 treatments; (C) Direct injection venography presents revealed a high-flow foci; (D) Intralesional injection of polidocanol foam under DSA.

or bleomycin. Ethanol is the most effective sclerosing agent, particularly for the treatment of high-flow types, but ethanol injection produces severe pain and can cause extensive tissue necrosis and nerve damage [24]. Therefore, in the treatment of children's penile venous malformations, relatively conservative and mild sclerosing agents are recommended, such as polidocanol, pingyangmycin or bleomycin, in our experience. Polidocanol is widely used in Europe and the United States, although its clinical application is still in its infancy in China [25,26]. Chen et al. [26] treated 70 patients with head and neck VMs with foam sclerotherapy under digital subtraction angiography, with a total response rate of 100%. Cabrera et al. used 0.5-3% polidocanol foam sclerosing agent under ultrasound guidance to treat venous

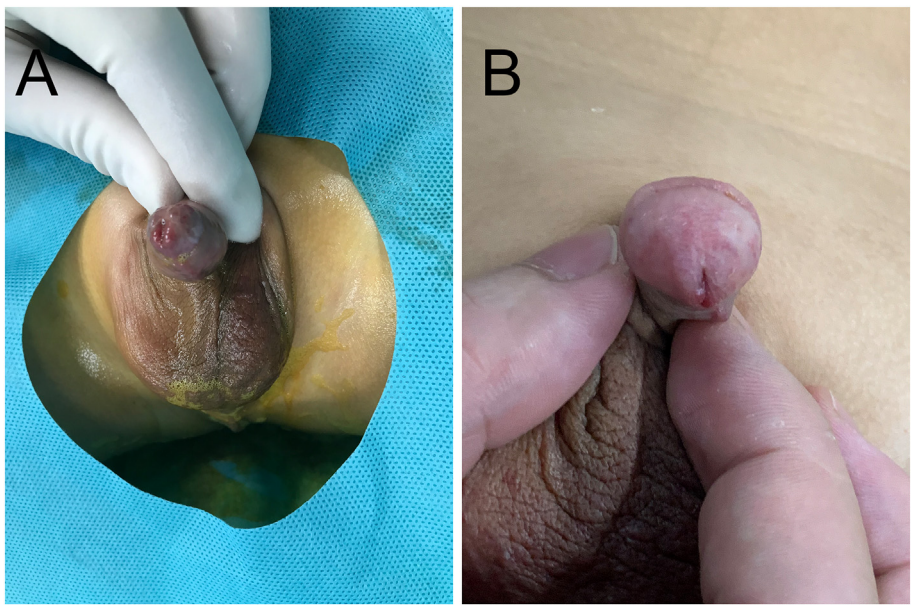

Fig. 2. Venous malformation of penile lesion. (A) Baseline before sclerotherapy; (B) Complete regression after 3 treatments.

malformations, with an efficacy rate of 92%, and no serious complications were observed [27]. Foam sclerosing agents have been gradually developed for the sclerotherapy for VMs which is more effective than liquid sclerotherapy. The rationale for treatment with pingyangmycin for VMs is to destroy the vascular endothelial cells. Pingyangmycin is bleomycin A5 made in China and has been isolated from many components of bleomycin. Bleomycin is effective in reducing the size of venous malformations, and leads to a lower adverse event rate and fewer severe complications than other sclerosants [28]. All of these are less potent sclerosant than ethanol, with minimal risks of ulceration and nerve impairment [29].

There were 12 foci in 9 patients with 28 times of sclerotherapy in this study. Intralesional injection of pingyangmycin and dexamethasone was administrated in 8 low-flow foci via direct puncture venography with an excellent result. The combined application of pingyangmycin and dexamethasone can not only improve the response rate and shorten the treatment period, but also reduces the symptoms of swelling and fever. Steroid hormones have dual effects of anti-inflammatory and inhibition of vascular formation of a venous malformation. Polidocanol foam sclerosing agent was injected into 4 high-flow foci with a reliable curative effect. The most common complication after injection of a sclerosing agent in patients with VMs is marked swelling due to a combination of intralesional thrombus and edema. Postoperative swelling in all cases and mild pain in 3 cases presented in our study. No nerve injury, necrosis, urethral injury and erectile dysfunction were found in any patients.

Given the good tolerance of the medication in the cases treated and the apparent absence of side effects, we believe that sclerotherapy is an important addition to the treatment armamentarium for penile VMs, and should be considered first among the available therapeutic modalities.

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