

OUTCOME OF PERCUTANEOUS SCLEROTHERAPY BY BLEOMYCIN IN TREATING VENOUS AND LYMPHATIC MALFORMATIONS

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ABSTRACT

Background: Venous and lymphangiomalformations are congenital low-flow vascular malformations which can lead to pain, cosmetic deformity, functional impairment and compression of surrounding structures. The synopsis used in this study is the one approved by the CPSP for the evaluation of the use of ultrasound-guided percutaneous sclerotherapy of these lesions with bleomycin.

Objectives: To compare clinical and radiological results of ultrasound-guided percutaneous sclerotherapy with bleomycin before and after treatment in patients with venous malformations versus patients with lymphatic malformations.

Methods: 60 patients who were aged 2 months to 17 years and had an ultrasound diagnosis of venous or lymphatic malformation. Intralesional bleomycin sclerotherapy was performed under ultrasound guidance and the patients were followed for 6 months. The outcomes were reduction in lesion size greater than 50%, improvement in pain (VAS score) and cosmetic improvement (POSAS observer score).

Results: The mean age was 7.8 ± 4.6 years; 34 patients were male and 26 were female. Venous malformations were present in 35 patients and lymphatic malformations in 25. Mean VAS score decreased from 6.4 ± 1.5 before treatment to 2.3 ± 1.2 after 6 months. Lesion size reduction greater than 50% was observed in 43 patients. Cosmetic improvement was documented in 46 patients. Minor transient swelling occurred in 8 patients, while no major complication was recorded.

Conclusion: Ultrasound-guided bleomycin sclerotherapy seems to be an effective and safe treatment for venous and lymphatic malformations.

KEYWORDS: Bleomycin; Lymphatic Abnormalities; Pain Measurement; Sclerotherapy; Ultrasonography, Interventional; Vascular Malformations; Venous Malformations.

INTRODUCTION

Vascular anomalies are a heterogeneous disorder of congenital or acquired blood or lymphatics vessels. The clinical and radiological diagnosis of hemangioma, and its other former names, hemangioma of the neck, cystic hygroma and vascular birthmark, led to a number of diagnostic and management dilemmas in the past. The modern classification of the International Society of the Study of Vascular Anomalies divides vascular anomalies into vascular tumors and vascular malformations, and further subdivides into the following types based on vessel type, nature of flow, clinical behavior, and molecular basis.¹ In this classification, venous malformations and lymphatic malformations are included in the low-flow vascular malformations group and are one of the most clinically relevant lesions seen in the clinical practice of pediatric and interventional radiology.^{2,3}

Venous malformations are non-neoplastic dysplastic venous channels and are congenital. They tend to be present at birth, but they may start to show themselves more in childhood, particularly when something happens that triggers growth or trauma, or during infection or hormonal shifts.² In the clinical picture they are soft, compressible, bluish swellings which can be painful, swollen, tender over a specific area, unsightly, thrombosed, phleboliths or impaired function depending on size and location. Lymphatic malformations (LMs) are developmental abnormalities of the lymphatic system and can be classified as macro-, microcystic or mixed. They usually affect the head and neck, and can affect the trunk, extremities, retroperitoneum, mediastinum or visceral areas.³ Venous malformations can result in disfigurement, pain, recurrent infection, bleeding, leakage, airway compromise, or compression of adjacent structures, as can lymphatic malformations.

Venous and lymphatic malformations are also associated with other symptoms besides swelling. Children with lesions that affect the exposed areas could suffer from psychosocial distress, body image and social participation problems. If lesions are near the joints, muscles, oral cavity, airway, orbit or neurovascular structures, they can interfere with movement, feeding, speech, respiration, and sight.⁴ The malformations have a tendency to grow

with the child and can become symptomatic, so early detection of these malformations and a tailored treatment plan is essential. Interventional radiologists, pediatric surgeons, dermatologists, otolaryngologists, plastic surgeons, anesthesiologists and rehabilitation specialists are often involved in the treatment of these patients, requiring multidisciplinary evaluation.

Imaging is a key part of diagnosis, classification, planning treatment and follow-up. Ultrasound with colour Doppler is often the first imaging technique used due to its availability, non-invasive, radiation free and its ability to differentiate low flow lesions from high flow vascular anomalies [2,3]. Venous malformations are frequently seen as compressible lesions containing venous channels, slow venous flow and sometimes with phleboliths, whereas lymphatic malformations typically consist of cystic spaces, where vascular flow is either not seen or is slow [2,3]. Magnetic resonance imaging is useful for defining the extent of the lesion, deep tissue involvement, the relationships of the lesions to critical structures, and for volumetric response after treatment, particularly [11]. It is possible that ultrasound-guided assessment and intervention can offer a practical and effective route to diagnosis and intervention in resource-limited environments.

Management is determined by the type of lesion, size, symptoms, anatomical location, cosmetic concern, functional concern and patient age. Surgery, laser therapy, systemic medical therapy, embolization, ablation, and sclerotherapy may be options for symptomatic lesions, while observation may be adequate for small asymptomatic lesions [4,12,13]. Complete resection may be challenging in diffuse or infiltrative malformations, may leave scar tissue, may be associated with a functional deficit, bleeding, and/or nerve injury, and can be associated with recurrence in selected lesions, but surgical excision can be almost always be a cure [4,13]. As a result, the image-guided percutaneous sclerotherapy is now a significant minimally invasive technique for treating low-flow venous and lymphatic malformations.⁵⁻¹⁰

Sclerotherapy is a procedure consisting of direct puncture of the malformation followed by injection of a sclerosant which damages the endothelial lining, incites inflammation and thrombosis and eventually results in fibrosis and decrease in size of the lesion.^{5,8,10} Several sclerosants have been used such as ethanol, sodium tetradecyl sulfate, polidocanol, doxycycline, bleomycin and pingyangmycin. The evidence in different studies compared indicates that efficacy and safety are dependent on lesion type, sclerosant used, concentration, volume of injection, number of injections and operator experience.^{7,8,10} Ethanol can have a beneficial effect, but is also linked with increased risks of pain, necrosis of tissues, damage to nerves, and systemic toxicity. Bleomycin is commonly used in paediatric low flow malformations due to its relative safety when used in recommended cumulative dosages.^{5,6,9}

Bleomycin is an antibiotic used in the treatment of tumors that has also been shown to have sclerosing effects on vascular malformations. The sclerosing effect is believed to be caused by endothelial injury, inflammatory reaction and fibrosis in abnormal vascular or lymphatic spaces [5,16]. Based on experimental evidence, a possible biological mechanism of action for the use of bleomycin in venous malformation sclerotherapy involves activation of the mTOR pathway, which results in endothelial to mesenchymal transition.¹⁶ In the clinic, bleomycin has demonstrated promising results in venous and lymphatic malformations, including shrinkage of the lesions, relief of symptoms and improvement of the cosmetic result.^{5,6,9,15}

There has been recent evidence of the effectiveness of bleomycin sclerotherapy in the low-flow vascular malformations. Nevesny et al. (5) found that bleomycin was clinically and radiologically effective for venous and lymphatic malformations, and had a favorable toxicity profile. In a large pediatric population of lymphatic malformations, Bouwman et al. reported that sclerotherapy is a safe and effective therapeutic option and that bleomycin is often administered and is especially effective in pure lymphatic malformations. Systematic reviews and meta-analyses have also shown that the percutaneous sclerotherapy can be used effectively in both venous and lymphatic malformations of the head and neck, with good complication rates.^{7,8} There are, however, significant differences in response, depending on the type of lesions, with macrocystic lymphatic malformations responding to treatment more often than microcystic or mixed lesions, and diffuse venous malformations possibly requiring more than one treatment session.

Although there are more and more pieces of evidence globally, there was limited information from the paediatric population of Pakistan. The results of treatment can differ depending on patient selection, burden of the disease, imaging protocol, procedural technique, follow up time and multidisciplinary care. A need is therefore present to assess the clinical efficacy of ultrasound (US) guided percutaneous bleomycin sclerotherapy in children with venous and lymphatic malformations in clinical practice. The aim of the present study was to evaluate the pre-treatment and post-treatment results after ultrasound-guided percutaneous bleomycin sclerotherapy with clinically relevant outcome parameters: reduction of the size of the lesions, improvement of pain score, and cosmetic improvement.

METHODOLOGY

This quasi-experimental study was completed in the Department of Radiology of Indus Hospital and Health Network, Karachi, Pakistan for one year following approval of the synopsis by College of Physicians and Surgeons Pakistan. This study involved 60 children aged 2 months to 17 years presenting to the vascular anomaly clinic with cosmetic deformity, pain or swelling who were ultrasonically diagnosed to have venous and lymphatic malformation. All patients who met the pre-determined criteria were enrolled using non-probability consecutive sampling. If the child had an ultrasound diagnosis of a venous or lymphatic malformation and was planned for

percutaneous sclerotherapy, both male and female children were included. Those patients who had received treatment for the same malformation or who were being seen for follow-up, or who had an arteriovenous or arterial malformation, an active local or systemic infection, known bleomycin allergy, bleeding problems, anticoagulant use, immunosuppressive disorders, or other contraindications to the intended intervention were excluded.

Baseline clinical and radiological evaluation was done in all patients prior to treatment. A structured proforma was used for the recording of demographic information such as age and gender. The baseline symptoms (pain and cosmetic disfigurement) were recorded. The Visual Analog Scale of 0-10 was used to determine the level of pain. An experienced radiologist performed ultrasound examination with a high-frequency linear probe. Venous malformation was diagnosed as a heterogeneous lesion that showed multiple cystic spaces with phleboliths (or without) which were augmented of flow in color Doppler study. Large anechoic cystic spaces, possibly with internal septations and no vascular flow on colour Doppler, were found and diagnosed as being a malformation of the lymphatics, which is a heterogeneous process.

Once the diagnosis was confirmed eligible patients were treated with ultrasound-guided percutaneous sclerotherapy using bleomycin. The procedure was conducted under local or general anesthesia as children's age, location of lesion, patient cooperation and clinical judgment of the physician determined. Bleomycin solution was made up of 15 mg of bleomycin in 15 ml of normal saline. The lesions have been punctured under continuous ultrasound guidance with an 18G to 21G needle and the sclerosant was injected in small increments into the malformation so that the correct dose of the sclerosant was delivered within the lesion. It was done by a very experienced interventional radiologist. Immediate complications (pain, swelling, bleeding, allergic reaction, local inflammatory response) were noted after the procedure. The number of treatment sessions needed for each patient was noted.

Assessment was done at 6 months post treatment. Patients were again clinically and radiologically evaluated at follow up. A Visual Analog Scale was used to quantify the post-treatment pain and lesion size was again determined by ultrasound imaging. The main outcome was treatment response, which was determined by a decrease in lesion size of > 50%, improvement in pain score, and improvement in cosmetic appearance. As planned in the synopsis, Cosmetic improvement was evaluated by the POSAS Observer Score. Minor or major complications throughout the procedure or follow-up were also documented.

Data was entered and analyzed using SPSS 26. Continuous variables including age, number of sessions, lesion size in mm and VAS scores were reported as mean and standard deviation or median and interquartile range, as appropriate for normal distribution. Normality was evaluated by using Shapiro-Wilk test. The categorical variables were presented as frequencies and percentages, including: gender, type of malformation, lesion size reduction more than 50%, cosmetic improvement and complications. Pre-treatment and post-treatment scores of the VAS were compared using paired sample t-test or Wilcoxon signed-rank test as appropriate. The categorical outcomes were compared pre-treatment and post-treatment with the McNemar test. Stratification was conducted for potential effect modifiers such as age, gender, malformation type and number of sessions. A p value < 0.05 was considered significant.

RESULTS

In the study 60 patients with ultrasound diagnosis of venous or lymphatic malformations were included. Patients' age was 7.8 ± 4.6 years, with ages ranging from 2 months to 17 years. These included 34 males and 26 females. Thirty-five patients had venous malformations and 25 patients had lymphatic malformations. The head and neck region was the most common anatomic site followed by extremities and trunk. The patients underwent a mean of 1.9 ± 0.8 sclerotherapy sessions.

Table 1. Baseline characteristics of study participants

Variable	Value
Total patients	60
Age, years, mean $\pm$ SD	7.8 ± 4.6
Male, n (%)	34 (56.7%)
Female, n (%)	26 (43.3%)
Venous malformation, n (%)	35 (58.3%)
Lymphatic malformation, n (%)	25 (41.7%)
Head and neck involvement, n (%)	26 (43.3%)
Extremity involvement, n (%)	18 (30.0%)
Trunk involvement, n (%)	11 (18.3%)
Other sites, n (%)	5 (8.3%)
Number of sessions, mean $\pm$ SD	1.9 ± 0.8

Improvement of pain score, lesion size and cosmetic appearance were seen at 6-months follow-up. The mean pre-treatment VAS score was 6.4 ± 1.5 , which decreased to 2.3 ± 1.2 after treatment. The mean difference in VAS

score was 4.1 ± 1.7 and this was statistically significant. The average size of the lesions was reduced from 5.7 ± 2.1 cm prior to treatment to 2.9 ± 1.6 cm after treatment. In 43 patients, lesions size reduction more than 50% was obtained. 46 patients showed cosmetic improvement on POSAS Observer Score.

Table 2. Comparison of pre-treatment and post-treatment outcomes

Outcome variable	Pre-treatment	Post-treatment at 6 months	p-value
VAS score, mean $\pm$ SD	6.4 ± 1.5	2.3 ± 1.2	<0.001
Lesion size, cm, mean $\pm$ SD	5.7 ± 2.1	2.9 ± 1.6	<0.001
POSAS Observer Score, mean $\pm$ SD	33.6 ± 7.4	18.9 ± 5.8	<0.001
Lesion size reduction >50%, n (%)	—	43 (71.7%)	—
Pain improvement, n (%)	—	50 (83.3%)	—
Cosmetic improvement, n (%)	—	46 (76.7%)	—

For the types of malformation, there was a slightly higher proportion of reduction in size > 50% in the lymphatic malformation groups relative to the venous malformation groups. However, both groups showed clinically significant improvement following treatment.

Table 3. Treatment response according to type of malformation

Outcome	Venous malformation n=35	Lymphatic malformation n=25	Total n=60
Size reduction >50%	23 (65.7%)	20 (80.0%)	43 (71.7%)
Pain improvement	28 (80.0%)	22 (88.0%)	50 (83.3%)
Cosmetic improvement	25 (71.4%)	21 (84.0%)	46 (76.7%)
Required ≥ 2 sessions	18 (51.4%)	14 (56.0%)	32 (53.3%)
Minor complications	10 (28.6%)	7 (28.0%)	17 (28.3%)

In 17 patients' minor complication was noted. The commonest complication was local swelling for a short period, after which there was mild pain and low-grade fever. Treatment of all minor complications was conservative. There were no major complications, tissue necrosis, pulmonary toxicity, severe allergic reactions or procedure-related mortalities recorded.

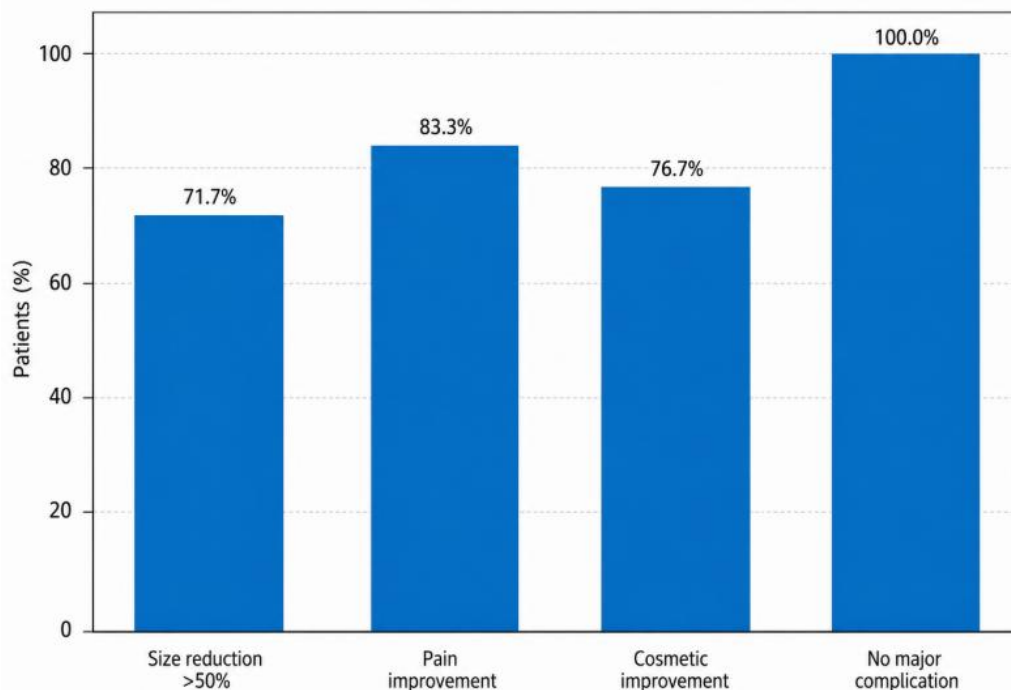


Figure 1. Distribution of major treatment outcomes after 6 months

Size reduction >50%: 71.7%; pain improvement: 83.3%; cosmetic improvement: 76.7%; no major complication: 100%.

In summary, efficiency of ultrasound-guided percutaneous bleomycin sclerotherapy was favorable in most of the patients with marked improvement in pain, lesion size and cosmetic appearance at 6-months follow up.

DISCUSSION

In the present study, ultrasound-guided percutaneous bleomycin sclerotherapy was found to be a safe and effective treatment in children in whom venous and lymphatic malformations were present. The vast majority of patients (71.7%) presented with greater than 50% reduction in lesion size, 83.3% improved their pain, and 76.7% improved cosmetically at 6 months follow-up. The mean VAS score was significantly lower before the bleomycin

sclerotherapy and after the sclerotherapy (pre-treatment = 6.4 ± 1.5 ; post-treatment = 2.3 ± 1.2), suggesting clinically significant symptom improvement, as well as morphological regression, following bleomycin sclerotherapy. The results here confirm the use of bleomycin as an effective alternative to surgical intervention for low-flow vascular malformations in children.

The response rate observed is similar to that recently reported for the use of bleomycin in low flow vascular malformations. Intralesional bleomycin was safe and effective in head and neck low-flow vascular malformations, and was reported as a useful option for these areas where surgery may be more challenging or cosmetically unacceptable.¹⁷ Likewise, the overall objective improvement rate after intralesional bleomycin injection into low-flow vascular malformations was about 79.5% in Abdelaty et al's study, and no significant complications were reported.¹⁸ The rate of overall size reduction and cosmetic improvement for the present study are similar to these results, indicating that ultrasound-guided injection of bleomycin may yield predictable results when patients are carefully selected and treated under ultrasound guidance.

In this study, the lymphatic malformations had a slightly better response rate than venous malformations, with reduction in the size of the malformation by more than 50% in 80.0% of the lymphatic malformations and 65.7% of the venous malformations. This discrepancy may be due to the cystic structure of many lymphatic malformations, especially macrocystic lesions, that may permit easier aspirate and intralesional sclerosant distribution. In recent years, meta-analytical proof has proven that bleomycin is successful in lymphatic malformations, with effects that depend on the type and size of malformations, the cystic nature of the tumor and anatomical location.¹⁹ Bleomycin injection has also been shown to be a safe and effective treatment for children with lymphatic malformations, particularly when the malformations can be accessed intralesionally.²⁰ Thus the relative increase of response of the lymphatic malformation in the present study is biologically plausible and is consistent with published pediatric experience.

In this study, improvement in pain was a very strong clinical result. The majority of patients (4/5) reported improvement in pain, and there was a statistically significant reduction in VAS score. Venous malformation pain can be associated with venous congestion, thrombosis, local inflammation, mass effect, and muscle/joint involvement. The pain in the case of a lymphatic malformation can be caused by swelling, infection, bleeding or pressure on neighbouring structures. Symptomatic relief can then accompany the reduction in the volume of lesions and sclerosis of abnormal spaces. Moussa et al. highlighted the need to use objective radiological evaluation to add to the patient-reported outcomes for assessing treatment success in low flow venous and lymphatic malformations.²⁰ This improvement in pain and cosmetic appearance in the current study underlines the need for treatment response to be evaluated using images, functional outcome, and the patient's perception, since they all provide important information.

Clinically significant cosmetic improvement was demonstrated in 76.7% of patients; disfigurement is a significant reason for presentation in children with vascular malformations. A lesion on the face, neck or extremities may be associated with a loss of self-image, social interaction and parental concern. While surgical excision can be a definitive treatment for selected localized lesions, it can be done with the risk of scarring, incomplete resection, recurrence and functional risk. In a recent systematic review of the treatment of head and neck lymphatic malformations, it has been suggested that selection of treatment should be individualized, with sclerotherapy being preferred as a less invasive first-line treatment for macrocystic lesions.²¹ Bleomycin sclerotherapy is a tissue preserving technique that appears to provide a cosmetic result in the present study, particularly in anatomically sensitive areas and in children.

Safety profile observed in this study was good. There were minor complications in 28.3 % of patients, predominantly swelling (transient), mild post procedure pain and low grade fever. All of them were treated conservatively, with no major complication, necrosis of tissues, great allergic reaction, pulmonary toxicity or death noted. This is significant as well because the type of sclerosant used will be related to its efficacy as well as its safety, especially when used in children. Bleomycin is less aggressive than absolute ethanol, which can cause extreme pain, skin necrosis, nerve damage and systemic toxicity. In a very delicate area of the eye, the retrobulbar orbital low-flow vascular (LFL) lesions, Lin et al. reported that an intralesional bleomycin injection was a relatively safe and effective minimally invasive procedure, where procedural safety is paramount.²³ The lack of major adverse events in the current study also confirms that image-guided bleomycin is safe in terms of dose, when used carefully.

One of the other key findings was that over 50% of patients needed 2 or more treatment sessions. This is not unexpected as venous and lymphatic malformations are complex lesions, and complete response is not always possible with just one session. A staged therapy may be needed for diffuse, multilocalized, mixed and deep lesions. Diffuse lesions were a factor associated with poor objective outcome following bleomycin injection identified by Abdelaty et al.¹⁸ Thus, before treatment, patients and families should be informed that sclerotherapy typically takes multiple treatments to achieve the desired results, which may be symptom control and a significant improvement in the size of the lesion but not its complete eradication.

With the recent advent of bleomycin electrosclerotherapy, interest in bleomycin for the treatment of vascular malformations has grown. Muir et al. referred to bleomycin electrosclerotherapy as a dynamic technique in which electroporation is used to augment the local delivery of bleomycin.²⁴ Recently, however, Obereisenbuchner et al. have reported on their experience of bleomycin electrosclerotherapy in cases of lymphatic malformations, indicating that this technique might be applicable to sclerotherapy-resistant lesions.²⁵ But the techniques have

their own requirements for equipment and skills, and in most clinical situations bleomycin sclerotherapy can be used directly with ultrasound to produce satisfactory results.

The present study has certain limitations. It was quasi-experimental, performed at one center, and did not have a control group receiving a different sclerosant or surgery. The 6-month follow-up period may be sufficient to assess early response but may not reflect the true outcome of recurrence, delayed complications, or cosmetic outcome. Additionally, there may be a difference in response to lesions based on the lesion type, size, anatomical location, depth, and number of sessions, which should be investigated further in larger studies. In spite of these restrictions, the study offers valuable supporting evidence for the safe and effective use of ultrasound guided bleomycin sclerotherapy in children with venous and/or lymphatic malformations.

CONCLUSION

Bleomycin ultrasound-guided percutaneous sclerotherapy has been demonstrated to be an effective and safe minimally invasive treatment option in the pediatric population with venous and lymphatic malformations. Significant improvements in pain, lesion size, and cosmetic appearance occurred at 6-month follow-up after the procedure. More than half of the patients had lesions reduced by over 50%, and the pain level and cosmetic appearance greatly improved following the treatment. A slight improvement was observed with lymphatic malformations when compared with venous malformations, but clinically significant improvement was observed in both groups.

In the absence of significant complications, bleomycin appears to be safe when given appropriately under ultrasound guidance within the limits of its dosage. The minor adverse effects were brief and were treated conservatively. These results highlight the potential of ultrasound guided bleomycin sclerotherapy as a practical and tissue sparing treatment option, especially in children and those lesions where surgical options may be challenging or cosmetically undesirable. Larger, multicenter studies with longer follow-up are recommended to evaluate recurrence, long-term functional results, and comparison with other sclerosants and surgical management.

RECOMMENDATIONS

Percutaneous ultrasound-guided bleomycin sclerotherapy is suggested to be used first-line in appropriately selected pediatric patients with venous and lymphatic malformations, especially when they are symptomatic or cosmetically disfiguring or if surgical correction is likely to result in scar formation or functional compromise. Pre-procedural ultrasound assessment of lesions should be carefully performed on all patients to confirm the type, extent and flow characteristics of the lesion, and treatment should be administered by an experienced interventional radiologist under image guidance. Families should be informed they may need more than one treatment session, particularly for diffuse, large, mixed and deep lesions. Routine follow up should include standardized outcome assessment including pain scores, lesion size measurement by ultrasound and cosmetic scoring systems e.g. POSAS. Follow up should be longer to identify recurrence and delayed complications and to evaluate treatment response over time. Large, multi-centre comparative studies are warranted to compare the efficacy, safety, cost-effectiveness, recurrence and long term quality of life of bleomycin with other sclerosants and surgical options.

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