Efficacy and safety of foam sclerotherapy with sodium tetradecyl sulfate as the preferred sclerosant of venous malformations based on the experience from a single specialist center.

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ARTICLE HIGHLIGHTS

Type of Research: Single centre observational study

Key Findings: Puig type I lesions were significantly less likely to be treated with sclerotherapy with foam STS 3% (p=<0.001), and more likely surgically excised (p=<0.001). Patients with type I lesions received less volume of STS 3% when compared to those with type II and III lesions. Ten (4.8%) patients experienced complications and the proportions of complication were significantly different across the categories (p=0.030) with more complications reported in type I VM.

Take home Message: Interventional therapy with foam sclerotherapy STS 3% is clinically effective and safe for patients with VM

Table of Contents Summary

This study retrospectively analysed the efficacy and safety of interventional therapy in the treatment of venous malformations (VM) over a 5-year period in a single specialist centre. Interventional therapy in particular with foam sclerotherapy STS 3%, is clinically effective and safe for patient with VM. Sclerotherapy with foam STS 3% is most successful among Puig's type I and II venous malformation (VM). Puig's classification system may provide an important guide to volume of sclerosant required and the potential success rate.

Abstract

Objectives

To assess the efficacy and safety of interventional therapy of venous malformations (VM) with foam sclerotherapy as the treatment of choice based on the experience of a single specialist centre.

Methods

All patients with VM who underwent interventional therapy i.e. EST and/or open surgery from January 1st, 2015 – December 31st, 2019 were identified through a prospective database. Types of venous malformation (VM) were classified according to Puig's classification. The outcome measures assessed included efficacy and complications. The former was divided into four groups: no response, mild response, moderate response, and complete response. Complications were defined as any tissue or functional damage, distal embolization or tissue reaction. Continuous variables were compared using analysis of variance (ANOVA) F test and discrete variables were analysed using Chi-squared tests. $P<0.05$ was considered significant.

Results

A total of 207 patients were included. Puig type I lesions were significantly less likely to be treated with foam sclerotherapy using STS 3% (p=<0.001), and more likely surgically excised (p=<0.001). In the patient's first procedure during the study period, the volumes of foam STS 3% were significantly different across all types of VM (p=<0.001); patients with type I VM received less volume of STS 3% when compared to those with type II and III lesions. The efficacy outcome categories were significantly different across all types of VM (p=<0.001). Overall only 14 (6.8%) patients reported no improvement in efficacy, and 38 patients 38 (18%) patients did not attend follow-up. Therefore 154 (74.8%) patients achieved some form of efficacious outcome. Ten (4.8%) patients experienced complications such as

hematoma, thrombophlebitis and ulceration. The proportions of complication were significantly different across the categories (p=0.030) with more complications reported in type I VM.

Conclusions

Interventional therapy with foam sclerotherapy using STS 3% is clinically effective and safe for patients with VM and was most successful among Puig's type I and II VM.

Keywords

Interventional therapy, embolo-sclerotherapy, low-flow vascular malformation, foam sclerotherapy

Conflicts of Interest

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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Introduction

Congenital vascular malformations are lesions that occur during early vascular development resulting in dysplastic abnormally formed vessels that consists of arteries, veins, capillaries and/or lymphatics or a combination of these vessels. Anatomically, vascular malformations are subcategorized into capillary, lymphatic, venous, arteriovenous or a combination of the above. Hemodynamically, these lesions may demonstrate slow/low or fast/high fluid flow. Low-flow malformations consist of capillary, lymphatic, venous whereas high-flow malformations are any that contain an arterial component (1–4). The current classification systems, especially the International Society of the Study of Vascular Anomalies (ISSVA), have been widely used by both clinicians and scientists (1). Venous malformations (VM) are the most frequent low-flow vascular malformations with an estimated incidence of 1-2% (7,8). VM can occur anywhere in the body but 40% occur on the extremities, 40% on the cervicofacial area and 20% on the trunk (9). Lesions are typically soft and compressible and manifest as a light to dark blue skin discolouration.. VMs can be classified according to Puig's classification where Type I describes isolated malformation without peripheral drainage; type II are malformations that drain into normal veins; type III are malformations that drain into dysplastic veins and type IV represents venous ectasia (10). The current management options for LFVMs are often conservative and supportive while invasive interventions including embolo-sclerotherapy (EST) and open surgery are used especially for those that are significantly symptomatic such as lesional pain, swelling, recurrent superficial venous thrombosis, ulceration and bleeding (1). EST is often regarded as the mainstay intervention for congenital vascular malformation either as a stand-alone therapy or in conjunction with open surgery (4,11). General measures include physiotherapy, graduated compression hosiery, support and education, and psychological counselling. A study by Lidsky et al (12) reported minimal alteration in patient (i.e. no change). EST is considered a

relatively safe and effective treatment, with success rates reported up to 84% (13). Surgery has been the mainstay treatment for decades, however, recent advances in the understanding of vascular malformations and technological developments within radiology have favored minimal invasive treatments. Surgery still plays an important role and may be used in combination with EST with successful rates reported in 89% and 100%, respectively (12). The increased understanding of the molecular pathogenesis of vascular malformations has led to the deployment of several targeted medical therapies such as sirolimus (mTOR inhibitor) and thalidomide (anti-angiogenic agent). A systematic review by Freixo and colleagues reported a lesion reduction in 89% of VMs and a 95% improvement in clinical symptoms in lymphatic malformations when treated with sirolimus in selected cases (14).

However, data on outcomes of interventional therapy, particularly sclerotherapy with foam sodium tetradecyl sulphate (STS) 3% of VMs including the efficacy and safety is often limited to small sample sizes. Therefore, this study aimed to assess the efficacy and safety of interventional therapy of VM based on the experience of a single specialist centre where sclerotherapy with STS 3% was regarded as the mainstay procedure.

Methods

This is a retrospective audit study of a prospectively collected departmental database, with no patient identifiable data used, that was approved by the institution's local clinical audit and governance committee board.

Interventional therapies

All patients referred to our centre with non-central nervous system VM underwent evaluation by a multi-disciplinary team consisting of vascular surgeons, interventional radiologists, and

a clinical nurse specialist who subsequently directed decision on intervention. VM was differentiated from arteriovenous malformations with clinical examination, duplex ultrasonography, and cross-sectional imaging especially magnetic resonance (MR) or computed tomographic (CT) angiography. All sclerotherapy and open surgery were carried out by consultant interventional radiologists and/or consultant vascular surgeons with subspecialty interest and training in treating vascular anomalies. Sclerotherapy, in particular with foam STS 3%, was our favoured treatment for patients with rapidly growing and/or symptomatic VM, which included pain, disfigurement, pressure effect, ulceration, bleeding, and recurrent venous thromboembolism. Open surgery which consisted of excision and/or debulking surgery was reserved to relatively discrete, small and superficial VMs which were symptomatic. Hybrid procedures combining both sclerotherapy and open surgery, either in stages or in one sitting, were also an option in selective cases. These procedures would be performed first with sclerotherapy under fluoroscopic guidance followed by surgery although some patients might need further sclerotherapy for the remaining lesions in future. Patients with asymptomatic or minimally symptomatic lesions which were stable in size were managed conservatively. Pre-procedural cross-sectional imaging i.e. computed tomography (CT) and/or magnetic resonance (MR), with or without duplex ultrasonography were performed on all patients to aid planning. All sclerotherapy during the study period were performed under general anaesthesia. All sclerotherapy of VM were carried out with direct injection under fluoroscopic guidance with digital subtraction angiography performed to confirm accurate position of the needles, and to assess the flow; either in a vascular hybrid theatre or interventional radiology angiosuite with a floor mounted C-arm, or standard operating theatre with a mobile C-arm. Ultrasound was also used in some cases. ESTs were performed either with foam sclerosant i.e. STS 3% (mixed with air in a 1:4 ratio), ethanol, embolization coils, and other substances such as triamcinolone, or a combination of them.

The choice of agents used was at the operator's discretion. Our preferred sclerotherapy agent was foam STS 3%. The volume of STS 3% used was up to a maximum of 16 ml as per recommended by the manufacturer's instructions (15).The amount of STS 3% used is at the discretion of the operator but guided by DSA where injection of foam sclerosant is stopped immediately once contrast medium in lesion is completely displaced. Sclerotherapy were also performed at times prior to or as stage for open surgery to reduce the risk of bleeding. The majority of the sclerotherapy were carried out as day cases. Post-operatively, patients were followed up in the out-patient clinic at six to twelve weeks.

Patients and data collection

All patients with VM who underwent interventional therapy i.e. EST and/or open surgery, in our centre from January 1st, 2015 – December 31st, 2019 were identified through a prospectively collected database. Patient demography, anatomical features of the VM, presenting symptoms, procedural information, adjuvant therapies such as targeted medication and other surgery, treatment outcomes, and follow-up data including duration and the number of sclerotherapy needed during the study were collected and reviewed retrospectively. Types of VM were classified according to Puig's classification (10) which was based on the venous drainage pattern of VM. The outcome measures assessed included efficacy and complications. These were assessed in the out-patient clinic at six to twelve weeks to allow resolution of swelling and changes directly related to sclerotherapy. Both lesion size and patient symptoms were assessed clinically. Efficacy outcome were divided into four groups: no response, mild response (symptoms still persist that are affecting quality of life without complete resolution of lesion), moderate response (alleviation of symptoms without complete resolution of lesion) , and complete response (lesion completed resolved clinically). Complications were defined as any tissue or functional damage, distal embolization or tissue reaction and were determined by our multi-disciplinary team prospectively.

Statistical analysis

All statistical analysis was performed using SPSS version 25 statistical software package (SPSS, Armonk, NY: IBM Corporation). There was only one patient with type IV VM and was therefore not considered for statistical analysis but included in the descriptive statistics. Continuous variables were compared using analysis of variance (ANOVA) F test and discrete variables were analysed across the categories using Chi-squared tests. $P<0.05$ was considered significant.

Results

Patient demography and clinical characteristics

A total of 207 patients with VM and had interventional therapy during the study period were included. Their mean age was 32 years (range 1 – 71 years). Eleven patients (5.8%) had VM; Klippel-Trenaunay Syndrome (n=10) and blue rubber bleb nevus syndrome (n=1). Table 1 summarizes the demography, presenting symptoms, and previous interventions of all the patients included in the study based on the Puig's classification. Meanwhile, table 2 summarizes the anatomical location, tissue involvement, and syndromic association of the VM of all the patients included in the study based on the Puig's classification. Most patients presented with swelling (95.2%) and pain (79.7%). Majority of the VM were located in the lower limbs followed by upper limbs, head and neck, chest and abdomen, and pelvis and genitals. Over 90% and 80% of the VM involved the subcutaneous tissue and skin, respectively. There were no significant differences in age or gender for different Puig's types of VM. Only chest and abdomen showed significantly higher proportion with type III VM than other anatomical locations (p=0.004). Meanwhile, both skin and intramuscular involvement demonstrated significantly lower proportion with type I VM than other tissue

(p=<0.001 and p=0.003 respectively). Intraosseous involvement was significantly lower in type II VM (p=0.031) when compared to type I and type III lesions. There was no significant difference across all types of VM in terms of the patients' previous intervention categories and presenting symptoms.

Interventional therapy

Table 3 summarizes the interventional therapy received by all the patients included in the study during the trial period of 5 years based on the Puig's classification. When compared to the other types of VMs, type I lesions were significantly less likely to be treated with foam sclerotherapy STS 3% (p=<0.001), and more likely surgically excised (p=<0.001). In the patient's first procedure, the volume of foam STS 3% was significantly different across all types of VM (p=<0.001); patients with type I VM received less volume of STS 3% when compared to those with type II and III lesions. From the second procedure onwards, only a few patients received interventional therapy and most of them were carried out in Type II and III patients. Hence, not meaningful to determine statistical significance. No patients received more than six procedures.

Outcomes and follow-up

Table 4 summarizes the adjuvant therapy received by all the patients recruited in the study based on Puig's classification. Meanwhile, table 5 summarizes the outcomes and follow-up of all the patients included in the study based on Puig's classification. The efficacy outcome categories were significantly different across all types of VM (p=<0.001). Overall, majority of patients have shown an improvement in symptoms and lesion size following interventional therapy. Patients with type I VM seemed to report "complete response" more than the other types. Ten (4.8%) patients experienced complications including hematoma, contrast reaction,

thrombophlebitis, fixed flexion deformity of finger, facial nerve neuropraxia, ulceration, scalp full thickness necrosis, radial nerve palsy, restriction in range of movement and scar tethering. The proportions of complication were significantly different across the categories (p=0.030); Patients with type I VM seemed to report more complications than the others. We observed a higher rate of complications amongst type I lesions. However, despite type I lesions being more likely to be surgically excised, out of the five complications reported within type I lesions only one was surgically excised. Therefore, there was no evidence to suggest that these complications were related to their surgical excision. Table 6 and 7 summarizes the efficacy outcomes for different categories of intervention, and anatomical locations respectively. The efficacy outcome categorizes were significant with STS 3% foam (p=0.003), surgery (p=0.006) and medication (0.021) but no significance across different anatomical locations.

Discussion

In the literature, EST is often regarded the preferred interventional therapy of choice for LFVM, with ethanol, polidocanol and STS 3% as the most commonly used sclerosant (16–19)). This study found that our multi-disciplinary specialist centre's approach of interventional therapy for patients with symptomatic VM with the preference use of sclerotherapy particularly with foam STS 3% was clinically efficacious and safe. Of 207 patients who had interventional therapy, only 14 patients (7%) reported no improvement in symptoms, and 38 patients (18%) did not attend follow up, presumably due to poor outcome. Therefore, three-quarter of the patients with VM reported some degree of symptoms improvement. This is in line with earlier studies who have reported the efficacy of sclerotherapy in the treatment of venous malformations (18,21,22).

Puig et al showed that EST of type I and II malformations was successful in 93% of cases. However, type III and IV lesions were untreatable with sclerotherapy in 33% and 60%, respectively (23). Gorman and colleagues (16), and other studies, also showed most successful outcomes among type I and II venous malformations with sclerotherapy using a combination of ethanol and STS 3% (4,24). Similarly, in this study, type I and II lesions were successfully treated with sclerotherapy, in particular with foam STS 3%, with an improvement in 75% of cases. Meanwhile, sclerotherapy of type III lesions were unsuccessful in approximately 10% of cases. Therefore, the efficacy of sclerotherapy, in particular with foam STS 3% is best for Puig's type I and II VM but less for type III and IV lesions although it is still effective in some cases. This is not surprising since sclerotherapy is more likely to be successful in lesions that are more discrete and with reduced outflow drainage (type I and II) hence, allowing longer period of sclerosants in contact with the endothelium hence maximizing endothelial damage, when compared with those that are more diffuse, dysplastic and with more outflow drainage (type III and IV) (24). In addition, our results demonstrated that type I lesions were often surgically excised while those treated with foam sclerotherapy STS 3% received less volume compared to other types of VM. The overall results may reinforce the conclusion from the study by Puig et al that the pattern of venous drainage may affect the success rates of sclerotherapy for venous malformations.

Commonly used sclerosants for LFVM included foam polidocanol and STS, ethanol, doxycycline and bleomycin (25,26). Studies on the efficacy of various sclerosants often differed and conflicting (18,27). A single sclerotherapy is often insufficient for an adequate treatment response and therefore, a series of procedures is required until there is no further recanalization or swelling (18). This is evident in our study where patients received approximately 1.6 sclerotherapy sessions (range 1-6) within 5 years. Despite the success of

sclerotherapy, a systematic review by Horbach et al demonstrated no clear evidence on which agent is the safest and most effective (28).

Patients that required multiple sclerotherapy interventions were distributed amongst Puig's classification of lesions in the following order: type I 7 (20.6%), type II 38 (34.2%), type III 28 (45.9%) and type IV 1 (100%). Therefore, based on the classification we can anticipate that type III and IV lesions are more likely to require multiple sclerotherapy sessions compared to type I and II. This is not surprising as type II, III and IV lesions exhibit rapid venous reflux, and therefore good therapeutic outcomes cannot be achieved with just a single sclerotherapy session and perhaps sclerosing agent alone (29). In terms of anatomical location, there was little difference upon which area required multiple sclerotherapy sessions besides pelvis and genitals, of which 9 (64.3%) patients required more than one EST intervention. This could be due to rarity and deeper location of the lesion, and therefore, providing a more difficult challenge to the operator. In the authors' opinion, increases in lesion size and Puig's types are likely to be associated with increase dose of sclerosant used. The authors also aimed at the most symptomatic areas for those patients with diffuse or multiple lesions. Ideally, the time interval between interventions should be between three and six months depending on the individual patient's symptoms, although this was often limited by the waiting list of our public hospital.

The complication rate reported in our study of 4.8% by number of cases over five years was favourable when compared to the literature. All but one case resolved with time. The complication that did not resolve was a fixed flexion deformity of the middle finger, requiring hand therapy. We have previously published our incidence of major complication rate following EST of LFVM of the upper and lower extremity of 21.4%, and head and neck of 5.9% over 5 years (30,31). Complication rates reported in the current literature differed

dependent on factors such as type of sclerosing agent and definition of complication. For example, ethanol sclerotherapy has been reported to have an overall complication rate of 7.5-76% (17,22,32,33) whereas bleomycin has been reported with a complication rate of 6% (28). Our study demonstrated that when comparing different treatment modalities that STS 3% foam, surgery and medication were associated with a better efficacy outcome. This is consistent with the literature which has demonstrated similar successful outcomes (12,35,36) A comparison of anatomical locations and outcome success did not show any significance suggesting that there is no particular region in the body that has better outcomes. However, it should be noted that upper and lower limb, and head and neck had no response rates of 3 (6.4%), 8 (9.1%) and 5 (8.9% respectively. These results were similar to a study by Lidsky which showed lowest symptomatic improvement in lesions located in the upper and lower extremities (12).

There were several limitations of the study. Firstly, the prospective data collection, single unit, and non-randomized design of the study would have introduced biases. Secondly, the outcome measure assessed by the clinicians were not blinded. However, it was our routine practice to ask and document the subjective patient reported post-procedure symptom change as categorized in this study. Our technique as described in the Methods was standardised i.e. direct injection with fluoroscopy with or without ultrasound guidance under general anaesthetics with the foamed STS 3% in air as our preferred sclerosant. The procedures were often done in a multi-disciplinary setting. Therefore, the difference in technique that would have accounted for any differences in outcome would be minimal. However, this study included a relatively large sample size when compared to other similar trials in the literature, and therefore further improved our insights and understanding of the efficacy and safety of foam sclerotherapy STS 3% as an interventional treatment option for patients with VM. The

choice of treatment modality should be personalized according to the type, extension and location of the lesion, the operators' skill set, and individual patient's expectation (37). EST and surgery have their own clinical benefits and limitations. This study did not assess the efficacy and safety of surgery as the preferred choice of treatment of VM hence we could not comment on this therapy in detail. Just like EST, it is likely that open surgical treatment of Puig types III and IV lesions is more challenging when compared to types I and II lesions. Given that both EST and surgery have their own clinical benefits and limitations, a hybrid approach should also be considered for Puig types III and IV to achieve the optimal outcome.

Conclusion

Interventional therapy with foam sclerotherapy STS 3% as the preferred procedure is clinically effective and safe for patients with VMs. This study showed that foam sclerotherapy with STS 3%, is most successful among Puig's type I and II VM. The Puig classification provided an important guide to the treatment outcome of patients with VM needing interventional therapy. However, further prospective and randomized study with large sample size would be required to assess the efficacy and safety of interventional therapy including EST for patients with VM, as well as factors that would determine the outcomes.

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