

Prospective randomized efficacy of ultrasound-guided foam sclerotherapy compared with ultrasound-guided liquid sclerotherapy in the treatment of symptomatic venous malformations

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Objective: To compare the clinical outcome between ultrasound-guided foam sclerotherapy (UGFS) and ultrasound-guided liquid form sclerotherapy (UGLS) in patients with venous malformations (VM).

Methods: Eighty-nine patients with symptomatic VM were treated with ultrasound-guided sclerotherapy. There were 22 males and 67 females with mean age of 14.5 years. The sclerosing agents used were 1% polidocanol (POL) or 10% ethanolamine oleate (EO). POL was injected predominantly into smaller, superficial lesions, whereas EO was used for large, deeper lesions. Foam sclerosing solution was provided using Tessari's method. Patients were randomized to receive either UGFS or UGLS. Post-sclerotherapy surveillance was done at 6 months after last session using duplex ultrasound. Findings obtained by duplex scanning were divided into four groups: (1) disappeared group: the venous space was occluded and was totally shrunk; (2) partially recanalized group: the venous space was partially recanalized and was partially shrunk; (3) totally recanalized group: the venous space was totally recanalized and returned at the same size; and (4) worsened group: the venous space was totally recanalized and became worse.

Results: Forty-nine patients were treated with UGFS and the remaining 40 were treated with UGLS. There were no significant differences in age and men:women ratio. There was no significant difference in the anatomic distribution of VMs between the two groups. The amount of POL was significantly smaller in patients who were treated with UGFS ($P = .022$). Similarly, there was a significant reduction in the use of EO in patients treated with UGFS ($P = .005$). The proportion of VM with total disappearance and partial recanalization was significantly higher in patients treated with UGFS ($P = .002$). No major complications related to sclerotherapy were encountered in both groups.

Conclusions: These findings suggest that UGFS could have greater promise compared with UGLS in the treatment of VMs. (*J Vasc Surg* 2008;47:578-84.)

The symptoms of congenital venous malformations (VMs) are related to size and distribution, however, thrombosis, swelling and pain are commonly observed. The lesions grow in muscles, nerves and blood vessels, and are difficult to delineate. Aggressive excision of VMs can lead to significant loss of motor function, nerve damage, or massive bleeding in patients with extensive involvement. Therefore, the treatment of VMs still remains a matter of debate.¹ Injection sclerotherapy has now been accepted as a less invasive alternative, and good midterm results have been obtained using liquid detergent sclerosing form.² However, VMs with extensive involvement often require stronger sclerosing agents and multiple sessions of sclerotherapy since inappropriate therapy and significant recanalization can always lead to recurrence. Numerous sclerosing

agents have been developed but none of them were ideal or absolutely safe for the treatment of venous disorders.

Recently, administration of new sclerosing foam has been introduced by Cabrera Garrido, predominantly for the treatment of varicose veins of lower extremities³ and appeared to have the advantage of causing more severe damage on the intima compared with the liquid form. However, few studies have been reported on the use of sclerosing foam for the treatment of symptomatic VMs.³⁻⁷ Therefore, we conducted this study to determine efficacy and durability of foam sclerotherapy compared with liquid sclerotherapy in the treatment of VMs.

MATERIALS AND METHODS

Patients

Between January 2001 and December 2006, 89 patients with consecutive, symptomatic extratruncular venous defect predominance were treated with ultrasound-guided sclerotherapy in the Department of Plastic and Reconstructive Surgery at Tokyo Women's Medical University. The patients comprised of 22 males and 67 females, ranging in age from 1 to 62 years (mean 14.5 years). As most patients with VMs cannot be completely cured of all manifestations of their problem, a goal was set for each patient before treatment began.⁴ Treatment session was stopped when the

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Competition of interest: none.

Presented at the Twentieth Annual Meeting of the American Venous Forum, Charleston, South Carolina, Feb 20-23, 2008.

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0741-5214/\$34.00

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doi:10.1016/j.jvs.2007.11.026

patient's cosmetic satisfaction was obtained or no further improvement was expected.

Preoperative evaluation

The diagnosis of VMs was established by demonstrating non-pulsatile blood flow and venous space using duplex ultrasound (LOGIQ 500MD, GE Medical Systems, Milwaukee, Wis). Magnetic resonance imaging sequences were also reviewed to document the location and size of VMs. Identification of the existence of patent deep veins was confirmed by compression ultrasound in patients who had VMs in the lower extremity. Venous reflux in the lateral marginal venous collector in patients with Klippel-Trenaunay syndrome (KTS) was also confirmed by duplex ultrasound.

Following Hamburg classification, patients were divided into three categories: those with localized or extensive subcutaneous lesions (limited VMs), those with intramuscular infiltrations (infiltrating VMs), and those with complex-combined VMs which involve both extensive subcutaneous and intramuscular lesions.^{8,9}

Exclusion criteria included patients who underwent any operative procedure including excision of the VMs and ligation or stripping of the refluxing lateral marginal venous collector in patients with KTS. The presence of pulsatile flow indicates the presence of a strong arterial component suggesting hemangioma and arterial venous malformations, and these lesions were also excluded from the study.

Ultrasound-guided sclerotherapy

This was a randomized controlled trial of ultrasound-guided foam sclerotherapy (UGFS) vs ultrasound-guided liquid sclerotherapy (UGLS) in the treatment of VMs. A portable ultrasound with 5 to 10 MHz 38-mm linear array transducer (SonoSite 180 plus, SonoSite Inc, Bothell, Wash) was used for ultrasound-guided sclerotherapy. The sclerosing solution used in this study was 1% polidocanol (POL; Aethoxysklerol, Kaigen, Osaka, Japan) or 10% ethanolamine oleate (EO; Oldamin, Takeda Pharmaceutical, Osaka, Japan). In general, POL was injected predominantly into smaller, superficial lesions, whereas EO was used for large, deeper lesions. The volume injected and the total number of sessions depended on the size and distribution of the VMs. However, the maximum dose of injected sclerosants did not exceed 1ml/kg for POL and 0.4ml/kg for EO per session. Sclerosant of higher concentration such as 3% POL was not used because the amount of solution is extremity-limited especially in infants. The study protocol and consent forms were approved by the local institutional review board (IRB).

Ultrasound-guided foam sclerotherapy (UGFS). The sclerosing foam was produced by Tessari's method using POL or EO with the liquid-to-air ratio of 1:4.^{10,11} Two syringes were attached by a three-way stopcock, and one syringe was filled with either POL or EO, and another with the air. The stable sclerosing foam was obtained by mixing them through multiple passages between the two syringes. The venous space was identified intraoperatively by duplex scanning, and then venous flow was confirmed again by pulse Doppler mode. A 20-gauge

plastic needle (JELCO PLUS, Smith Medical Japan Ltd, Tokyo, Japan) was inserted into the venous space under the ultrasound visualization, and aspiration of the blood confirmed its intraluminal position. After fine plastic tubing filled with normal saline was attached to the needle, a 10 ml syringe containing sclerosing foam was connected, and sclerosing foam was infused slowly. The ultrasound monitoring assured intravascular placement of the sclerosing solution. After the treatment session, compression dressing was applied for promoting endosclerosis.⁴ The compression was maintained for 3 days (Fig 1).

Ultrasound-guided liquid sclerotherapy (UGLS). Likewise, the venous space was identified intraoperatively by duplex scanning in B-mode, and then venous flow was confirmed in pulse Doppler mode in patients who had UGLS. After a 20-gauge plastic needle was inserted into the venous space under visualization with duplex scanning, fine plastic tubing filled with normal saline was attached to the needle. Several needles were inserted in the same manner, with the number of needles depending on the extent of venous malformations. The iodinated contrast material was mixed with either POL or EO with the ratio of 1:1 to visualize the injected liquid under fluoroscopy. The compression dressing was applied after sclerotherapy and maintained for 3 days (Fig 2).

Post-sclerotherapy follow-up

Post-sclerotherapy surveillance was done at 6 months after last session using duplex ultrasound. Findings obtained by relatively short-term follow-up were divided into four groups: (1) disappeared group: the venous space was occluded and was totally shrunk; (2) partially recanalized group: the venous space was partially recanalized and was partially shrunk; (3) totally recanalized group: the venous space was totally recanalized and returned at the same size; and (4) worsened group: the venous space was totally recanalized and became worse.

Statistical analysis

All data were analyzed using StatView for Windows (Version 5.0, SAS Institute Inc, Cary, NC). Wilcoxon nonparametric rank sum test and χ^2 analysis or Fisher exact test were used to evaluate differences between the groups of patients. Statistical significance was defined as $P < .05$.

RESULTS

Table I summarizes the baseline characteristics of the two study groups. Of 89 patients, 49 patients were treated with UGFS and remaining 40 were treated with UGLS. Successful needle placement, repositioning, and ultrasound-monitored foam injection or image-monitored injection of the mixture was accomplished in all cases without complication. There were no significant differences in age and men:women ratio. The most common type of VMs in UGFS was infiltrating VMs that accounted for 74% of the patients. Similarly, in the UGLS, proportion of infiltrating VMs was the most predominant (78%). Patients with limited and complex-combined VMs are not common in this

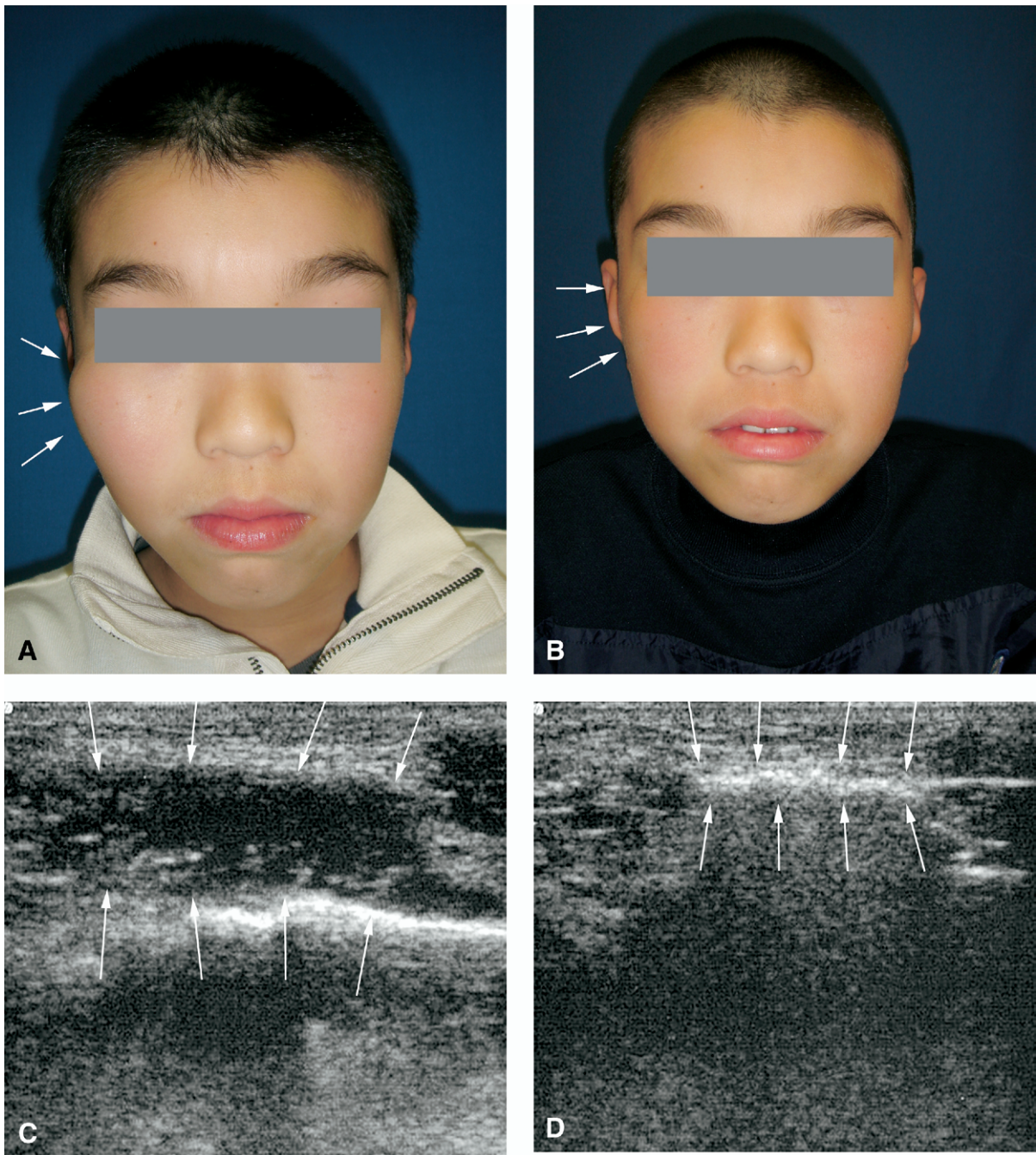


Fig 1. Ultrasound-guided foam sclerotherapy (UGFS). **A**, Before treatment. **B**, After treatment. **C**, Venous space demonstrated by ultrasound. **D**, Complete disappearance of the venous malformations.

study. There was no significant difference in the type of VMs between the two groups. The most common location of VM in UGFS was head and neck region, followed by upper extremity, and lower extremity region (51%, 19%, and 14%, respectively). Similarly, in the UGLS group, head and neck was involved in 42% of the patients, 35% had lower extremity and 10% had upper extremity involvement.

There was no significant difference in the anatomic distribution of VMs between the groups.

Fig 3 shows the amount of sclerosing solution administered per session. The mean use of POL was 1.4 ml (range: 0.5-7.0 ml) for UGFS group and 3.4 ml (range: 0.5-7.0 ml) for UGLS group, and there was a significant difference in the amount of sclerosing solution between the

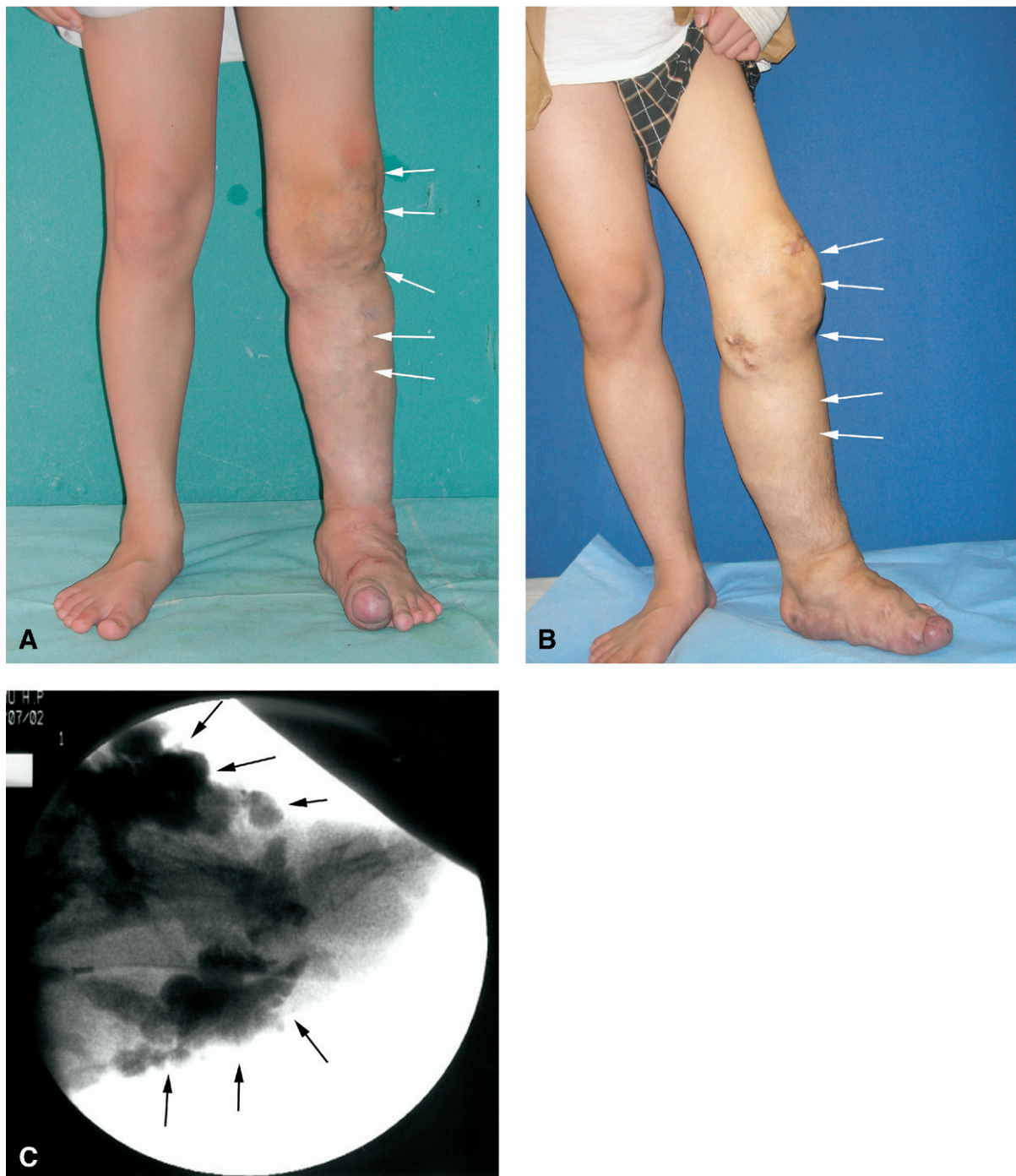


Fig 2. Ultrasound-guided liquid sclerotherapy (UGLS). A, Before treatment. B, After treatment. C, Visualization of the iodinated contrast material mixed with sclerosant under fluoroscopy.

two groups ($P = .022$). Similarly, the mean use of EO was 1.7 ml (range: 0.5-6.0 ml) for UGFS group and 3.8 ml (range: 0.5-10.0 ml) for UGLS group, and the injected amount of EO was significantly larger in patients who received UGLS ($P = .0005$).

Table II shows the total treatment sessions of ultrasound-guided sclerotherapy. In UGFS group, 63% of the patients had only one session. Similarly, in the UGLS group, 58% of the patients had only one session. On the contrary, 37% of the patients with UGFS group required sequential staged

Table I. Baseline characteristics of the study patients

	UGFS (n = 49)	UGLS (n = 40)	P value
Mean age	16.2 ± 15.5	12.8 ± 8.4	.315
Gender (male)	14 (28.6%)	9 (22.5%)	.515
Type of VMs			
Infiltrating	36 (73.5%)	31 (77.5%)	.661
Limited	8 (16.3%)	6 (15.0%)	.864
Complex-combined	5 (10.2%)	3 (7.5%)	.657
Distribution of VMs			
Head and neck	25 (51.0%)	17 (42.5%)	.423
Upper extremity	7 (14.3%)	4 (10%)	.541
Trunk	7 (14.3%)	4 (10%)	.541
Lower extremity	9 (18.4%)	14 (35.0%)	.075
Upper extremity	7 (14.3%)	4 (10%)	.541
Genitalia	1 (2.0%)	1 (2.5%)	.884

UGFS, Ultrasound-guided foam sclerotherapy; UGLS, ultrasound-guided liquid sclerotherapy; VMs, venous malformations.

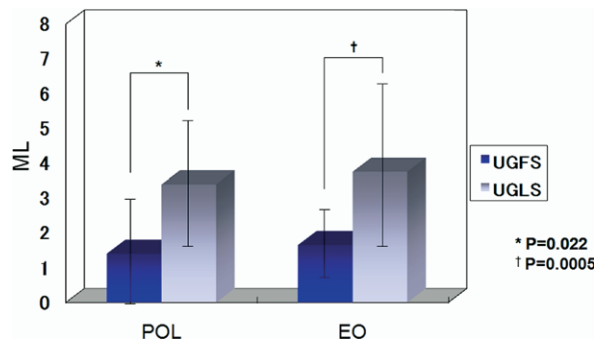


Fig 3. Amount of sclerosants injected. UGFS, Ultrasound-guided foam sclerotherapy; UGLS, Ultrasound-guided liquid sclerotherapy; POL, 1% polidocanol; EO, 10% ethanolamine oleate.

Table II. Number of treatment sessions

Sessions	UGFS (n = 49)	UGLS (n = 40)
1	31 (63.3%)	23 (57.5%)
2	10 (20.4%)	14 (35%)
3	3 (6.1%)	2 (5%)
4	4 (8.2%)	0 (0%)
More than 5	1 (2%)	1 (2.5%)

UGFS, Ultrasound-guided foam sclerotherapy; UGLS, ultrasound-guided liquid sclerotherapy.

treatment, and 2% of patients required more than five sessions. Similarly, in UGLS group, 42% of the patients required multiple sessions, and 2.5% of patients required greater than five sessions.

Table III shows the findings obtained by duplex scanning 6 months after last session. Follow-up ultrasound demonstrated no residual venous space in 45% of patients with UGFS group and 25% with UGLS group. Similarly, 45% of the patients with UGFS group and 15% of the patients with UGLS group showed partial recanalization with duplex ultrasound. The proportion of VMs with total

Table III. Outcome of the ultrasound-guided sclerotherapy

	UGFS (n = 49)	UGLS (n = 40)	P value
Disappeared	22 (44.9%)	10 (25.0%)	
Infiltrating	15 (30.6%)	9 (22.5%)	
Limited	6 (12.2%)	1 (2.5%)	
Complex-combined	1 (2.1%)	0 (0%)	
Partially recanalized	22 (44.9%)	15 (37.5%)	
Infiltrating	18 (36.7%)	10 (25.0%)	
Limited	2 (4.1%)	5 (12.5%)	
Complex-combined	2 (4.1%)	0 (%)	
Subtotal	44 (89.8%)	25 (62.5%)	.002
Totally recanalized	5 (10.2%)	12 (30%)	
Infiltrating	3 (6.1%)	11 (27.5%)	
Limited	0 (0%)	0 (0%)	
Complex-combined	2 (4.1%)	1 (2.5%)	
Worsened	0 (0%)	3 (7.5%)	
Infiltrating	0 (0%)	1 (2.5%)	
Limited	0 (0%)	0 (0%)	
Complex-combined	0 (0%)	2 (5.0%)	
Subtotal	5 (10.2%)	15 (37.5%)	
Total	49 (100%)	40 (100%)	

UGFS, Ultrasound-guided foam sclerotherapy; UGLS, ultrasound-guided liquid sclerotherapy.

Table IV. Complications of the ultrasound-guided sclerotherapy

	UGFS (n = 49)	UGLS (n = 40)
Pain	44 (89.8%)	32 (80%)
Marked swelling	40 (81.6%)	29 (72.5%)
Epidermal necrosis	1 (2%)	1 (2.5%)
Cutaneous necrosis	0 (0%)	1 (2.5%)
Hemoglobinuria	2 (4.1%)	4 (10%)
Renal failure	0 (0%)	1 (2.5%)
Allergic reactions	0 (0%)	0 (0%)
Superficial thrombophlebitis	0 (0%)	0 (0%)
Deep vein thrombosis	0 (0%)	0 (0%)
Pulmonary embolism	0 (0%)	0 (0%)
Stroke	0 (0%)	0 (0%)

UGFS, Ultrasound-guided foam sclerotherapy; UGLS, ultrasound-guided liquid sclerotherapy.

disappearance and partial recanalization was significantly higher in patients treated with UGFS group ($P = .002$). On the contrary, 10% of the patients treated with UGFS showed total recanalization 6 months after last session. Similarly, in UGLS group, 30% of the patients demonstrated complete recanalization and returned at the same size. Eight percent of patients treated with UGLS showed total recanalization and became worse after treatment. Successful results were obtained in patients with limited lesions using either UGFS or UGLS. However, in patients with infiltrating and complex-combined lesions, UGFS gave better results.

Table IV shows the early complications related to ultrasound-guided sclerotherapy. Pain was the most common complication, but this was resolved within a week. After treatment sessions, each patient demonstrated an immediate swelling and inflammatory reaction, which re-

quired 1-2 weeks to subside. But no patients required corticosteroid to decrease inflammatory reaction. Hemoglobinuria was less common in this study. However, one patient treated with UGLS with the use of EO, required administration of haptoglobin for severe macroscopic hemoglobinuria. One patient developed acute renal failure with the use of EO, and recovered within 1 week by infusion of K^+ -free fluid and diuretics. Epidermal necrosis was seen in one patient receiving UGFS and one patient receiving UGLS. Cutaneous necrosis was found in one patient, but no further surgical procedure was necessary. No other serious complications, such as allergic reactions, deep vein thrombosis, pulmonary embolism, or cerebral infarct.

DISCUSSION

Vascular malformations are errors of morphogenesis and consist of abnormal channels linked by normal endothelium. In 1982, Mulliken and Glowacki divided vascular malformations into high flow and low flow vascular malformations.¹² Among the latter, VMs can be most commonly found. Although there is no generally accepted classification, they include focal, multifocal, and diffuse forms.¹³ Focal lesions may be intramuscular, cutaneous, or mucosal and usually consist of collections of abnormal interconnecting channels or spaces. Diffuse venous malformations involve multiple tissue layers including muscle, subcutaneous fat, skin, and sometimes bone. On the contrary, the Hamburg classification, which is also well accepted, describes five types of vascular malformations.^{8,9} The Hamburg classification is excellent with minimum confusion because the terminology provides substantial information on the basis of embryologic development. Of these, type 2, predominately venous defects can be subclassified as truncular or extratruncular, either of these. The terms "infiltrated form" and "limited form" are basic morphological conceptions for extratruncular VMs. The infiltrating VMs show invasion in neighboring tissues (eg, muscles, bones, glands, and parenchymatous organs) and are associated with the most difficult therapeutic problem. The limited form, on the other hand, demonstrates expansive growth, which alleviates significantly its treatment.

VMs often involve multiple contiguous anatomic structures, and the treatment of VMs remains problematic. Aggressive surgical intervention often results in significant loss of motor function and nerve damage when important structures are sacrificed. Indeed, surgical excisions are often not possible because of functional and anatomic limitations. Moreover, incomplete surgical removal of VMs often results in recurrence. For this reason, percutaneous injection sclerotherapy has been advocated as an effective alternative to surgery. A small volume of sclerosing solution can obliterate large saccular venous malformations because the blood flow is extremely low and multiple small injections provide adequate inflammatory response.¹⁴

Various sclerosants have been used for the treatment of VMs. Absolute alcohol has been widely used for symptomatic VMs, and considered to give the lowest recurrence rate.^{15,16} Svendsen et al used alcohol, and reported excellent or good results in 84% of the patients.¹⁶ Yakes et al

used absolute alcohol in patients with symptomatic vascular malformations in whom previous treatment had failed and found that 95% of the patients showed persistent occlusion.¹⁷ Lee et al described the treatment of congenital VMs with the use of alcohol and obtained the immediate success rate of the sclerotherapy in 92%.¹⁸ Absolute alcohol is thus effective but destructive, and there are some complications reported using alcohol. Lee reported 9 cases with ischemic bullae, 2 with tissue fibrosis, 2 with tissue necrosis, 1 with deep vein thrombosis, 1 with pulmonary embolism, and 5 with nerve palsy in 98 sessions of alcohol sclerotherapy in 30 patients.¹⁸ Berenguer et al showed one patient who had transient bradycardia during the alcohol sclerotherapy.¹ Yakes and Baker reported four episodes of cardiac arrest during sclerotherapy with alcohol.¹⁹ Maison et al studied the relationship between the serum alcohol level and the amount of alcohol administered, and found that patients who receive up to 1.0 ml/kg ethanol during embolization or sclerotherapeutic procedures may have elevated serum ethanol levels that could put them at risk of respiratory depression, cardiac arrhythmias, seizures, rhabdomyolysis, and hypoglycemia.²⁰ Ethanol should be injected only after contrast injection has confirmed appropriate placement of the cannula or catheter in the malformation.¹³

The sodium tetradecyl sulfate (STS) and POL are detergent sclerosants that have been also widely used for the treatment of VMs. Like ethanol, these drugs damage the endothelial cells, resulting in thrombosis and fibrosis. Thrombosis occurs more slowly than with ethanol, and there is probably a greater tendency for recanalization. As with ethanol, the cannula position should be confirmed with contrast medium injection or ultrasonography before injection of sclerosant, as arterial injection causes severe tissue damage. However, these drugs are not potent sclerosants as ethanol. Siniluoto et al reported excellent or good results in 68% of the patients with the use of STS.²¹ They concluded that they might use alcohol if treatment with STS failed. Berenguer et al discussed the experience with the use of absolute alcohol and STS, and they used STS for smaller, superficial malformations, and applied alcohol for larger, deeper malformations.¹ Complications related to the use of these drugs are less frequently compared with ethanol. De Lorimier reported anaphylaxis using STS.¹⁴ There has been only one report of a cardiovascular complication using POL.²² EO is also used for CVMs, and effective result has been also reported with the use of EO.^{23,24} EO is a salt of an unsaturated fatty acid and has been commonly used for the treatment of esophageal and gastric varices as a sclerosing agent because it has excellent thrombosing properties.

Injection into varices leads to thrombogenesis as a result of chemical damage to the vascular wall. However, some degree of nonspecific red blood cell hemolysis may occur with its use. To prevent renal damage caused by EO-induced hemolysis, administration of haptoglobin may be necessary to protect against renal damage.²⁵

After the introduction of foam form of sclerosing solution, foam sclerotherapy rapidly gained its popularity in the treatment of primary valvular insufficiency of the lower ex-

trinity. However, few studies have focused on the use of foam sclerosant for the treatment of VMs. Historically, Orbach first described the macrobubble foam preparation with sclerosing solution in 1950.²⁶ Using his technique, however, only 20% of the sclerosant was transformed into foam with bubbles of relatively large and irregular caliber, and foam sclerotherapy did not become popular till mid 1990s after the introduction of new methods of transforming sclerosing solutions. There have been several different methods reported in the production of a foam form.^{3,11,27} In 2000, Tessari reported a new method for the production of foam with two syringes connected with a three-way stopcock, and it has been widely accepted in producing a stable foam.¹¹ Yamaki et al applied ultrasound-guided POL-foam sclerotherapy for the treatment of symptomatic VMs of the face and found significant reduction of the VMs without any adverse event.⁴ Pascarella et al also used POL-foam in 14 patients with VMs and found the use of POL-foam to be effective, essentially pain-free, and durable in the short term.⁶ In general, limited lesions are easily treated by UGFS (Fig 1, A and B). This type of lesion can be treated on an outpatient basis without anesthesia. Complex-combined VMs, however, are difficult to treat effectively because injected sclerosant can directly enter the circulation (Fig 2, A and B). In these cases, sclerotherapy is useful for superficial components but is not fully effective for deep components. In this study, limited lesions can be treated with single session of UGFS. However, multiple treatment sessions are almost always required in patients with infiltrating VMs with extensive involvement.

CONCLUSION

This study indicated that UGFS with the use of POL or EO is safe and effective in the treatment of symptomatic VMs. The advantage of foam sclerosant includes the possibility of reducing the amount of necessary sclerosing solutions as well as the concentration with an acceptably low rate of adverse events. These findings suggest that UGFS could have greater promise compared with UGLS in the treatment of VMs. In recent years, much progress has been made in the treatment of a variety of venous conditions using UGFS.

AUTHOR CONTRIBUTIONS

Conception and design: TY

Analysis and interpretation: TY, MN, HS, MT, KS, TK

Data collection: TY, HS, MT, KS, TK

Writing the article: TY

Critical revision of the article: TY, MN, HS, MT, KS, TK

Final approval of the article: TY, MN, HS, MT, KS, TK

Statistical analysis: TY

Obtained funding: Not applicable

Overall responsibility: TY

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Submitted Sep 13, 2007; accepted Nov 10, 2007.