Original article

Article title:

Prospective randomized comparative study of visual foam sclerotherapy alone or in combination with ultrasound-guided foam sclerotherapy for treatment of superficial venous insufficiency: Preliminary report

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Brief title: Ultrasound-guided versus visual foam sclerotherapy

Abstract

Objective: To compare ultrasound-guided foam sclerotherapy (UGFS: injection of foam sclerosant under ultrasound guidance) of the great saphenous vein (GSV) combined with visual foam sclerotherapy (VFS: injection of foam sclerosant under visual control) for varicose tributary veins and VFS alone in the treatment of GSV reflux.

Design & Methods: One-hundred and three limbs in 97 patients with GSV reflux were randomized to receive either VFS alone or VFS combined with UGFS. In both groups, 1% polidocanol foam was used. Assessments included duplex ultrasonography, evaluation of Venous Clinical Severity Scores (VCSS) and CEAP (clinical, etiologic, anatomic, and pathophysiologic) scores. Ultrasonographic inspection of the foam in the GSV was carried out during 5 minutes before compression was applied. The primary endpoint of the study was obliteration of the GSV at 6 months.

Results: Fifty-one limbs in 48 patients were treated with UGFS + VFS and the remaining 52 limbs in 49 patients were treated with VFS alone. There were no significant inter-group differences in patient age, male:female ratio, height, weight, body mass index, CEAP clinical scores or VCSS. The GSV diameter was 6.0 ± 1.7 (median ± inter-quartile range) mm in the UGFS+VFS group and 5.7 ± 1.6 mm in the VFS group (p = 0.419). The mean injected volume of foam for varicose tributary veins was 4 ± 2 mL in the UGFS+VFS group and 6 ± 2 mL in the VFS group, a significantly higher amount of foam being used in the latter (p <0.001). However, the mean total amount of foam was greater in limbs treated with UFGS+VFS than in those treated with VFS alone (p = 0.017). Ultrasonographic inspection revealed complete vasospasm of the GSV in 37 (72.5%) limbs in the UGFS+VFS group and 29 (55.8%) in the VFS group during sclerotherapy (p = 0.097). At 6-month follow-up, complete occlusion was found in 23 limbs (45.1%) treated with UGFS+VFS and in 22 limbs (42.3%) treated with VFS. The difference between the two groups was not significant (p = 0.775). Reflux was absent in 30 limbs (58.8%) treated with UGFS+VFS and in 37 (71.2%) treated with VFS (p = 0.190). There was no inter-group difference in post-treatment VCSS (p = 0.223).

Conclusions: These results show that UGFS+VFS and VFS are as equally effective for the treatment of GSV reflux, despite the lower volume of foam used for VFS alone.

Key words: superficial venous insufficiency, varicose veins, ultrasound-guided foam sclerotherapy

Introduction

Over the last decade, ultrasound-guided foam sclerotherapy (UGFS) has largely replaced liquid sclerotherapy in the treatment of superficial venous insufficiency.[1-9] The use of liquid sclerosants has the limitations of dilution, inactivation and irregular distribution of the sclerosant on the endothelium. In contrast, foam sclerosants displace the blood and concentrate their effect on the intima more intensely than liquid sclerosants due to homogeneous distribution of the sclerosant over the endothelial surface. This has facilitated a reduction in both the volume and concentration of these agents compared with liquid sclerotherapy. [10, 11] Thus, foam sclerotherapy has become popular in the treatment of superficial venous insufficiency, and the use of liquid polidocanol has now been reserved for only spider, reticular and small varicose veins. Alternative treatments include conventional surgery and endovenous laser or radiofrequency ablation of the incompetent truncal veins.

In clinical practice, most patients receiving foam sclerotherapy are managed with ultrasound-guided injection of foam into the GSV combined with direct injection of foam into tributary veins. However, if excess foam is injected into the tributary veins, it often travels to the GSV and can cause immediate and dramatic spasm along the whole length of the vein. This prevents the effective use of UGFS. To our knowledge, no previous reports have described the effect of excessive foam migration on GSV vasospasm. The purpose of the present study was to compare the effectiveness of visual foam sclerotherapy (VFS) alone for varicose tributary veins with that of VFS combined with UGFS in patients with primary varicose veins associated with truncal vein incompetence.

Materials and Methods

Patients

The study subjects comprised 97 patients (31 male: 66 female; age 27-88 (mean 68.8); 103 limbs) who were treated for GSV reflux associated with sapheno-femoral junction (SFJ) incompetence between January 2010 and July 2010. The patients were prospectively randomized to receive either VFS alone or VFS combined with UGFS of the GSV. Patients' height, weight and body mass index (BMI; kg/m^2) were also recorded as well as their CEAP (clinical, etiologic, anatomic, and pathophysiologic) score.[12] In this study, all of the patients were classified as $C_{2,3,4a,4b}$,E_p,A_s,$P_{r2,3}$. To assess any improvement in symptoms in response to treatment, the patients were assessed using the revised Venous Clinical Severity Score (VCSS) before and 1, 3, and 6 months after foam sclerotherapy.[13] Patients with myocardial ischemia, arterial insufficiency with an ankle brachial index of less than 0.9, in the first trimester of pregnancy and after the 36^{th} week of gestation, local infection in the area for sclerotherapy, active thrombophlebitis and acute deep vein thrombosis were excluded from the study. The study was approved by the institutional review board, and informed consent was obtained from all participants.

Pre-treatment ultrasonographic evaluation

Pre-treatment examination was performed using a color duplex scanner (LOGIQ 7 PRO; GE Yokogawa Medical Systems, Tokyo, Japan) with a 5- 10 MHz transducer to detect venous reflux at the SFJ and in the GSV. Venous reflux was assessed while the patient was standing. For evaluation of the SFJ, a pneumatic thigh cuff (Hokanson, Bellevue, WA, USA) was attached to the thigh, inflated to 80 mmHg, and then rapidly deflated. For evaluation of the GSV, the transducer was placed 10 cm above knee level, and a cuff was applied to the calf, inflated to 100 mmHg, and then rapidly deflated. The diameter (mm) of the GSV was measured in cross-sectional view while the patient was standing. Venous reflux was considered to be present if the reflux time (RT) exceeded 0.5s. Additional ultrasound-derived parameters assessed were peak reflux velocity (PRV; cm/s), mean reflux velocity (MRV; cm/s) and total reflux volume (TRV; mL) calculated using the equation: TRV (mL) = MRV x Area (r^2) x RT. The vessel cross-sectional area was estimated from the

diameter, assuming a circular vessel shape.

Foam sclerotherapy

The sclerosant foam was prepared by Tessari's method using 1% Polidocanol (POL: Polidocasclerol, Zeria Pharmaceutical Co. Ltd., Tokyo, Japan).[1] Because one of the purposes of this study was to compare the success rates achieved in the two groups under the same conditions, all patients received the same sclerosant and were allowed only one additional treatment session during the follow-up period of 6 months. After detailed anatomical mapping with duplex ultrasound, patients were placed supine with their affected leg(s) elevated 30 degrees. Each visible varicose tributary vein was injected first using 23-gauge butterfly needles. Patients who were treated with UGFS combined with VFS received <0.5 mL POL foam per injection to minimize any foam migration beyond the target vein.[14] Subsequently 1% POL foam was injected into the GSV under ultrasound guidance, starting 3-4 cm distal to the SFJ.[15] A second injection was performed 5 to 10 cm distal to the initial point using a 21-gauge venous catheter. The GSV cannulae were inserted before injection of the tributaries. Patients who were treated with VFS alone received 0.6-1.0 mL POL foam per injection. Thus, the total amount of injected foam did not exceed 10 mL in any of the cases.[9] Ultrasonographic inspection of the foam was then performed for 5 minutes after completion of foam sclerotherapy using duplex ultrasound (DUS) in both longitudinal and transverse section to reduce artifacts produced by the foam. The findings on DUS were classified into one of three groups:

(1) Complete vasospasm: the GSV showed complete vasospasm throughout its length.

(2) Moderate vasospasm: a maximum reduction in GSV diameter > 50%.

(3) Poor vasospasm: a maximum reduction in GSV diameter < 50%.

If vasospasm was complete distally but only >50% proximally, it was graded as >50%.

After completion of the DUS examination compression pads and elastic bandages were applied, and kept on continuously for the first two days. All the patients were encouraged to ambulate after the treatment. On post-sclerotherapy day 3, the elastic bandages and compression

pads were removed, and a Class II thigh-high compression stocking was applied.

Post-sclerotherapy follow-up

To evaluate the efficacy of foam sclerotherapy, post-sclerotherapy surveillance was done at 2 weeks, and 1, 3 and 6 months using DUS. The primary endpoint of the study was obliteration of the GSV at 6 months. The results of DUS were classified as follows:

(1) Complete occlusion: the GSV had shrunk and was occluded.

(2) Partial GSV recanalization with no reflux.

(3) Partial GSV recanalization with reflux.

(4) Complete GSV recanalization with reflux.

Statistical analysis

All data were analyzed using the SPSS software package (Version 16.0; SPSS Inc., Chicago, IL). Comparisons of numerical data between groups of patients were made using Student's *t* test. Chi-squared contingency table analysis was used to evaluate differences between proportions. Continuous data were expressed as median ± inter-quartile range. Statistical significance was defined as $p < 0.05$.

Results

Patient characteristics

Table 1 summarizes the baseline characteristics of the two study groups. Fifty-one limbs in 48 patients were treated with UGFS+VFS, and 52 limbs in 49 patients were treated with VFS alone. There were no inter-group differences in age ($p = 0.918$) or male:female ratio ($p = 0.406$). Patients' height, weight and BMI were also similar in the two groups ($p = 0.381$, 0.903, 0.693,

respectively). Finally, there was no inter-group difference for each CEAP class in the two groups (p = 0.409, 0.989, 0.241, 0.631, respectively), with the majority (UGFS+VFS: 77%, VFS: 69%) having uncomplicated varicose veins (CEAP C_2). Successful cannula placement and ultrasound-monitored foam injection were accomplished in all patients without any immediate complications.

Ultrasound-derived hemodynamic variables before foam sclerotherapy

Table 2 shows the pre-treatment ultrasound-derived hemodynamic variables in the two groups. The mean GSV diameter was 6.0 mm in the UGFS+VFS group and 5.7 mm in the VFS alone group (p = 0.419). Similarly, there was no significant inter-group difference in the RT (p = 0.142), or in PRV, MRV or TRV (p = 0.757, 0.772, 0.571, respectively).

Volume of sclerosing foam

The mean injected volume of foam for varicose tributary veins was 4 ± 2 mL in the UGFS+VFS group and 6 ± 2 mL in the VFS group, a significantly higher amount of foam being used in the latter (p <0.001). However, the mean total amount of foam was greater in limbs treated with UFGS+VFS than in those treated with VFS alone (p = 0.017).

Ultrasonographic inspection of sclerosant foam

Table 3 shows the degree of vasospasm in each group 5 minutes after the completion of foam sclerotherapy. There was no difference between them in respect of either complete or moderate GSV vasospasm (p = 0.097, 0.869, respectively) although, a higher proportion of patients who received VFS alone had poor vasospasm in comparison with the UGFS+VFS group (p = 0.009).

Outcome of foam sclerotherapy

The outcomes for foam sclerotherapy are shown in Table 4. At 6-month follow-up,

there was no difference in the proportion of patients with complete GSV occlusion (UGFS+VFS 45.1%; VFS 42.3%: $p = 0.775$) or elimination of GSV reflux (UGFS+VFS 58.8%; VFS 71.1%: $p = 0.190$). Similarly, the proportion of patients showing partial recannalisation with reflux ($p = 0.465$), complete recannalisation ($p = 0.282$) or recurrent varicose veins was no different ($p = 0.485$). Post-sclerotherapy GSV diameters were reduced in both groups despite continuing reflux ($p = 0.788$) and there was no inter-group difference in the RT ($p = 0.836$), or in PRV, MRV or TRV ($p = 0.596$, 0.351, 0.579, respectively) in patients with reflux.

Table 5 shows the relationship between vasospasm during sclerotherapy and elimination of reflux at 6 months. The proportion of limbs showing complete vasospasm and no reflux was greater for UGFS+VFS than for VFS alone, but the difference was not significant (p = 0.159). Similarly, there was no significant inter-group difference in the proportion of limbs showing moderate vasospasm with elimination of reflux ($p = 0.974$). In contrast, a higher proportion of limbs treated with VFS alone had poor vasospasm in comparison with those treated with UGFS+VFS ($p = 0.021$), despite elimination of reflux.

Table 6 shows the changes in the VCSS score in the two treatment groups. There were no significant inter-group differences in either pre-treatment ($p = 0.706$), or post-treatment VCSS at 6 months ($p = 0.223$).

Complications related to foam sclerotherapy in this series were not serious. Superficial thrombophlebitis occurred in 1 patient in each of the groups and 1 patient treated with VFS experienced migraine. No other serious complications occurred.

Discussion

This study investigated the efficacy of VFS alone in comparison with VFS combined with UGFS for treatment of GSV reflux. We found that the volume of foam used was greater for UFGS+VFS than for VFS alone, but that elimination of reflux and the improvement in VCSS score was no different.

The safety and efficacy of UGFS as a minimally invasive treatment for varicose veins has become widely accepted, and a number of large case series have been reported.[3-8] The use of an appropriate concentration and volume of foam sclerosant yields good short-term GSV occlusion rates. At the 2nd European Consensus Meeting on Foam Sclerotherapy (ECMFS), most experts reported using 3% POL to prepare foam for the treatment of GSV reflux.[9] However, recent studies comparing 1% and 3% POL foam found that the two concentrations were equally effective when the GSV trunk was <8 mm in diameter.[16, 17] Nevertheless Ceulen et al. suggested that there was a clinically relevant, but non-significant, difference in the proportion with GSV occlusion between 1% and 3% POL-foam (69.5% versus 80.1%). [18] The volume of foam injected may also influence outcome. At the 2nd ECMFS (REQUIRES FULL TITLE), it was recommended that no more than 10 ml of foam should be injected in a single session. In reality, much less is usually required.[16]

To judge whether sufficient foam has been delivered into the GSV (vasospasm, confirmation that foam filled the vein) DUS inspection is mandatory.[14, 16] This approach can minimize the volume of foam required during sclerotherapy. However, the occurrence of vasospasm in the injected vein is considered merely to indicate that the initial foam injection was satisfactory and re-opening of the vein may occur despite the occurrence of vasospasm.[16] In the present study, we found that only 73% of the limbs treated with UGFS+VFS and 53% of those given VFS and showing complete vasospasm had elimination of reflux at 6 months. Conversely, in 16% of limbs treated with VFS and showing poor vasospasm reflux was subsequently abolished. Thus, vasospasm is not a reliable predictor of efficacy.

Adverse events do not seem to occur as often if a limited volume of foam is used in large varicose veins. Deep vein thrombosis has been reported as a significant complication of foam sclerotherapy only when a large amount of foam is used.[19] Myers and associates reported 9 cases of occlusive posterior tibial vein thrombosis and 7 cases of partially occlusive femoro-popliteal thrombosis with the use of 5-35ml (median 14ml) of foam, representing 1.8% and 1.4% of the 489 studied patients, respectively.[20]

Stroke has also been reported in association with UGFS for GSV incompetence after

administering 20 ml of POL foam prepared by the Tessari method.[21] Theoretically, an air embolism can be fatal if a volume of >1 ml/kg is administered to the venous system.[22] At lower foam doses, the total gas load within the bubbles is better solubilised, and the bubbles may become better separated spatially, thus reducing coalescence.[23] However, another report has stated that there is no evidence for an increased risk of embolism resulting from larger foam volumes in UGFS. [7]

To reduce the risk of large amounts of foam migrating to the right heart, with the potential for embolisation to the central nervous system, Hill et al. have reported an injection technique in which the leg is elevated without occlusive pressure at the saphenofemoral junction when performing UGFS.[24] Initial treatment of GSV reflux and delayed sclerotherapy of the varicose tributaries may also reduce the rate of foam migration. Finally, our previous study demonstrated that the multiple small-dose injection (<0.5 ml per injection) technique can reduce foam migration into the deep venous system during sclerotherapy.[14]

To our knowledge, no previous reports have documented a positive effect of foam injected via incompetent tributary veins on damage to the GSV beyond the target vein. Although the correlation between vasospasm during UGFS and clinical outcome is contentious,[9,25] the present study confirmed that foam injected into the tributaries promoted GSV vasospasm in some patients. This suggests that foam remained in the superficial venous system and DUS may not be required unless the clinician wishes to document GSV spasm and ensure no passage of foam into the deep venous system.

Our study had some potential limitations. In particular, the 6-month follow-up period was too short to allow full evaluation of the efficacy of foam sclerotherapy. In addition, the limited sample size could have introduced a type II statistical error. Finally, the volume of foam employed was much smaller than that recommended at the 2nd ECMFS, resulting in a relatively higher proportion of patients showing poor vasospasm in the VFS alone group. UGFS was performed for the proximal GSV alone and a better outcome may have been obtained if the distal saphenous trunk had been treated simultaneously.[26]

In conclusion, this present findings indicate that UGFS+VFS and VFS alone have

equivalent efficacy in the treatment of GSV reflux, despite the lower volume of foam used for VFS alone. Further studies are required in order to define the predictive factors for successful outcome, especially in patients with uncomplicated varicose veins, including factors such as vein diameter, foam production techniques, the optimal volume of foam, the use of physiologic gases, injection techniques, and the optimal period of use of compression stockings.

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Authors’ contributions

Yamaki T: study conception and design; Hamahata A: acquisition of data; Soejima K: acquisition of data; Kono T: acquisition of data; Nozaki M: critical revision; Sakurai H: critical revision.

Conflict of interest

No significant conflicts of interest are declared.

	UGFS+VFS n= 48 patients	VFS n= 49 patients	*p*-value
Age (yr)	69 ± 13	69 ± 13	0.918
Female gender, no (%)	36 (75.0)	33 (67.3)	0.406
Height (m)	1.58 ± 0.91	1.58 ± 1.45	0.381
Weight (kg)	55.0 ± 11.1	56.5 ± 12.0	0.903
BMI (kg/m^2)	22.8 ± 3.7	22.0 ± 2.9	0.693
CEAP Clinical classification*	n=51 limbs	n=52 limbs	*p*-value
C_2 (%)	39 (76.5)	36 (69.2)	0.409
C_3 (%)	1 (1.9)	1 (1.9)	0.989
C_{4a} (%)	8 (15.7)	13 (25.0)	0.241
C_{4b} (%)	3 (5.9)	2 (3.9)	0.631

UGFS: ultrasound-guided foam sclerotherapy, VFS: visual foam sclerotherapy

*CEAP Clinical classification: C_2, varicose veins; C_3, edema without skin changes; C_{4a}, pigmentation or eczema; C_{4b}, lipodermatosclerosis or atrophie blanche

VCSS: Venous Clinical Severity Score

Table 1. Baseline characteristics grouped by use or non-use of ultrasound-guided foam sclerotherapy

Ultrasonographic evaluation	UGFS+VFS n=51 limbs	VFS n=52 limbs	*p*-value
Diameter (mm)	6.0 ± 1.7	5.7 ± 1.6	0.419
Reflux times (s)	4.5 ± 4.1	5.3 ± 4.4	0.142
Peak reflux velocity (cm/s)	48.4 ± 26.0	49.8 ± 29.2	0.757
Mean reflux velocity (cm/s)	18.2 ± 13.1	18.0 ± 12.3	0.772
Total reflux volume (mL)	30.8 ± 32.3	48.9 ± 49.7	0.571

UGFS: ultrasound-guided foam sclerotherapy, VFS: visual foam sclerotherapy

Table 2. Comparison of ultrasound-derived hemodynamic variables before foam sclerotherapy

	UGFS+VFS n= 51 limbs	VFS n= 52 limbs	*p*-value
Complete vasospasm (%)	37 (72.5)	29 (55.8)	0.097
Moderate vasospasm (%)	13 (25.5)	14 (26.9)	0.869
Poor vasospasm (%)	1 (2.0)	9 (17.3)	0.009

Complete vasospasm: the GSV showed complete vasospasm

Moderate vasospasm: maximum reduction in GSV diameter of more than 50%

Poor vasospasm: maximum reduction in GSV diameter of less than 50%

Table 3. Ultrasonographic evaluation of GSV vasospasm 5 minutes after completion of foam sclerotherapy

Ultrasonographic inspection	UGFS+VFS n= 51 limbs	VFS n= 52 limbs	*p*-value
Complete occlusion (%)	23 (45.1)	22 (42.3)	0.775
Partial recanalization with no reflux (%)	7 (13.7)	15 (28.8)	0.061
Total	30 (58.8)	37 (71.1)	0.190
Partial recanalization with reflux (%)	15 (29.4)	12 (23.1)	0.465
Complete recanalization (%)	6 (11.8)	3 (5.8)	0.281
Recurrent varicose veins (%)	6 (11.8)	4 (7.8)	0.485
Post-sclerotherapy reflux parameters	UGFS+VFS n= 21 limbs	VFS n= 15 limbs	*p*-value
Diameter (mm)	3.9 ± 1.6	4.3 ± 1.6	0.788
Reflux time (s)	2.2 ± 2.3	2.5 ± 1.8	0.836
Peak reflux velocity (cm/s)	17.2 ± 17.0	18.7 ± 29.2	0.596
Mean reflux velocity (cm/s)	8.1 ± 8.2	8.8 ± 10.3	0.351
Total reflux volume (mL)	2.8 ± 3.5	3.0 ± 3.8	0.579

Table ~~5~~4. Outcome of foam sclerotherapy

	UGFS+VFS n= 30 limbs	VFS n= 37 limbs	*p*-value
Complete vasospasm (%)	22 (73.3)	21 (56.8)	0.159
Moderate vasospasm (%)	8 (26.7)	10 (27.0)	0.974
Poor vasospasm (%)	0 (0)	6 (16.2)	0.021

Table ~~6~~5. Relationship between degree of vasospasm 5 minutes after sclerotherapy and elimination of reflux at 6-month follow-up

VCSS	UGFS+VFS n= 51 limbs	VFS n= 52 limbs	*p*-value
Pre-treatment	5 ± 2	6 ± 2	0.706
Post-treatment			
1 mo	3 ± 2	3 ± 1.	0.123
3 mo	2 ± 1	2 ± 1	0.198
6 mo	1 ± 2	1 ± 2	0.223

Table ~~7~~6. Changes in VCSS score after treatment in each of the two groups