Eur J Vasc Endovasc Surg (2009) **37**, 343–348

Multiple Small-Dose Injections Can Reduce the Passage of Sclerosant Foam into Deep Veins During Foam Sclerotherapy for Varicose Veins

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Submitted 5 May 2008; accepted 25 August 2008
Available online 14 October 2008

KEYWORDS
Superficial venous insufficiency;
Varicose veins;
Ultrasound-guided foam sclerotherapy

Abstract *Objective:* To compare the proportion of foam sclerosant that enters deep veins between multiple injections of <0.5 ml foam per injection and a few injections of >0.5 ml foam per injection.
Design & methods: One hundred and seven patients with superficial venous incompetence were randomised to receive either multiple injections of <0.5 ml 1% polidocanol (POL) -foam (multiple injections) or a few injections of >0.5 ml 1% POL-foam per injection (few injections) for the treatment of varicose tributaries. All patients then received ultrasound-guided foam sclerotherapy for refluxing great saphenous vein (GSV) using 3% POL-foam. Only a single session was allowed per patient in order to standardise treatment. Qualitative ultrasonographic inspection of the foam was carried out during a 5-min period before compression was applied. Post-sclerotherapy surveillance was done at day 3, 2 weeks, 1 month, 3 months, and 6 months.
Results: Fifty-six limbs in 53 patients were treated with multiple injections and the remaining 56 limbs in 54 patients were treated with a few injections. There were no significant differences in age or male:female ratio between the groups. The mean volume of 1% POL-foam was 2.2 S.D. 0.6 ml (range: 0.7–4.0 ml) in the multiple injections group and 2.5 S.D. 0.6 ml (range: 1.0–4.0 ml) in the few injections group ($p = 0.003$). The mean volume of 3% POL was 1.5 ml (range: 0.7–3.0 ml) and 1.4 ml (range: 0.7–3.0 ml), respectively ($p = 0.137$). Ultrasonographic inspection immediately after sclerotherapy demonstrated that foam was distributed significantly more commonly in the deep veins of patients treated with a few injections ($p = 0.0003$). Two (4%) of the patients treated with a few injections developed migraine during the procedure, but recovered quickly with no further complications. There was no significant difference in the success rate between the groups at 6 months ($p = 0.257$).

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doi:10.1016/j.ejvs.2008.08.021

Conclusions: These findings suggest that multiple small-dose injections can reduce the amount of foam sclerosant and the risk of foam sclerosant entering the deep veins in patients with superficial venous insufficiency.

Introduction

Compression sclerotherapy is associated with a significantly higher recurrence rate than surgical intervention[1,2] and is used as an adjunct for treating varicose tributary veins.[3–5] Ultrasound-guided liquid sclerotherapy has been recognised as an alternative to surgical interruption for control of saphenous junctional incompetence.[6–12] Ultrasound-guided foam sclerotherapy is considered promising in the management of saphenous truncal incompetence.[13–27] Compared to liquid sclerosants, the dose of foam sclerosant can be reduced in both volume and concentration.[27] This has been confirmed by histological studies of human endothelial cells.[28]

However, one possible hazardous complication that may be associated with foam sclerotherapy is air embolism. A patent foramen ovale (PFO), possibly responsible for paradoxical embolism, occurs in up to 27% of the population.[29] This complication may be minimized if a large amount of foam sclerosant does not enter the deep venous system.[22,23,29,30] Furthermore, it is likely to spill over into deep veins if more than 0.5–1.5 ml of solution is injected at a single side.[31] Therefore, the purpose of this study was to compare the proportion of foam sclerosant entering the deep veins between multiple injections of polidocanol (POL) foam using $<$0.5 ml per injection and a few injections of POL-foam using $>$0.5 ml per injection for varicose tributary veins in order to establish a safer injection procedure.

Materials and Methods

Patients

Between January 2007 and October 2007, 112 limbs in 107 patients who had isolated great saphenous vein (GSV) reflux associated with SFJ incompetence were selected for ultrasound-guided foam sclerotherapy (UGFS) at the Department of Plastic and Reconstructive Surgery, Tokyo Women's Medical University. Patients were prospectively randomised to receive either multiple injections of POL-foam using $<$0.5 ml per injection (multiple injections: 3 injections or more) or a few injections of foam using $>$0.5 ml per injection (few injections: less than 3 injections). The patients comprised 29 male and 78 female patients with a mean age of 65 (range: 24–87) years. The clinical manifestations of these patients were categorized according to the CEAP (clinical, aetiologic, anatomic, and pathophysiologic) classification of reporting standards for venous disease.[32,33] All of the patients' lesions were classifiable as $C_{2,3,4a,4b,5,6,S}$, E_p, A_s, $P_{r2,3}$. Patients with myocardial ischaemia, arterial insufficiency with an ankle brachial index of less than 0.9, pregnancy in the first trimester and after the 36th week of gestation, local infection in the area of sclerotherapy, active thrombophlebitis and acute deep vein thrombosis were excluded. Patients were followed up for 6 months following treatment. This study was approved by the institutional review board, and informed consent was obtained from all participants.

Pre-treatment evaluation

A diagnostic examination was performed using colour duplex ultrasonography (LOGIQ 7 PRO; GE Yokogawa Medical Systems, Tokyo, Japan) with a 5- to 10-MHz transducer to detect venous reflux at the SFJ and in the GSV. Venous reflux was assessed with the patient 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, a cuff was applied to the calf, inflated to 100 mmHg and then rapidly deflated. The diameter of the GSV was measured in cross-sectional view 3–4 cm distal to the SFJ with the patient standing. Venous reflux was considered to be present if the reflux time exceeded 0.5 s.

Ultrasound-guided foam sclerotherapy (UGFS)

The sclerosing foam was produced by Tessari's method using 1% and 3% POL (Aethoxysklerol, Kaigen, Osaka, Japan).[18] Foam was obtained from 0.5 ml of liquid polidocanol mixed with air at a ratio of 1:4 using a three-way stopcock to mix the sclerosant.

Because one of the purposes of this study was to compare the success rate between the two groups, all patients received only one treatment session during the follow-up period of 6 months. After detailed anatomical mapping with duplex ultrasound, patients were placed supine with their affected legs elevated 30 degrees. Each visible varicose tributary vein was injected first, with multiple injections or a few injections, using 27-gauge needles. In patients who received multiple injections, the number of injections depended on the locations of the varicose veins. In contrast, only 1–3 injections were used to occlude varicose tributaries in patients who received few injections. Then 3% POL-foam was injected under ultrasound guidance using 21-gauge needles, starting 3–4 cm distal to the SFJ,[11] and a second injection was made 5–10 cm distal to the initial point. Ultrasonographic inspection of the foam was then performed for 5 min before compression was applied. Ultrasonographic monitoring began with ankle (AP), leg (LP) and knee perforators (KP), and was moved to the posterior (PTV) and anterior tibial (ATV), peroneal (PV), soleal (SV) and gastrocnemius veins (GV). Afterwards, the popliteal (POPV), femoral (FV), common femoral veins (CFV), and thigh perforators (TP)

were monitored. The presence of sclerosant foam was scored as present or absent in each vein.

Post-sclerotherapy follow-up

To evaluate the early complications and efficacy of UGFS, post-sclerotherapy surveillance was done at day 3, 2 weeks, 1 month, and 3 and 6 months using duplex ultrasound. Findings obtained by duplex scanning 6 months after sclerotherapy were divided into four groups:

(1) Complete occlusion group: the GSV was occluded and was totally shrunk
(2) Partial recanalisation with no reflux: the GSV was partially recanalised with no evidence of reflux
(3) Partial recanalisation with reflux: the GSV was partially recanalised with reflux
(4) Complete recanalisation with reflux: the GSV was totally recanalised with reflux

Statistical analysis

All data were analysed using StatView for Windows (Version 5.0, SAS Institute Inc., Cary, NC). Wilcoxon's nonparametric rank sum test was used to estimate differences between numerical data, and chi-squared contingency table analysis was used to evaluate differences between proportions. Continuous data were expressed as mean and standard deviation (S.D.). Statistical significance was defined as $p < 0.05$.

Results

Patients

Table 1 summarises the baseline characteristics of the two study groups. Fifty-six limbs in 53 patients were treated with multiple injections and 56 limbs in 54 patients were treated with a few injections. There were no significant differences in age or male:female ratio. The mean diameter was 6.7 S.D. 1.4 mm for each group, and no significant difference was found in the mean diameter between the groups. Similarly, there was no significant inter-group difference in each CEAP class. Successful needle placement and ultrasound-monitored foam injection was accomplished in all cases without complication.

Table 1 Baseline characteristics of the study patients

	Multiple injections ($n = 53$ patients)	A few injections ($n = 54$ patients)	p-value
Mean age (years)	65.0 ± 12.6	64.4 ± 10.0	0.594
Gender (female)	41 (77.4%)	36 (66.7%)	0.218
Diameter of GSV (mm)	6.7 ± 1.4	6.7 ± 1.4	0.736
CEAP clinical class	n = 56 limbs	n = 56 limbs	
C2	39 (69.6%)	41 (73.2%)	0.676
C4a	9 (16.1%)	7 (12.5%)	0.589
C4b	6 (11.3%)	7 (12.5%)	0.768
C5, C6	2 (3.6%)	1 (1.8%)	0.558

Amount of sclerosing foam

There was no significant inter-group difference in the total number of treated tributary varicose veins (2.5 S.D. 0.9, 2.4 S.D. 0.9, respectively; not significant). The mean number of vein punctures was 5.3 for the multiple injections group and 2.8 for the few injections group. Similarly, the mean volume used for varicose tributary veins was 0.42 ml per puncture for the multiple injections group and 0.87 ml per puncture for the few injections group. The POL-foam produced immediate spasm along the injected veins. The mean volume of 1% POL-foam was 2.2 S.D. 0.6 ml (range: 0.7—4.0 ml) for the multiple injections group and 2.5 S.D. 0.6 ml (range: 1.0—4.0 ml) for the few injections group, and there was a significant difference in the amount of sclerosant foam between the two groups ($p = 0.003$). The mean volume of 3% POL was 1.5 ml S.D. 0.5 (range: 0.7—3.0 ml) for the multiple injections group and 1.4 ml S.D. 0.5 (range: 0.7—3.0 ml) for the few injections group, and there was no significant difference in the amount of 3% POL-foam between the two groups.

Ultrasonographic inspection

Table 2 shows the ultrasonographic inspection of the foam performed during the 5 min after completion of foam sclerotherapy and the proportion of veins showing the presence of foam. Because spasm of the GSV and varicose

Table 2 Ultrasonographic inspection of POL-foam

	Multiple injections ($n = 56$ limbs)	A few injections ($n = 56$ limbs)	p-value
Deep veins	17 (30.4%)	36 (64.3%)	0.0003
CFV	12 (21.4%)	31 (55.4%)	<0.0001
FV	13 (23.2%)	35 (62.5%)	<0.0001
POPV	11 (19.6%)	33 (58.9%)	<0.0001
ATV	2 (3.6%)	3 (5.4%)	0.647
PTV	4 (7.1%)	18 (32.1%)	0.0005
PV	0 (0%)	14 (25.0%)	<0.0001
GV	6 (10.7%)	16 (28.6%)	0.017
SV	5 (8.9%)	19 (33.9%)	0.001
Perforating veins	18 (32.1%)	40 (71.4%)	<0.0001
TP	3 (5.4%)	12 (21.4%)	0.013
KP	14 (25.0%)	20 (35.7%)	0.218
LP	4 (7.1%)	12 (21.4%)	0.031
AP	1 (1.8%)	2 (3.6%)	0.558

Proportion of veins showing evidence of foam during 5 min of surveillance following treatment.
POL, polidocanol; CFV, common femoral vein; FV, femoral vein; POPV, popliteal vein; ATV, anterior tibial vein; PTV, posterior tibial vein; PV, peroneal vein; GV, gastrocnemius vein; SV, soleal vein; TP, thigh perforators; KP, knee perforators; LP, leg perforators; AP, ankle perforators.

tributary veins was confirmed using duplex ultrasound in all patients, no additional injection was required. Foam was detected in the deep venous system in 17 (30.4%) of the patients who received multiple injections and in 36 (64.3%) of the patients who received a few injections ($p = 0.0003$). Detailed anatomical examination using duplex ultrasound demonstrated that foam was significantly more common in patients who received a few injections in each venous segment, with the exception of the ATV. Similarly, in perforating veins, a significantly higher proportion of the foam was found in patients who received few injections ($p = 0.0001$), and foam was significantly more common in the thigh and leg perforators ($p = 0.013$ and 0.031, respectively).

Complications of UGFS

Table 3 shows the early complications related to ultrasound-guided sclerotherapy. Pain was detected in one (2%) patient in both groups. Superficial thrombophlebitis was also found in 2 patients in both groups. Two (4%) of the patients who received a few injections developed migraine during the procedure, but recovered quickly with no further complications. No other serious complications, such as allergic reactions, deep vein thrombosis, pulmonary embolism, or cerebral infarction were found during the follow-up period.

Follow-up

Table 4 shows the findings obtained by duplex ultrasound 6 months after the treatment. Follow-up ultrasound demonstrated complete occlusion in 52% of patients in the multiple injections group and in 59% of those in the few injections group. Similarly, 21% of the patients who received multiple injections and 23% of those who received few injections showed partial recanalisation with no reflux. Patients who received few injections had a higher success rate, but this was not statistically significant. In contrast, 27% of the patients who received multiple injections showed reflux in the GSV 6 months after treatment. Similarly, in the few injections group, 18% of the patients demonstrated reflux in the treated GSV.

Discussion

Because of its efficacy and safety, UGFS has gained great popularity as a minimally invasive treatment for varicose veins, and large case series have been reported.[18,20,24,26,27]

Table 3 Complications of UGFS

	Multiple injections ($n = 53$ patients)	A few injections ($n = 54$ patients)
Pain	1 (1.9%)	1 (1.9%)
Paraesthesia	0 (0%)	1 (1.9%)
Superficial thrombophlebitis	2 (3.8%)	2 (3.7%)
Migraine	0 (0%)	2 (3.7%)

UGFS, ultrasound-guided foam sclerotherapy.

Table 4 Outcome of UGFS

	Multiple injections ($n = 56$ limbs)	A few injections ($n = 56$ limbs)	p-value
Occlusion	29 (51.8%)	33 (58.9%)	
Partial recanalisation with no reflux	12 (21.4%)	13 (23.2%)	
Subtotal	41 (73.2%)	46 (82.1%)	0.257
Partial recanalisation with no reflux	6 (10.7%)	4 (7.1%)	
Complete recanalisation with reflux	9 (16.1%)	6 (10.7%)	
Subtotal	15 (26.8%)	10 (17.8%)	
Total	56 (100%)	56 (100%)	

Proportion of saphenous veins showing outcomes as classified in the text 6 months following a single treatment session.
UGFS, ultrasound-guided foam sclerotherapy.

Recent reports have focused attention on the safety of foam for this purpose. Compared to liquid sclerosant, foam sclerosant shows a greater tendency to provoke inflammation, and is associated with mild adverse effects including pain, inflammatory signs, and skin pigmentation.[34] Neurological complications including transient visual disturbance, transient confusion, and even cerebral infarction have been described.[35–37] The gas mixture used to create the foam determines bubble characteristics. Bubble life is shorter if the oxygen concentration within the bubble is increased and the nitrogen concentration is decreased.[38] Morrison et al. compared the incidence of side effects between carbon dioxide foam and air-based foam, finding that carbon dioxide foams reduce side effects.[39]

The On-Line International Event on Sclerosing Foam and Patent Foramen Ovale (PFO) recommended a number of procedures to prevent possible neurological complications. These included requesting patients not to dress or put on shoes and stockings by themselves, avoiding the Valsalva manoeuvre, and avoiding constipation before the procedure. However, the Committee did not reach a final conclusion as to whether there was a clear relationship between clinical events and the use of foam. While chronic cerebral damage resulting from PFO has been suggested, there has been no clear evidence of any acute cerebral effects resulting from injection of foam.[30]

Our study had some potential limitations. The method of assessing the deep veins for the presence of foam following sclerotherapy is subjective and not quantitative. We believe that it reflects the extent of foam in the deep veins but acknowledge that the study was not done in a blinded fashion. The total volume of foam injected is substantially less than has been recommended in the recent 2nd European Consensus Meeting on Foam Sclerotherapy.[23] This may well have prejudiced the long-term outcome in these patients. The 6-month follow-up period is sufficient to judge the ultrasonographic outcome in the short term, but does not allow the long-term clinical evaluation of this

strategy. Nevertheless, we found a significant reduction in the proportion of POL-foam entering the deep venous system when the multiple small-dose injection technique was used. Spasm of the GSV and varicose tributary veins was confirmed using duplex ultrasound, and a significant proportion of the sclerosant foam remained in the superficial venous system. One possible explanation for this could be migration of excess POL-foam via perforating veins or the SFJ into the deep venous system in patients treated with a few injections, each with a large amount of foam.

Conclusion

The present findings indicate that multiple small-dose injections can reduce the amount of sclerosant foam to treat patients with superficial venous insufficiency and lead to less foam entering the deep veins. This strategy could be added to other methods aimed at minimising the systemic side effects of foam sclerotherapy.

Conflict of Interest

No significant conflicts of interest are declared.

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