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Air versus Physiological Gas for Ultrasound Guided Foam Sclerotherapy Treatment of Varicose Veins

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Abstract *Objectives:* We have used Ultrasound Guided Foam Sclerotherapy (UGFS) to treat varicose veins in 2029 limbs since 2006. In 2009 we introduced physiological gas (30% O_2 and 70% CO_2) for makingfoam with sodium tetradecyl sulphate (Fibrovein, STD Pharmaceutical Products Ltd, Hereford UK) instead of air. The aim of this study was to compare our early experience of UFGS using CO_2/O_2 with our prior experience using air.
Methods: Data were collected in a prospectively maintained database. In this series 470 limbs were treated with UGFS and followed up at 6 weeks with clinical and duplex ultrasound assessment. The 235 consecutive limbs undergoing UGFS immediately before and the 235 after the introduction of CO_2/O_2 were selected for comparison.
Results: The age, gender and CEAP classifications for the two groups were not significantly different. 73% were primary veins and 70% great saphenous, with no differences between the groups. Transient neurological events are rare in our experience (0.7%) with only one visual disturbance occurring in this series. There was a significant reduction in the incidence of skin staining in the CO_2/O_2 (7.2% *vs* 3.3%, $p = 0.02$, χ^2 test) as compared to the air treated group, but no difference in the incidence of thrombophlebitis. The total volume of foam injected was similar in both groups but use of CO_2/O_2 foam was associated with a significant improvement in the truncal occlusion rate, from 86% to 91% ($p < 0.05$, χ^2 test).
Conclusion: UGFS with CO_2/O_2 instead of air was associated with a slightly increased saphenous truncal occlusion rate and reduced the incidence of skin staining without increasing thrombophlebitis in this clinical series. We observed only one transient neurological event in this series so could not evaluate the effect of CO_2/O_2 foam in reducing these events.

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Introduction

Ultrasound guided foam sclerotherapy (UGFS) is increasingly being used as a first line treatment for varicose veins and there is a number of reports in the literature confirming its efficacy and safety.[1–4] In contrast to endoluminal thermal or laser ablation, foam sclerotherapy provides a single technique that can address both the truncal incompetence and the varicose tributaries. The most common side effects of foam sclerotherapy are thrombophlebitis and skin pigmentation. There is also the potential for systemic side effects resulting from foam embolisation. This is of greatest concern in subjects with a patent foramen ovale (PFO) and the prevalence of PFO has been reported to be as high as 10%.[5] The most commonly reported systemic side effects are chest tightness, a dry cough, dizziness or a transient visual disturbance.[6] There are also reports of stroke[7,8] and whilst it is difficult to confirm causality, experimentally bubbles have been tracked at the time of UGFS, to the middle cerebral artery using transcranial Doppler.[9,10]

The frequency of these side effects is probably related to the volume of foam injected.[6] One strategy to minimise side effects would be to limit the volume of foam injected to less than 10 ml as recommended by the European consensus document.[11] In addition there is some data to suggest that the injection technique is important.[12,13] In one non-randomised retrospective study Hill reported that for the great saphenous system, leg elevation without manual sapheno-femoral junction compression reduced the incidence of echocardiographically detected emboli to the right heart.

There is some evidence that using carbon dioxide, in place of air, to make the foam may also reduce the incidence of side effects.[6,13] In his non-randomised study[6] using large volumes (25 S.D. 12 ml) of 1% polidocanol foam, Morrison reported that the use of CO_2 based foam reduced the incidence of systemic effects from 39% to 11%. Subsequently it has been reported that use of a more physiological combination of carbon dioxide and oxygen may result in a further reduction in these side effects while still resulting in a good quality foam.[14]

We began treating varicose veins with ultrasound guided sclerotherapy as a "first line" modality in 2006 and have now treated and completed follow-up for 1510 legs. In 2009 we introduced physiological gas to our practise for producing foam using a mixture of 70% carbon dioxide and 30% oxygen. In this study we aimed to establish if the introduction of physiological gas for UGFS reduces the incidence of side effects.

Materials and Methods

This is a prospective study of 470 consecutive patients treated with UGFS alone for the management of primary or recurrent varicose veins between 10th August 2008 and 20th January 2010. Data was extracted from a prospectively maintained database of all patients treated with UGFS. The database is kept for ongoing clinical audit purposes in keeping with NICE guidelines. 235 subjects underwent foam sclerotherapy using physiological gas following its introduction on 6th January 2009 and we have selected the 235 consecutive patients treated (using air) immediately prior to this date for comparison.

Patient population

All patients were given a patient information sheet prior to their treatment appointment and informed consent was obtained. As is our routine practise all patients underwent venous duplex ultrasound examination of the superficial and deep venous system prior to attending for treatment. The only absolute exclusion criteria for this study were; age <18, pregnancy or an inability to comply with compression hosiery. Unless there is a history of severe migraine with aura or of a heart murmur we do not routinely screen patients for a PFO prior to foam sclerotherapy. Nevertheless we consider a known PFO or history of deep venous thrombosis to be relative contraindications to UGFS and no patients with a history of prior deep vein thrombosis were treated with UGFS in this series.

Technique

Foam was made by a modification of the Tessari dual syringe technique[15] using a 5 micron filter (B Braun Medical Ltd, Sheffield, UK) in place of a three-way tap. The physiological gas comprising 70% carbon dioxide and 30% oxygen was purchased in a pre-mixed cylinder and was drawn up into a sealed 50 ml syringe in aliquots to facilitate easy mixing of foam. The gas was mixed in a 3:1 ratio with 3% or 1% sodium tetradecyl sulphate (Fibrovein™ STD Pharmaceutical Products Ltd, UK). We use 3% STS for truncal varicosities and 1% for any extra -fascial tributaries.

All patients were given a patient information sheet before attending for treatment, which provided details of the most frequent systemic side effects of chest tightness, dizziness and transient visual disturbance, and the potential complications of thrombophlebitis, skin staining and deep vein thrombosis. Following administration of 1% lidocaine local anaesthetic, cannulation was undertaken under ultrasound guidance. Our primary cannulation technique is a Seldinger technique, placing a 20G 8 cm long catheter into the great or small saphenous veins as appropriate, with butterfly cannulation of any large extra-fascial tributaries. Following cannulation the limb is elevated prior to injection of foam and patients actively dorsiflexed and plantarflexed the ankle to maintain deep venous blood flow. We manually compressed the sapheno-femoral junction during injection into the great saphenous vein. Foam migration was monitored with ultrasound during injection of each 3 ml aliquot and the injection was discontinued when the foam had reached the junction and good filling was evident resulting in vasospasm. Upon completion of treatment a class II thigh length compression stocking was immediately fitted and worn by the patient for 10 days. A registered nurse monitored the patients during the procedure and patients were directly questioned regarding any dizziness, transient visual disturbance or chest tightness and those side effects were recorded. After treatment patients were asked to walk for 15 min and report back to the nurse prior to discharge.

We aimed to follow-up all patients in this series six weeks following foam sclerotherapy. Follow-up was

conducted either by a nurse practitioner who is trained in vascular ultrasound or by the senior author. At follow-up patients were questioned about any symptomatic improvement and about side effects. They were also examined for evidence of any residual varicosities, thrombophlebitis or skin staining. The treated veins were examined using colour duplex ultrasound and the level of occlusion noted. Venous occlusion was defined as an incompressible vein in which no flow could be demonstrated, and in the case of the great saphenous vein complete occlusion was recorded as occlusion of the treated segment to within 2 cm of the sapheno-femoral junction. An incomplete occlusion was also recorded if we had failed to occlude 85% of the treated venous trunk.

Statistical analysis

Statistical analysis was undertaken using PASW™ (formerly SPSS, Statistical Package for the Social Sciences). Non-parametric analysis has been used for comparison between the two groups (Mann—Whitney *U* test), with Chi squared contingency table analysis used for frequency analysis. Data is presented as median (inter-quartile range).

Results

The median age of the patients was 58 (47—69) years and 59% were female. 75% of patients treated had primary varicose veins and in 69% the system treated was the great saphenous vein. In 81% of patients a Seldinger technique was used for cannulation with only 19% requiring a butterfly cannulation alone. 49% of patients were C of CEAP classification 2, 37% class 4 and 10% classes 5 and 6. The median volume of foam used in this study was 9 (6—12) ml of 3% STS and 6 (3—9) ml of 1% and as such the median total volume was 9 (6—12) ml. There was no significant difference in the age, sex, classification of veins, system treated or volume of foam administered between these two groups (Table 1). No subjects were lost to follow-up in this series, however whilst we set out to follow-up all subjects at 6 weeks, in fact the median follow-up interval was 56 days.

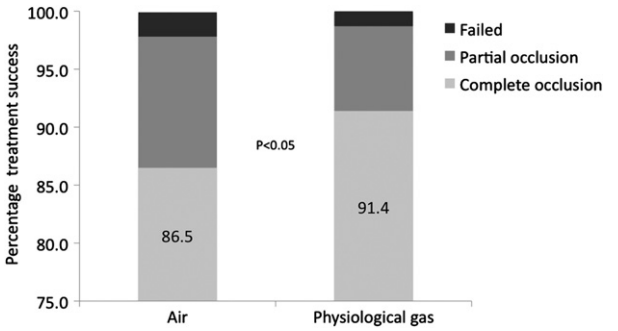

Figure 1 The Proportion of duplex documented occlusions following UGFS at 8 weeks of follow-up. Complete occlusion was observed in 91.4% of subjects treated with physiological gas as compared to 86.5% treated with air, $p < 0.05$. Please note axis range is from 75% to 100%.

In our experience systemic side effects are rare and only one (0.2%) of these patients experienced transient blurring of vision. Whilst this event occurred in the air treated group, there was no statistically significant difference between the two groups because the incidence was so low. None of the patients in this series experienced the most commonly reported side effects of chest tightness, a dry cough or dizziness.[6] Similarly there was only one deep vein thrombosis amongst this series of 470 patients (0.2%) and whilst this did occur in the physiological gas treated group the low frequency of this complication prevented statistical analysis.

When we compared the incidence of local side effects between the two groups there were significant differences. There was a reduction in the incidence of skin staining from 7.2% in the air treated to 3.3% in the physiological gas treated group ($p < 0.02$). This was not accompanied by a reduction in the incidence of superficial thrombophlebitis, at 3.4% in the air and 5.1% in the physiological gas treated group ($p = 0.15$).

The introduction of physiological gas was also associated with an increase in the efficacy of treatment (Fig. 1). There was an increase in the proportion of patients observed to have a complete truncal occlusion upon follow-up duplex scanning increasing from 86.5% in the air treated group to 91.4% in the physiological gas treated group ($p < 0.05$),

Table 1 Demographic data describing each group. The descriptors for continuous variables are median with inter-quartile range.

	Air $n = 235$		Physiological gas $N = 235$		
Age	55 yrs (20)		55 yrs (24)		$p = 0.79$
Sex	136 female	58%	142 female	60%	$p = 0.76$ (χ^2 test)
Classification	180 primary	77%	171 primary	73%	$p = 0.52$ (χ^2 test)
Venous System treated	Anterior accessory saphenous v	21 (9%)	Anterior accessory saphenous	22 (9%)	$p = 0.624$ (χ^2 test)
	Great saphenous	159 (68%)	Great saphenous	166 (71%)	
	Small saphenous	51 (21%)	Small saphenous	36 (15%)	
Cannulation technique	Seldinger	57%	Seldinger	59%	$P = 0.71$ (χ^2 test)
	Butterfly	20%	Butterfly	17%	
	Combined	23%	Combined	24%	
Foam Volume administered (ml)		9 (5—13) ml		9 (2—16) ml	$p = 0.22$ (Mann—Whitney)

primarily as a result of a reduction in the incidence of partial occlusions. At present only 6 week follow-up data is available for this patient cohort. Prior to this series 409 patients treated by UGFS using foam manufactured with air had completed 1 year of follow-up and the medium-term occlusion rate was similar to that reported in this series, with 85% of subjects maintaining complete truncal occlusion.

Overall 23% of the patients in this series had some residual varicosities upon clinical examination, however only 4.9% went on to request further treatment.

Discussion

These data confirm that ultrasound guided foam sclerotherapy is a safe and effective first line treatment for varicose veins. We found that the incidence of systemic side effects is very low, occurring in only 0.2% of patients in this series. It is therefore not possible to conclude whether the theoretical benefit of reduced systemic embolisation witnessed using echocardiography and transcranial Doppler[9,10] is of any clinical significance.

We also report a low incidence of deep vein thrombosis of only 0.2% associated with ultrasound guided foam sclerotherapy, which did not differ between the two groups in this study. This is lower than that reported in most series[1] and whilst this may be a result of our technique and the relatively low volumes of foam used, it may also reflect the follow-up interval. In this series subjects were followed up at a median of 56 days and were only imaged sooner if there was clinical concern. It is however clear that when deep vein thromboses occur they are an early event[16] and it is therefore possible that some asymptomatic thromboses were not identified in this series.

There is a clear discrepancy between the incidence of systemic side effects reported in this series and those reported by Morrison. In his first series[6] he used polidocanol foam sclerotherapy as an adjunct to thermal ablation of the great saphenous vein. He reported that 39% (19/49) of subjects undergoing UGFS with air based foam experienced side effects. The use of carbon dioxide in place of air reduced this incidence to 11% (14/128), but this remains an order of magnitude greater than the results we report. Some of this discrepancy may be accounted for by the rigour with which his study sought side effects, with a registered nurse monitoring patients for an hour following the procedure. However, this discrepancy is most likely to be a result of the injection of large foam volumes (median of 25 ml (6–57)). Furthermore these were injected into a reduced capacity superficial venous system following thermal ablation of the great saphenous vein, resulting in a greater risk of systemic embolisation.

It was of particular interest that the incidence of systemic side effects reported[6] was volume related, with very few events occurring below a volume threshold of 16 ml, a finding which supports the European Consensus limiting the volumes used to less than 10 ml.[11]

In contrast to Morrison, we report a 91.4% complete occlusion rate when using a median of only 9 ml of sodium tetradecyl sulphate foam as a first line intervention for varicose veins. The lower foam volume used may not only reflect the effectiveness of our treatment and our concerns regarding systemic side effects, but it may also be a function of our differing treatment goals. Our primary goal is to achieve symptomatic relief as a result of truncal occlusion, not necessarily ablation of all cosmetic varicosities.

Morrison has also more recently reported the introduction of physiological gas for UGFS in a series of 100 subjects.[14] In this series using polidocanol foam as an adjunct to thermal ablation, the foam volumes used were again above the 10 ml recommended by the European Consenus,[11] but of note the use of physiological gas reduced the incidence of reported systemic side effects to 3%.

Using smaller but clinically effective doses of physiological gas based foam, this study has been unable to demonstrate any reduction in the systemic side effects associated with UGFS. We do however report a significant increase in the rate of truncal occlusion and a reduction in the incidence of skin staining. Despite the potential safety benefits, the introduction of physiological gas to our practise has not led to an increase in the volumes of foam administered. As such the improved occlusion rate witnessed in this series does not appear to be a volume related effect. The mechanisms for this benefit are not known, but it may be that the high solubility of the carbon dioxide has a positive effect upon the interaction between the sclerosant drug and the endothelium. This will require further investigation.

We acknowledge the limitations associated with non-randomised data, with the inherent introduction of potential sources of bias. In particular, one potential criticism of this data is that the improvement witnessed may result from an experience effect. We do not believe this to be the case, as we had treated more than 1000 legs prior to this series and other than the introduction of physiological gas our treatment protocol has not changed. There was no improvement in the complete occlusion rate of this cohort of 235 patients air treated patients (86.5%) when compared with an earlier series of subjects who have completed twelve months follow-up (85%).

We conclude that the use of physiological gas for ultrasound guided foam sclerotherapy increases treatment efficacy and may also reduce the incidence of skin staining. Given the potential safety benefits and its small incremental cost (<1 euro per treatment), we continue to use physiological gas for ultrasound guided foam sclerotherapy and suggest that this is a treatment that warrants further investigation.

Conflict of Interest/Funding

None.

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