

NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

INTERVENTIONAL PROCEDURES PROGRAMME

Interventional procedure overview of ultrasound- guided foam sclerotherapy for varicose veins

Varicose veins are veins that have become wider than normal and are unable to transport blood properly. Symptoms include heaviness, aching, throbbing, itching, cramps or fatigue in the legs. In severe cases, patients may have skin discoloration or inflammation, or skin ulcers. Foam sclerotherapy involves mixing a chemical with air or another gas to produce a foam which is injected into the affected vein. This inflames the vein and causes it to shrink. Sometimes patients may need more than one injection to block the vein.

Introduction

The National Institute for Health and Clinical Excellence (NICE) has prepared this overview to help members of the Interventional Procedures Advisory Committee (IPAC) make recommendations about the safety and efficacy of an interventional procedure. It is based on a rapid review of the medical literature and specialist opinion. It should not be regarded as a definitive assessment of the procedure.

Date prepared

This overview was prepared in February 2009.

Procedure name

- Ultrasound-guided foam sclerotherapy for varicose veins

Specialty societies

- Vascular Surgical Society of Great Britain and Ireland.

Description

Indications and current treatment

Varicose veins are a sign of underlying venous insufficiency and affect 20–30% of adults. Most people with varicose veins have no symptoms. Long

saphenous vein insufficiency is the most common form of venous insufficiency in people presenting with symptoms.

Venous disease of the lower limb is often classified according to the CEAP (clinical, etiological, anatomic and pathophysiologic) classification from the American Venous Forum. This classification includes clinical, aetiological, anatomic and pathophysiologic findings (clinical signs classified as: C0 – no signs of venous disease; C1– telangiectases or reticular veins; C2 – varicose veins; C3 – oedema; C4a – pigmentation or eczema; C4b – lipodermatosclerosis or atrophie blanche; C5 – healed venous ulcer; C6 – active venous ulcer).

People with venous insufficiency may have the following symptoms: fatigue, heaviness, aching, throbbing, itching and cramps in the legs. Chronic venous insufficiency can lead to skin discoloration, inflammatory dermatitis and ulceration.

As most varicose veins do not cause serious problems, treatment is not usually required on medical grounds. Conservative methods such as compression hosiery (support stockings or tights) may help people with symptomatic varicose veins. If symptoms are severe the main treatment options are sclerotherapy and/or surgery (usually stripping and ligation of the long and short saphenous veins, and phlebectomies).

What the procedure involves

Ultrasound-guided foam sclerotherapy for varicose veins is slightly different from standard sclerotherapy, which uses a liquid sclerosant. This procedure uses a sclerosant solution that is forcibly mixed with air or another gas to produce a foam. Compared with liquid, foam has increased contact with the inside of the veins walls and remains in the vein for a longer period of time, with the intention of increasing the efficacy of the procedure.

The procedure is carried out with the patient under local anaesthesia. A needle is inserted into the main affected superficial vein, using ultrasound guidance. Sclerosant foam is then injected and monitored with ultrasound. Once the foam has filled the main superficial vein, the upper end of the vein may be compressed to prevent the foam entering the deeper veins. The foam inflames the vein wall, destroys the vein's lumen and blocks the vein. Compression is applied to the leg for a variable number of days using bandages or stockings.

Further injections may be given during the same session to make sure all varicose veins have been completely filled. More than one session may be needed if the veins have not been blocked.

Various sclerosants and aeration methods may be used to produce the foam for this procedure.

List of studies included in the overview

This overview is based on approximately 822 patients from two randomised controlled trials (RCTs), 3 case series, 4 case reports, and UK clinical audit data provided by a Specialist Adviser on approximately 7027 patients.

Other studies that were considered to be relevant to the procedure but were not included in the main extraction table (table 2) have been listed in appendix A.

Efficacy

A multicentre, double-blind RCT of 74 patients treated by 3% polidocanol and 74 patients treated by 1% polidocanol reported successful elimination of venous reflux in 69% and 68% of patients, respectively, at 2-year follow-up (14 patients were lost to follow-up: 5 in the 3% group and 9 in the 1% group)³. The authors reported that there was no significant difference between the two groups with respect to immediate injection response or rate of recanalisation at 2-year follow-up. Recanalisation was reported in 36% and 37% of saphenous veins treated with 3% and 1% polidocanol, respectively.

A multicentre RCT that compared 48 patients treated with liquid sclerotherapy and 47 patients treated with foam sclerotherapy reported success rates (defined as no recanalisation) to be 12% (4) and 53% (25/47), respectively, at 2-year follow-up (5 patients from the foam group were lost to follow-up but were included as failures; denominator not given for liquid group; significance level not stated)⁴.

The same study reported venous spasm immediately after injection in 31% (15) and 66% (31) of those treated with liquid and foam, respectively ($p < 0.0001$). In the foam group, venous spasm predicted success in 100% of patients, but the absence of venous spasm did not predict failure (there was no association with success in the liquid group).

A case series of 489 patients treated with sclerotherapy, reported a primary success rate of 52.4% (95% confidence interval [CI] 46–58%) and a secondary success rate of 76.8% (95% CI 71–82%) after 3 years of follow-up ('success' was defined as persistent occlusion/absence of reflux; secondary success rate was calculated after further treatment sessions; denominators not given; authors state that liquid was used in the first 98 of 1198 treatment sessions but results are not separated and the total number of patients treated with liquid is not given)⁵. The study reported persistent reflux after recanalisation in the posterior tibial segment in five limbs (reflux was defined as reverse flow persisting for 0.5 or more seconds on the release of manual compression of the calf).

A multivariate Cox regression analysis showed that the use of liquid had worse success rates than the use of foam. The analysis also predicted failure with the use of smaller concentrations and volumes of sclerosant, and a vein diameter greater than 5 mm. The study also reported that the procedure was less successful in small saphenous veins than in great saphenous veins.

Safety

Foam embolism/arterial events

A case report of three patients treated with foam sclerotherapy reported arterial injury causing gangrene in all three patients following the procedure⁸. A 16-year-old woman with Klippel-Trenaunay syndrome and associated varicosities and venous lakes developed dry gangrene in both toes that were injected with 3% foam. She was given conservative treatment and was under observation at the time of the report. A 23-year-old man with varicosities with atrophie blanche reported severe pain and cold foot as a result of foam embolisation following 3% foam injection. This developed into gangrene which required partial foot amputation and free flap muscle transfer. A 54-year-old man with varicosities developed deep pain as a result of incorrect placement of the injection needle. Duplex scanning revealed a double saphenous system with a subfascial position of the main trunk. This led to gangrene which required a below-knee amputation.

Clinical audit data of ultrasound-guided foam sclerotherapy in 7027 patients (11,537 procedures) from nine UK centres⁶ indicated that 36 patients had deep vein thromboses, 67 had visual disturbance and there were no cases of stroke.

Two cases of microembolism were reported in a journal commentary⁹. Immediately after a single 5-ml injection of 1% polidocanol foam, transient scotomas were reported in a 51-year-old man and migraine was reported in a 33-year-old woman (both otherwise asymptomatic and 'healthy'). The same authors reported foam microemboli in the right atrium and ventricle in 33 patients, although none were reported to have had neurological symptoms. Microemboli were also discovered in the left atrium and ventricle in five patients later detected to have right-to-left shunts through a patent foramen ovale.

In response to this commentary, another author reported that intracardiac gas emboli were discovered in all 45 patients treated with low nitrogen (<0.8%) polidocanol foam¹⁰. The same author referred to an ongoing multicentre study examining whether adverse events occurred in patients with detected microvascular bubbles while being treated with polidocanol foam. The study included a test for right-to-left shunt. Preliminary results on 11 patients in a published abstract revealed right-to-left shunts in one third, and that 90% had a very low number of microvascular bubbles in the cerebral circulation during the procedure (exact figures not stated)¹¹.

A case report described major neurological events after foam sclerotherapy in two women aged 72 and 35¹². The first woman was found slumped in her chair 25 minutes after the injection. After 3 hours the condition had resolved, but a small shunt was detected after injection of agitated blood and saline. The second woman had a transient loss of consciousness 20 minutes after the procedure. She was then described as having a spastic right hand and an inability to move her left leg or arm but was able to answer questions. She later developed seizure activity in the right upper extremity. Air was detected

in the right venous circulation on CT scan (and a small air bubble in the middle cerebral artery), although the results of a neurological exam 2 weeks after the incident were mostly normal (despite a persistent, mild numbness).

In a survey of 281 UK surgeons, one surgeon reported a transient ischaemic attack and two surgeons reported a stroke⁷. It is uncertain whether these observations were of the same events as previously reported in the literature. It is also unclear why these results were not revealed in the clinical audit data.

A study comparing air-based foam with carbon dioxide-based foam reported that overall side effects following the procedure decreased from 39% (19/49) to 11% (14/128) when carbon dioxide replaced air in the foam preparation ($p < 0.001$)¹⁵. For example, visual disturbance decreased from 8% (4/49) to 3% (4/128), chest tightness from 18% (9/49) to 3% (4/128), and dizziness from 12% (6/49) to 3% (4/128).

A study of 20 patients with suspected patent foramen ovale or describing respiratory or cerebral symptoms (migraine and visual disturbance, among others) reported that transthoracic echocardiography showed bubbles in the left heart immediately after the procedure in 65% of patients (13/20)¹³. Five patients with a positive test also had bubbles in their middle cerebral artery demonstrated on transcranial Doppler. The seven patients without bubbles in the left heart reported visual disturbance, migraine, shortness of breath, dizziness and numbness.

A study that assessed techniques to reduce sclerosant foam migration during ultra-sound guided foam sclerotherapy reported that the procedure should be performed with the leg elevated and with no occlusive pressure at the saphenofemoral junction to reduce the risk of gas embolisation, but stated that more studies are required¹⁴.

Two RCTs of 148 and 95 patients reported that there were no cases of neurological complications, chest symptoms, visual disturbance, and cutaneous necrosis^{3,4}.

A case series of 489 patients reported that three patients with a history of migraine headaches developed visual aura during mobilisation after their injection; this settled within 20 minutes without further headaches or neurological problems⁵. The same study reported that there were no instances of pulmonary embolism, other cardiovascular complications, or neurological symptoms.

Anaphylaxis

There were two case reports of allergic reaction to the sclerosant^{16, 17}. One described a 62-year-old woman initially treated with 3% foam and treated with 1% foam 6 months later. Within 20 minutes of the second procedure, the woman was reported to have developed tachycardia and became hypotensive. She recovered following treatment and was discharged after 24 hours without any further events¹⁶.

Another case report described a 49-year-old woman treated with 1% foam. After 10 minutes she appeared to have an anaphylactoid reaction (with a weak pulse and tachycardia), but stayed conscious. Following treatment she recovered fully with no further events.

Literature review

Rapid review of literature

The medical literature was searched to identify studies and reviews relevant to ultrasound-guided foam sclerotherapy for varicose veins. Searches were conducted of the following databases, covering the period from their commencement to 9 December 2008: MEDLINE, PREMEDLINE, EMBASE, Cochrane Library and other databases. Trial registries and the Internet were also searched. No language restriction was applied to the searches (see appendix C for details of search strategy).

The following selection criteria (table 1) were applied to the abstracts identified by the literature search. Where selection criteria could not be determined from the abstracts the full paper was retrieved.

Table 1 Inclusion criteria for identification of relevant studies

| Characteristic | Criteria |
|-------------------|--|
| Publication type | Clinical studies were included. Emphasis was placed on identifying good quality studies. Abstracts were excluded where no clinical outcomes were reported, or where the paper was a review, editorial, or a laboratory or animal study. Conference abstracts were also excluded because of the difficulty of appraising study methodology, unless they reported specific adverse events that were not available in the published literature. |
| Patient | Patients with varicose veins. |
| Intervention/test | Ultrasound-guided foam sclerotherapy. |
| Outcome | Articles were retrieved if the abstract contained information relevant to the safety and/or efficacy. |
| Language | Non-English-language articles were excluded unless they were thought to add substantively to the English-language evidence base. |

Existing assessments of this procedure

A systematic review of the safety and efficacy of foam sclerotherapy for venous disease of the lower limbs was commissioned by NICE in 2006¹⁹.

A Cochrane review of injection sclerotherapy for varicose veins was identified¹. The review examined the results from two studies comparing foam and liquid sclerotherapy. Both of these studies were included in the above

systematic review, so they are not considered in this overview. The protocol for a Cochrane review comparing conventional surgery with endovenous ablation (both radiofrequency and laser) and foam sclerotherapy is currently being completed¹⁸.

A second consensus document on foam sclerotherapy has been published based on the European meeting in Germany in 2006 (the first document was published following the first meeting in 2003)². The document outlines statements on issues such as equipment, indications, concentration of foam, and safety and efficacy.

Related NICE guidance

Below is a list of NICE guidance related to this procedure. Appendix B gives details of the recommendations made in each piece of guidance listed.

Interventional procedures

- Ultrasound-guided foam sclerotherapy for varicose veins. NICE interventional procedures guidance 217 (2007). Available from www.nice.org.uk/IPG2177
- Transilluminated powered phlebectomy for varicose veins. NICE interventional procedures guidance 37 (2004). Available from www.nice.org.uk/IPG37
- Radiofrequency ablation of varicose veins. NICE interventional procedures guidance 8 (2003). Available from www.nice.org.uk/IPG8

Table 2 Summary of key efficacy and safety findings on ultrasound-guided foam sclerotherapy for varicose veins

| Abbreviations used: CEAP classification – clinical, etiological, anatomic and pathophysiologic findings; CI, confidence interval; DVT, deep vein thrombosis; GSV, great saphenous vein; MRI, magnetic resonance imaging; POL, polidocanol; RCT, randomised controlled trial; SFJ, sapheno-femoral junction; STD, sodium tetradecyl sulphate; UGFS, ultrasound-guided foam sclerotherapy; VV, varicose vein | | | | | | | | | | | | | | | | | | | |
|---|---|---|-------------|-----------------|------------------|---|-----------|---|---------------------------------|----|---|-----|--------------|---|-----|---|--------|---|---|
| Study details | Key efficacy findings | Key safety findings | Comments | | | | | | | | | | | | | | | | |
| <p>Hamel-Desnos (2007)³</p> <p>Study type: multicentre, double-blind RCT Country: France Study period: September 2003–January 2004</p> <p>n = 148 (74 in each group)</p> <p>Study population: patients with varices arising from GSV incompetence (from 5 centres) 3% POL: mean age 53 years, 80% women 1% POL: mean age 56 years, 78% women</p> <p>Inclusion criteria: 18–80 years old, GSV diameter between 4 and 8 mm when standing, CEAP C2–C6, Ep, AS2, Pr.</p> <p>Exclusion criteria: pregnant or breastfeeding women; patients with history of mental or psychiatric disorder or other factors limiting ability to participate; incompetent SFJ of the GSV without GSV trunk incompetence at the thigh; trunk incompetence below the knee with no GSV trunk incompetence at the thigh; chronic liver disease; renal impairment; risk of pregnancy (absence of effective contraception); known progressive malignant disease; cardiac or respiratory failure; history of DVT; known acquired or constitutional coagulopathy; intolerance to alcohol or having taken product blocking metabolism of ethyl alcohol (in the past month); known allergy to lauromacrogol 400</p> | <p>Venous reflux at 2-year follow-up</p> <p>Elimination of reflux in 68% for 1% POL; 69% for 3% POL (14 lost to follow-up: 9 in 1% group and 5 in 3% group)</p> <p>Reflux was defined as persistent reverse flow for 1 or more seconds on the release of manual compression of the calf, as assessed by duplex ultrasonography.</p> <p>Rate of recanalisation at 2-year follow-up</p> <p>37% for 1% POL; 36% for 3% POL (not significantly different; chi-square 0.96).</p> <p>All patients had one treatment session only (which consisted of 1–2 injections in most and 3 injections in 16% of patients).</p> <p>‘Unblinding’ was done at 2-year follow-up. In 50% of cases, investigators had ‘no idea’ which solution had been used. In 21% of cases, investigators were wrong about which solution was used.</p> | <p>Postoperative complications</p> <p>The only immediate side effect was flushing and a tightening sensation in the throat in one patient (there were no reports of chest symptoms, neurological complications such as visual disturbance or migraine, malaise, pain or allergy).</p> <p>Complications after 3-week follow-up</p> <table border="1"> <thead> <tr> <th>Side effect</th> <th>No. of patients</th> </tr> </thead> <tbody> <tr> <td>Minor ecchymosis</td> <td>2</td> </tr> <tr> <td>Haematoma</td> <td>0</td> </tr> <tr> <td>Minor pain or skin inflammation</td> <td>9*</td> </tr> <tr> <td>Skin inflammation with lumps (thrombophlebitis)</td> <td>3**</td> </tr> <tr> <td>Pigmentation</td> <td>3</td> </tr> <tr> <td>SVT</td> <td>0</td> </tr> <tr> <td>DVT***</td> <td>1</td> </tr> </tbody> </table> <p>*Two patients had adjuvant treatment. **Two patients had thrombectomy. ***This was a non-obtrusive, parietal clot in a patient in the 3% group with previous undiagnosed thrombophilia; it appeared at day 19 and disappeared following treatment after 3 weeks. The GSV was still destroyed at 2 years.</p> | Side effect | No. of patients | Minor ecchymosis | 2 | Haematoma | 0 | Minor pain or skin inflammation | 9* | Skin inflammation with lumps (thrombophlebitis) | 3** | Pigmentation | 3 | SVT | 0 | DVT*** | 1 | <p>The results from this study at 6 months were included in the systematic review that the Committee based their previous guidance on. The authors report that these results are consistent with the results at 6 months.</p> <p>The authors calculated that the sample size required (estimating a success rate of 85% for 3% POL and 20% inferiority of 1%) was 140 patients. Fourteen of the 148 patients were lost to follow-up at 2 years.</p> <p>This study only treated GSV at the thigh; the authors stated that the efficacy of the treatment may have been prejudiced because they did not treat saphenous tributaries, perforators or other varices.</p> <p>There was no concomitant treatment on other veins, no precautions were taken</p> |
| Side effect | No. of patients | | | | | | | | | | | | | | | | | | |
| Minor ecchymosis | 2 | | | | | | | | | | | | | | | | | | |
| Haematoma | 0 | | | | | | | | | | | | | | | | | | |
| Minor pain or skin inflammation | 9* | | | | | | | | | | | | | | | | | | |
| Skin inflammation with lumps (thrombophlebitis) | 3** | | | | | | | | | | | | | | | | | | |
| Pigmentation | 3 | | | | | | | | | | | | | | | | | | |
| SVT | 0 | | | | | | | | | | | | | | | | | | |
| DVT*** | 1 | | | | | | | | | | | | | | | | | | |

Abbreviations used: CEAP classification – clinical, etiological, anatomic and pathophysiologic findings; CI, confidence interval; DVT, deep vein thrombosis; GSV, great saphenous vein; MRI, magnetic resonance imaging; POL, polidocanol; RCT, randomised controlled trial; SFJ, sapheno-femoral junction; STD, sodium tetradecyl sulphate; UGFS, ultrasound-guided foam sclerotherapy; VV, varicose vein

| Study details | Key efficacy findings | Key safety findings | Comments | | | | | | | | |
|--|-----------------------|---|-------------|-----------------|-----------------|---|------------|---|----------|---|---|
| <p>or POL.</p> <p>Technique: 1% POL foam vs 3% POL foam to treat GSV at the thigh; only one treatment session was allowed during 2 years.</p> <p>Follow-up: 2 years</p> <p>Conflict of interest: Kreussler Pharma provided drugs used</p> | | <p>Events likely not attributable to procedure</p> <table border="1" data-bbox="1171 459 1554 655"> <thead> <tr> <th data-bbox="1171 459 1451 544">Side effect</th> <th data-bbox="1451 459 1554 544">No. of patients</th> </tr> </thead> <tbody> <tr> <td data-bbox="1171 547 1451 582">Lower back pain</td> <td data-bbox="1451 547 1554 582">1</td> </tr> <tr> <td data-bbox="1171 585 1451 620">Other pain</td> <td data-bbox="1451 585 1554 620">1</td> </tr> <tr> <td data-bbox="1171 624 1451 659">Asthenia</td> <td data-bbox="1451 624 1554 659">1</td> </tr> </tbody> </table> | Side effect | No. of patients | Lower back pain | 1 | Other pain | 1 | Asthenia | 1 | <p>to prevent entrance into deep veins, no leg elevation or compression of the SFJ, ankle dorsiflexion, compression bandages, or postoperative instructions on exercise or walking.</p> <p>Four authors were also involved in Ouvry (2008)⁴.</p> |
| Side effect | No. of patients | | | | | | | | | | |
| Lower back pain | 1 | | | | | | | | | | |
| Other pain | 1 | | | | | | | | | | |
| Asthenia | 1 | | | | | | | | | | |

| Abbreviations used: CEAP classification – clinical, etiological, anatomic and pathophysiologic findings; CI, confidence interval; DVT, deep vein thrombosis; GSV, great saphenous vein; MRI, magnetic resonance imaging; POL, polidocanol; RCT, randomised controlled trial; SFJ, sapheno-femoral junction; STD, sodium tetradecyl sulphate; UGFS, ultrasound-guided foam sclerotherapy; VV, varicose vein | | | | | | | | | | | | | | | | | | | | | | | | | |
|---|--|---|-------------|--------------|--------------------------------------|---|----------|---|-----------|---|---------------|---|--------------|---|-------------|--------------|-----------------------------|---|--------------------------|---|----------------------------------|---|---|---|--|
| Study details | Key efficacy findings | Key safety findings | Comments | | | | | | | | | | | | | | | | | | | | | | |
| <p>Ouvry (2008)⁴</p> <p>Study type: multicentre RCT</p> <p>Country: France</p> <p>Study period: May 2001–March 2002</p> <p>n = 95 (48 liquid, 47 foam)</p> <p>Study population: patients from 6 centres</p> <p>Foam: mean age 54 years, 92% women</p> <p>Liquid: mean age 55 years, 94% women</p> <p>Inclusion criteria: 18–80 years old, GSV diameter between 4 and 8 mm when standing, CEAP C2–C6.</p> <p>Exclusion criteria: pregnant or breastfeeding women; patients with history of mental or psychiatric disorder; progressive malignant disease; intolerance to alcohol; allergy to lauromacrogol or POL; history of DVT; acquired or constitutional thrombophilia; absence of effective contraception; chronic hepatic, cardiac, renal or respiratory insufficiency.</p> <p>Technique: 3% POL in either foam or liquid form mixed with sterile air injected into GSV under ultrasound guidance (2 ml for veins with 4–6 mm diameter and 2.5 ml for veins with 6–8 mm diameter); no special precautions after surgery or special postoperative instructions (compression stocking if secondary pain or inflammation).</p> <p>Follow-up: 2 years</p> <p>Conflict of interest: not stated</p> | <p>Success rate (elimination of GSV reflux) at 3-week follow-up</p> <p>Foam: 85% (40/47); liquid: 35% (17/48); p < 0.001</p> <p>Success rate (no recanalisation) at 2-year follow-up</p> <p>Foam: 53% (25/47)</p> <p>Liquid: 12% (4) (significance level not given; denominator for liquid group not given)</p> <p>The study stated that 86 patients were seen for all follow-up visits, 5 showed up for some and 5 in the foam group were lost to follow-up (3 at 6 months, 1 at 1 year and 1 at 2 years). Those lost to follow-up were considered as treatment failures.</p> <p>Kaplan–Meier analysis showed that reflux recurrence is more frequent in the ‘liquid’ group (p < 0.0001).</p> <p>At 6-month follow-up, recanalisation occurred in 15 patients – 10 liquid, 5 foam. Reduction in diameter of saphenous vein was greater in foam than liquid (52% vs 38%).</p> <p>Average length of occluded vein at 3-week follow-up</p> <p>Foam: 26 cm; liquid: 9.1 cm; p < 0.0001</p> <p>Venous spasm</p> <p>Venous spasm immediately after injection occurred in 31% (15) of cases injected with liquid and 66% (31) of those injected with foam (p < 0.001).</p> <p>Spasm was not associated with success in the liquid group but there was a strong correlation between spasm and success in the foam group (p < 0.0001).</p> <p>There was a 100% positive predictive value of spasm, but a 44% negative predictive value in the absence of spasm.</p> | <p>Immediate complications</p> <p>One patient had a vaso-vagal response that resolved without treatment.</p> <p>One patient had a sensation of heat in the mouth.</p> <p>Complications at 3-week follow-up</p> <table border="1"> <thead> <tr> <th>Side effect</th> <th>No. of cases</th> </tr> </thead> <tbody> <tr> <td>Persistent inflammation of the thigh</td> <td>5</td> </tr> <tr> <td>Bruising</td> <td>2</td> </tr> <tr> <td>Mild pain</td> <td>8</td> </tr> <tr> <td>Moderate pain</td> <td>1</td> </tr> <tr> <td>Serious pain</td> <td>2</td> </tr> </tbody> </table> <p>(the authors reported no difference between groups)</p> <p>Other related adverse events</p> <table border="1"> <thead> <tr> <th>Side effect</th> <th>No. of cases</th> </tr> </thead> <tbody> <tr> <td>Thrombophlebitis of the leg</td> <td>2</td> </tr> <tr> <td>Asthenia lasting 15 days</td> <td>1</td> </tr> <tr> <td>Headache on evening of injection</td> <td>1</td> </tr> <tr> <td>Pain in thigh and knee 8 days after surgery resolving without treatment</td> <td>1</td> </tr> </tbody> </table> <p>The authors added that no patients had visual disturbance, chest symptoms, deep or superficial venous thrombosis or cutaneous necrosis.</p> | Side effect | No. of cases | Persistent inflammation of the thigh | 5 | Bruising | 2 | Mild pain | 8 | Moderate pain | 1 | Serious pain | 2 | Side effect | No. of cases | Thrombophlebitis of the leg | 2 | Asthenia lasting 15 days | 1 | Headache on evening of injection | 1 | Pain in thigh and knee 8 days after surgery resolving without treatment | 1 | <p>The authors state that the rate of immediate success in the foam group (85%) is less than that reported in the literature, which may be due to the fact that the treatment in this study was only a single injection.</p> <p>Spasm predicted immediate success but absence of spasm did not predict failure.</p> <p>The four authors of this study were involved in Hamel-Desnos (2007)⁵ (comparing two different concentrations of foam).</p> |
| Side effect | No. of cases | | | | | | | | | | | | | | | | | | | | | | | | |
| Persistent inflammation of the thigh | 5 | | | | | | | | | | | | | | | | | | | | | | | | |
| Bruising | 2 | | | | | | | | | | | | | | | | | | | | | | | | |
| Mild pain | 8 | | | | | | | | | | | | | | | | | | | | | | | | |
| Moderate pain | 1 | | | | | | | | | | | | | | | | | | | | | | | | |
| Serious pain | 2 | | | | | | | | | | | | | | | | | | | | | | | | |
| Side effect | No. of cases | | | | | | | | | | | | | | | | | | | | | | | | |
| Thrombophlebitis of the leg | 2 | | | | | | | | | | | | | | | | | | | | | | | | |
| Asthenia lasting 15 days | 1 | | | | | | | | | | | | | | | | | | | | | | | | |
| Headache on evening of injection | 1 | | | | | | | | | | | | | | | | | | | | | | | | |
| Pain in thigh and knee 8 days after surgery resolving without treatment | 1 | | | | | | | | | | | | | | | | | | | | | | | | |

| Abbreviations used: CEAP classification – clinical, etiological, anatomic and pathophysiologic findings; CI, confidence interval; DVT, deep vein thrombosis; GSV, great saphenous vein; MRI, magnetic resonance imaging; POL, polidocanol; RCT, randomised controlled trial; SFJ, sapheno-femoral junction; STD, sodium tetradecyl sulphate; UGFS, ultrasound-guided foam sclerotherapy; VV, varicose vein | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
|--|---|--------------|-----------|---------------------|---|--------------|--------|---------|-------|--|--|--|--|-----|-----|---|--|--|-----|-----|------|-----------|-------|--------------|--|--|--|--|------|-----|---|--|--|--------|----|------|-----------|-------|-----------|--|--|--|--|------|-----|------|----------|-------|----------|-----|------|-----------|-------|-------|-----|---|--|--|---------|--|--|--|--|-------|-----|---|--|--|---------|-----|------|-----------|-------|--------|-----|------|-----------|-------|-------|--|--|--|--|------|-----|---|--|--|------|----|------|-----------|-------|--|--|-------------|-----------------|------|---------------|--|--------------|--|--------------|---|
| Study details | Key efficacy findings | | | Key safety findings | | Comments | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| <p>Myers (2007)⁵</p> <p>Study type: case series</p> <p>Country: Australia</p> <p>Study period: early 1999 to mid 2005</p> <p>n = 807 venous saphenous veins (489 patients, 1189 treatment sessions; 82% women, mean age 53 years)</p> <p>Study population: patients presenting for first endovenous treatment by ultrasound guidance; CEAP classification category: 569 were C2–C3, 39 were C4, 21 were C5, 2 were C6; primary VV in 516 limbs (82%) and recurrent VV after previous saphenous vein surgery in 115 limbs.</p> <p>454 (56%) limbs; 449 limbs with GSV reflux (including 5 limbs with anterior accessory saphenous vein reflux); 177 limbs (22%) – saphenous territory vas; 176 limbs (22%) – tributaries without reflux.</p> <p>In 60 limbs, both the great and small saphenous vein was treated.</p> <p>Exclusion criteria: previous ultrasound-guided sclerotherapy.</p> <p>Technique: either POL or STD, 0.6–3% liquid with saline dilution, injection volume ranged from 3 to 40 ml (median 5 ml), compression with two-layer bandage or thigh-length stocking following injection and followed by 15 min of walking, after 3 days compression stocking worn during day for 2–3 weeks.</p> | <p>Three-year success rates (all veins)</p> <p>Primary success rate: 52.4% (95% CI 46–58) Secondary success rate: 76.8% (95% CI 71–82) (‘success’ is persistent occlusion/absence of reflux; secondary is after further UGFS).</p> <p>Persistent reflux after recanalisation in the posterior tibial segment occurred in five limbs (reflux was defined as reverse flow persisting for 0.5 or more seconds on the release of manual compression of the calf).</p> <p>Multivariate Cox regression analysis of covariates predicting treatment failure:</p> <table border="1"> <thead> <tr> <th></th> <th>n</th> <th>Hazard ratio</th> <th>95% CI</th> <th>p-value</th> </tr> </thead> <tbody> <tr> <td>Vein:</td> <td></td> <td></td> <td></td> <td></td> </tr> <tr> <td>GSV</td> <td>453</td> <td>1</td> <td></td> <td></td> </tr> <tr> <td>SSV</td> <td>174</td> <td>1.58</td> <td>1.11–2.24</td> <td>0.011</td> </tr> <tr> <td>Preparation:</td> <td></td> <td></td> <td></td> <td></td> </tr> <tr> <td>Foam</td> <td>557</td> <td>1</td> <td></td> <td></td> </tr> <tr> <td>Liquid</td> <td>70</td> <td>2.20</td> <td>1.28–3.78</td> <td>0.005</td> </tr> <tr> <td>Dilution:</td> <td></td> <td></td> <td></td> <td></td> </tr> <tr> <td>0.6%</td> <td>213</td> <td>2.05</td> <td>1.2–3.46</td> <td>0.007</td> </tr> <tr> <td>0.8–1.2%</td> <td>122</td> <td>1.38</td> <td>0.78–2.45</td> <td>0.268</td> </tr> <tr> <td>>1.2%</td> <td>292</td> <td>1</td> <td></td> <td></td> </tr> <tr> <td>Volume:</td> <td></td> <td></td> <td></td> <td></td> </tr> <tr> <td><6 ml</td> <td>320</td> <td>1</td> <td></td> <td></td> </tr> <tr> <td>6–12 ml</td> <td>158</td> <td>1.04</td> <td>0.71–1.52</td> <td>0.848</td> </tr> <tr> <td>>12 ml</td> <td>149</td> <td>0.51</td> <td>0.33–0.81</td> <td>0.004</td> </tr> <tr> <td>CEAP:</td> <td></td> <td></td> <td></td> <td></td> </tr> <tr> <td>C2/3</td> <td>565</td> <td>1</td> <td></td> <td></td> </tr> <tr> <td>C4/6</td> <td>62</td> <td>1.57</td> <td>0.91–2.73</td> <td>0.106</td> </tr> </tbody> </table> | | | | n | Hazard ratio | 95% CI | p-value | Vein: | | | | | GSV | 453 | 1 | | | SSV | 174 | 1.58 | 1.11–2.24 | 0.011 | Preparation: | | | | | Foam | 557 | 1 | | | Liquid | 70 | 2.20 | 1.28–3.78 | 0.005 | Dilution: | | | | | 0.6% | 213 | 2.05 | 1.2–3.46 | 0.007 | 0.8–1.2% | 122 | 1.38 | 0.78–2.45 | 0.268 | >1.2% | 292 | 1 | | | Volume: | | | | | <6 ml | 320 | 1 | | | 6–12 ml | 158 | 1.04 | 0.71–1.52 | 0.848 | >12 ml | 149 | 0.51 | 0.33–0.81 | 0.004 | CEAP: | | | | | C2/3 | 565 | 1 | | | C4/6 | 62 | 1.57 | 0.91–2.73 | 0.106 | <p>Complications</p> <table border="1"> <thead> <tr> <th>Side effect</th> <th>No. of patients</th> </tr> </thead> <tbody> <tr> <td>DVT*</td> <td>3.2% (16/489)</td> </tr> <tr> <td>Occlusive posterior tibial vein thromboses</td> <td>1.8% (9/489)</td> </tr> <tr> <td>Partially occlusive femoropopliteal thromboses</td> <td>1.4% (7/489)</td> </tr> </tbody> </table> <p>All were asymptomatic and resolved following heparin therapy (follow-up not stated).</p> <p>*Detected on routine postoperative exam, volume infused ranged from 5 to 35 ml (median 14 ml).</p> <p>Three patients with a history of migraine headaches developed visual aura during mobilisation after injection which settled within 20 min without further headache or neurological problems.</p> <p>There were no instances of pulmonary embolism or other cardiovascular complications, no other neurological symptoms, or any other complications.</p> | | Side effect | No. of patients | DVT* | 3.2% (16/489) | Occlusive posterior tibial vein thromboses | 1.8% (9/489) | Partially occlusive femoropopliteal thromboses | 1.4% (7/489) | <p>The authors stated that the first 98 of 1189 treatment sessions used liquid sclerosant, but foam was used from early 2000 onwards. Results have not been separated for foam and liquid. They stated that the higher occurrence of DVT in this study compared with other reported studies was because they actively scanned the deep veins after every treatment session and detected asymptomatic thromboses.</p> <p>The choice of sclerosant and volume used were dependent on the patient at the discretion of the surgeon.</p> <p>The multivariate Cox model was insufficiently explained in the table legend of the study, but the results were interpreted in the text</p> <p>The authors present regression analyses of factors predicting failure, but not how these factors affected the likelihood of particular safety events.</p> |
| | n | Hazard ratio | 95% CI | p-value | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Vein: | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| GSV | 453 | 1 | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| SSV | 174 | 1.58 | 1.11–2.24 | 0.011 | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Preparation: | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Foam | 557 | 1 | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Liquid | 70 | 2.20 | 1.28–3.78 | 0.005 | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Dilution: | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| 0.6% | 213 | 2.05 | 1.2–3.46 | 0.007 | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| 0.8–1.2% | 122 | 1.38 | 0.78–2.45 | 0.268 | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| >1.2% | 292 | 1 | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Volume: | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| <6 ml | 320 | 1 | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| 6–12 ml | 158 | 1.04 | 0.71–1.52 | 0.848 | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| >12 ml | 149 | 0.51 | 0.33–0.81 | 0.004 | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| CEAP: | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| C2/3 | 565 | 1 | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| C4/6 | 62 | 1.57 | 0.91–2.73 | 0.106 | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Side effect | No. of patients | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| DVT* | 3.2% (16/489) | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Occlusive posterior tibial vein thromboses | 1.8% (9/489) | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Partially occlusive femoropopliteal thromboses | 1.4% (7/489) | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |

Abbreviations used: CEAP classification – clinical, etiological, anatomic and pathophysiologic findings; CI, confidence interval; DVT, deep vein thrombosis; GSV, great saphenous vein; MRI, magnetic resonance imaging; POL, polidocanol; RCT, randomised controlled trial; SFJ, sapheno-femoral junction; STD, sodium tetradecyl sulphate; UGFS, ultrasound-guided foam sclerotherapy; VV, varicose vein

| Study details | Key efficacy findings | | | | Key safety findings | | Comments |
|--|---|--------------------------|---------------------------|-----------------------------------|-------------------------|--|----------|
| Mean follow-up: 3 years Conflict of interest: not stated | Side: right left | 313 314 | 1.19 1 | 0.89–1.57 | 0.239 | | |
| | Diameter: <5 mm 5 mm 6 mm >6 mm | 211 152 152 112 | 1 1.27 2.07 2.22 | 0.79–2.03 1.35–3.18 1.4–3.5 | 0.325 0.001 0.001 | | |
| | * The model was also adjusted for age and sex | | | | | | |

Abbreviations used: CEAP classification – clinical, etiological, anatomic and pathophysiologic findings; CI, confidence interval; DVT, deep vein thrombosis; GSV, great saphenous vein; MRI, magnetic resonance imaging; POL, polidocanol; RCT, randomised controlled trial; SFJ, sapheno-femoral junction; STD, sodium tetradecyl sulphate; UGFS, ultrasound-guided foam sclerotherapy; VV, varicose vein

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|--|---|---------------------|--------------------|----------------------|------------------------------|--------------------|------------------------|------------------------------|-------------------|----------------|----|------|------|-----|---|---|---|------------------|---|-----|-----|-----|---|---|---|--------------|---|---|------|------|---|---|---|--------------------|---|-----|---|-----|---|---|---|-----------------|---|-----|-----|-----|---|---|---|------------|---|-----|---|---|---|---|---|------|---|-----|-----|-----|---|---|---|------------------------|---|------|------|---|---|---|---|--------------|---|-----|---|---|---|---|---|--------------|---|-----|---|-----|---|---|---|--------------|---|------|------|------|------|----|---|--------------|--------------|--------------|-------------|-------------|-----------|-----------|----------|--|---|
| <p>Study type: clinical audit data (from nine centres)⁶</p> <p>Country: UK</p> <p>Study period: (see table)</p> <p>Study population: patients who had foam sclerotherapy</p> <p>n = 10,720 procedures (9718 legs and 753 patients)</p> <p>Technique: UGFS</p> | <p>The following are details of an audit of nine UK centres</p> <table border="1" data-bbox="678 427 1785 1061"> <thead> <tr> <th>Centre</th> <th>Number of procedures</th> <th>Number of legs</th> <th>Number of patients</th> <th>Number of DVTs</th> <th>Number of visual disturbance</th> <th>Number of strokes</th> <th>Dates of study</th> </tr> </thead> <tbody> <tr> <td>1*</td> <td>1446</td> <td>1158</td> <td>888</td> <td>2</td> <td>5</td> <td>0</td> <td>2004 to Feb 2009</td> </tr> <tr> <td>2</td> <td>217</td> <td>185</td> <td>176</td> <td>0</td> <td>2</td> <td>0</td> <td>2005 to 2008</td> </tr> <tr> <td>3</td> <td>–</td> <td>3474</td> <td>2406</td> <td>1</td> <td>7</td> <td>0</td> <td>2001 to April 2008</td> </tr> <tr> <td>3</td> <td>592</td> <td>–</td> <td>430</td> <td>1</td> <td>0</td> <td>0</td> <td>May to Dec 2008</td> </tr> <tr> <td>4</td> <td>204</td> <td>185</td> <td>165</td> <td>0</td> <td>5</td> <td>0</td> <td>Up to 2007</td> </tr> <tr> <td>4</td> <td>142</td> <td>–</td> <td>–</td> <td>0</td> <td>0</td> <td>0</td> <td>2008</td> </tr> <tr> <td>5</td> <td>891</td> <td>810</td> <td>749</td> <td>2</td> <td>3</td> <td>0</td> <td>Sept 2006 to June 2008</td> </tr> <tr> <td>6</td> <td>1064</td> <td>1228</td> <td>–</td> <td>2</td> <td>5</td> <td>0</td> <td>Not provided</td> </tr> <tr> <td>7</td> <td>274</td> <td>–</td> <td>–</td> <td>2</td> <td>0</td> <td>0</td> <td>Not provided</td> </tr> <tr> <td>8</td> <td>169</td> <td>–</td> <td>129</td> <td>0</td> <td>0</td> <td>0</td> <td>Not provided</td> </tr> <tr> <td>9</td> <td>6538</td> <td>2860</td> <td>2084</td> <td>26**</td> <td>40</td> <td>0</td> <td>Not provided</td> </tr> <tr> <td>Total</td> <td>11537</td> <td>9900</td> <td>7027</td> <td>36</td> <td>67</td> <td>0</td> <td></td> </tr> </tbody> </table> <p>* One patient treated by this centre developed blotchy marks on their face (no further description)</p> <p>**Four were femoral or popliteal and 22 were gastrocnemius or posterior tibial of minor extent. (Please note that centre 3 and 4 have both submitted two groups of data)</p> <p>Despite the fact that there was no report of a stroke in the above data, a survey of UK surgeons conducted by O'Hare and Earnshaw (2007) reported two surgeons (3%) who observed a stroke and one surgeon (1%) who observed a transient ischaemic event (this survey had a 47% response rate, including 281 responses)⁷.</p> | | Centre | Number of procedures | Number of legs | Number of patients | Number of DVTs | Number of visual disturbance | Number of strokes | Dates of study | 1* | 1446 | 1158 | 888 | 2 | 5 | 0 | 2004 to Feb 2009 | 2 | 217 | 185 | 176 | 0 | 2 | 0 | 2005 to 2008 | 3 | – | 3474 | 2406 | 1 | 7 | 0 | 2001 to April 2008 | 3 | 592 | – | 430 | 1 | 0 | 0 | May to Dec 2008 | 4 | 204 | 185 | 165 | 0 | 5 | 0 | Up to 2007 | 4 | 142 | – | – | 0 | 0 | 0 | 2008 | 5 | 891 | 810 | 749 | 2 | 3 | 0 | Sept 2006 to June 2008 | 6 | 1064 | 1228 | – | 2 | 5 | 0 | Not provided | 7 | 274 | – | – | 2 | 0 | 0 | Not provided | 8 | 169 | – | 129 | 0 | 0 | 0 | Not provided | 9 | 6538 | 2860 | 2084 | 26** | 40 | 0 | Not provided | Total | 11537 | 9900 | 7027 | 36 | 67 | 0 | | <p>Validation of data:</p> <p>The details have not been published so have not been through a peer-reviewed process. It is also unclear how long these patients were followed up for.</p> <p>Data were only provided on the safety events of DVT, visual disturbance and stroke.</p> <p>There is also an unpublished prospective US case series of UGFS in 4891 patients that raises no new safety concerns (received by personal communication from UK surgeon Specialist Adviser).</p> |
| Centre | Number of procedures | Number of legs | Number of patients | Number of DVTs | Number of visual disturbance | Number of strokes | Dates of study | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| 1* | 1446 | 1158 | 888 | 2 | 5 | 0 | 2004 to Feb 2009 | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| 2 | 217 | 185 | 176 | 0 | 2 | 0 | 2005 to 2008 | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| 3 | – | 3474 | 2406 | 1 | 7 | 0 | 2001 to April 2008 | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| 3 | 592 | – | 430 | 1 | 0 | 0 | May to Dec 2008 | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| 4 | 204 | 185 | 165 | 0 | 5 | 0 | Up to 2007 | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| 4 | 142 | – | – | 0 | 0 | 0 | 2008 | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| 5 | 891 | 810 | 749 | 2 | 3 | 0 | Sept 2006 to June 2008 | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| 6 | 1064 | 1228 | – | 2 | 5 | 0 | Not provided | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| 7 | 274 | – | – | 2 | 0 | 0 | Not provided | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| 8 | 169 | – | 129 | 0 | 0 | 0 | Not provided | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| 9 | 6538 | 2860 | 2084 | 26** | 40 | 0 | Not provided | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Total | 11537 | 9900 | 7027 | 36 | 67 | 0 | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |

| Abbreviations used: CEAP classification – clinical, etiological, anatomic and pathophysiologic findings; CI, confidence interval; DVT, deep vein thrombosis; GSV, great saphenous vein; MRI, magnetic resonance imaging; POL, polidocanol; RCT, randomised controlled trial; SFJ, sapheno-femoral junction; STD, sodium tetradecyl sulphate; UGFS, ultrasound-guided foam sclerotherapy; VV, varicose vein | | | |
|--|---|---------------------|--|
| Study details | Key efficacy findings | Key safety findings | Comments |
| <p>Nitecki and Bass (2007)⁸</p> <p>Study type: case reports of local arterial embolism</p> <p>Country: Israel</p> <p>n = 3</p> <p>Study population: patients with venous insufficiency</p> <p>Technique: UGFS</p> <p>Follow-up: over approximately 7 years at three centres</p> <p>Conflict of interest: not stated</p> | <p>The incidence of arterial injury is reported to be 0.25% (3/1200). The cause is said to be of chemical and irreversible nature and resulted in tissue loss.</p> <p>Case 1: a 16-year old woman with Klippel-Trenaunay syndrome with varicosities and venous lakes from buttocks and in right limb.</p> <p>Intervention: 3% POL foam injected into two toe arteries.</p> <p>Effects: rapid development of dry gangrene in both toes where the foam was injected. This was treated with conservative treatment (dressing, antibiotic, analgesics) and was under observation at the time of the report.</p> <p>Case 2: a 23-year old man with C4 varicosities with atrophie blanche.</p> <p>Intervention: 3% POL foam prepared with the Tessari method directed under direct vision into a Cockett 3 perforator (the study states that this was UGFS, but also that it was injected under direct vision).</p> <p>Effects: severe pain and 'ice cold' foot as a result of foam embolisation via small arteriovenous shunts to posterior tibial artery and its branches; this resulted in gangrene. The foot was treated with thrombolytic therapy, mechanical thrombectomy and hyperbaric oxygen followed by partial foot amputation and free muscle flap transfer. At 15-month follow-up, the patient was 'ambulating and active'.</p> <p>Case 3: a 54-year old man with C4 varicosities</p> <p>Intervention: 3% POL foam</p> <p>Effects: deep pain as a result of incorrect placement of the needle into the superficial femoral artery. Duplex scanning revealed a double saphenous system with a subfascial position of the main trunk. This led to the development of gangrene which required below-knee amputation.</p> | | <p>This study is a report of 6 cases out of approximately 1200 patients treated by UGFS (and 4800 treated by surgery) over 7 years from three medical centres. Three other cases are not reported here because they had complications as a result of surgery.</p> <p>The systematic review reported 6 instances of arterial events out of 253 patients which appeared in conference abstracts (median rate 2.1%, range 1.4–2.8).</p> |

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|--|---|---------------------|--|
| Study details | Key efficacy findings | Key safety findings | Comments |
| <p>Ceulen (2008)⁹ Rush (2008)¹⁰ Regan (2008)¹¹ Bush (2008)¹² O'Hare (2007)⁷ Morrison (2008)¹⁵ Hansen (2007)¹³ Hill (2008)¹⁴</p> <p>Study type: case series and case reports of systemic foam embolism</p> <p>Country: Netherland, US</p> | <p>Ceulen (2008)⁹ A commentary was published revealing transient scotomas in a 51-year-old man and migraine in a 33-year-old woman following a single injection of 5 ml of 1% POL foam (air:liquid, 4:1). The patients presented with symptomatic varicose GSV and were 'healthy'. The injection was administered with the leg elevated and manual compression on the SFJ until full vasospasm.</p> <p>The authors noted that all 33 patients studied had foam microemboli in both the right atrium and ventricle between 45 s and 15 min after injection. In five patients, microemboli were also detected in the left atrium and ventricle but there were no neurological signs. All five were later revealed to have right-to-left shunt through a patent foramen ovale on echocardiographic examination (tested because of the possibility of right-to-left shunt in the first two patients).</p> <p>Rush (2008)¹⁰ A commentary on the Ceulen report (above) revealed that intracardiac gas emboli were discovered in all 45 patients treated with low nitrogen (<0.8%) POL microfoam (Varisolve, Provensis). This commentary also reported preliminary results of an ongoing, multicentre trial with patients with GSV incompetence and right-to-left shunts (see Regan below). Pretreatment screening revealed a 40% prevalence of right-to-left shunt. Cerebral emboli and this extensive monitoring in 36 of these patients revealed no cerebral lesions or abnormalities on the perimetry or assessment of cardiac markers.</p> <p>Regan (2008)¹¹ This is a published abstract of the interim results of a multicentre study investigating whether there were adverse events in patients with microvascular bubbles detected while being treated with POL microfoam.</p> <p>Study inclusion: patients with SFJ incompetence and GSV reflux (CEAP 3–5), ≤60 years and without arteriovascular disease. Tests for the presence of right-to-left shunt were done before the procedure. The POL was a 'gas mixture' (Varisolve procedure). Patients with microvascular bubbles were observed using MRI (on 1, 7 and 28 days) and transcranial Doppler, neurological exam, perimetry, and cardiac markers.</p> <p>Preliminary results: right-to-left shunts were observed in one third of patients. In these patients, 90% were observed to have microvascular bubble emboli during the procedure but a very low number of bubbles (maximum 13 with grade V shunt). Of 11 patients evaluated, none developed MRI lesions, neurological or visual field abnormalities or elevated cardiac markers.</p> | | <p>The Ceulen, Rush, and Regan reports are not peer-reviewed publications, but are included here because they refer to serious adverse events.</p> <p>The Bush, Hansen, Hill and Morrison reports/studies are all peer-reviewed publications.</p> <p>Case 2 from Nitecki and Bass (2007)⁸ above also reported foam embolism.</p> <p>See discussion below.</p> |

| Abbreviations used: CEAP classification – clinical, etiological, anatomic and pathophysiologic findings; CI, confidence interval; DVT, deep vein thrombosis; GSV, great saphenous vein; MRI, magnetic resonance imaging; POL, polidocanol; RCT, randomised controlled trial; SFJ, sapheno-femoral junction; STD, sodium tetradecyl sulphate; UGFS, ultrasound-guided foam sclerotherapy; VV, varicose vein | | | |
|--|--|---------------------|----------|
| Study details | Key efficacy findings | Key safety findings | Comments |
| | <p>Bush (2007)¹² Case one: a 72-year-old woman with symptomatic saphenous insufficiency of the left leg and two incompetent Cockett's perforators; she had no significant medical history. Intervention: 2 cm³ of 2% sotradcol foam (Tessari method) in each perforator. Effects: the patient was discharged but 25 min after the injection the patient was found slumped in her chair. She was able to communicate with slurred speech, but she couldn't move her extremities. When she arrived at the emergency room she had bilateral weakness but her left side was more pronounced. A CT scan revealed air in her vertebral artery. Within 3 h, the patient's condition had resolved and she had no atrial defect (echogram). A very small shunt was identified after injection with a solution of agitated blood and saline (by transoesophageal echo). Case two: a 35-year-old woman with reticular veins and spider telangiectasia previously treated with foamed STD on two occasions. Intervention: this treatment consisted of 10 cm³ of foam over 20 min (concentration not stated). Effects: when sitting up to reach for her hose (not otherwise described), the patient fell off the bed, hitting her head on a side table. She was unconscious for 30 s and when she became responsive with a spastic appearance in her right hand and was unable to move her left leg or arm, but was able to answer questions. Later she developed seizure activity in her right upper extremity, her eyes deviated to the right, and she had 'purse-lip type breathing'. A CT scan revealed air in the right venous circulation and an air bubble in the middle cerebral artery. The patient had hyperbaric oxygen therapy. Despite some persistent, mild left-sided numbness, the patient's neurological exam was reported as normal 2 weeks after the incident.</p> <p>O'Hare (2007)⁷ A survey of UK surgeons revealed one surgeon who observed a transient ischaemic attack and two surgeons who observed a stroke. However, it is uncertain whether the observations above were of the same events reported in this survey.</p> <p>Morrison (2008)¹⁵ A study comparing air-based foam with carbon dioxide-based foam reported that the overall side effects following UGFS decreased from 39% (19/49) to 11% (14/128) when carbon dioxide replaced air in the foam preparation (p < 0.001). For example, visual disturbance decreased from 8% (4/49) to 3% (4/128), chest tightness from 18% (9/49) to 3% (4/128), and dizziness from 12% (6/49) to 3% (4/128).</p> | | |

Abbreviations used: CEAP classification – clinical, etiological, anatomic and pathophysiologic findings; CI, confidence interval; DVT, deep vein thrombosis; GSV, great saphenous vein; MRI, magnetic resonance imaging; POL, polidocanol; RCT, randomised controlled trial; SFJ, sapheno-femoral junction; STD, sodium tetradecyl sulphate; UGFS, ultrasound-guided foam sclerotherapy; VV, varicose vein

| Study details | Key efficacy findings | Key safety findings | Comments |
|---------------|--|---------------------|----------|
| | <p>Hansen (2007)¹³ A study of 20 patients suspected of having a patent foramen ovale or describing respiratory or cerebral symptoms (migraine, visual disturbance, among others) reported that transthoracic echocardiography demonstrated bubbles in the left heart of 65% (13/20) immediately after the procedure¹³. Five patients with a positive test also had emboli in their middle cerebral artery demonstrated on transcranial Doppler. The seven patients without bubbles in the left heart reported visual disturbance, migraine, shortness of breath, dizziness and numbness.</p> <p>Hill (2008)¹⁴ A study that assessed techniques to reduce sclerosant foam migration during UGFS reported a significant increase in the incidence of emboli in the right heart after injection with the leg flat and occlusive pressure at the saphenofemoral junction (based on small numbers)¹⁴.</p> | | |

| Abbreviations used: CEAP classification – clinical, etiological, anatomic and pathophysiologic findings; CI, confidence interval; DVT, deep vein thrombosis; GSV, great saphenous vein; MRI, magnetic resonance imaging; POL, polidocanol; RCT, randomised controlled trial; SFJ, sapheno-femoral junction; STD, sodium tetradecyl sulphate; UGFS, ultrasound-guided foam sclerotherapy; VV, varicose vein | | | |
|--|---|---|----------|
| Study details | Key efficacy findings | Key safety findings | Comments |
| <p>Scurr (2007)¹⁶ Brzoza (2007)¹⁷</p> <p>Study type: case reports of allergic reaction to foam</p> <p>Country: Poland, UK</p> <p>n = one each</p> <p>Technique: UGFS</p> <p>Conflict of interest: not stated for either study</p> | <p>Case one¹⁶: a 62-year old woman with body mass index >35, angina, hypertension and mild asthma with hay fever presented with a large anterolateral thigh vein (C2, S, Ep, As, Pr); she reported allergies to pollen and perfume but not to conventional medications.</p> <p>Intervention: 4 ml of 3% STD foam (Fibro vein). A compression bandage was applied following the procedure. After 6 months, a persistent patent and incompetent vein warranted further treatment (12 ml of 1% STD).</p> <p>Effects: within 20 min of the procedure, the patient reported a hot sensation in her mouth and appeared flushed. After administration of 10 mg of intravenous chlorphenamine, her tongue and lips swelled, her breathing became 'wheezy', she developed tachycardia (120 beats/min) and became hypotensive (79/50 mmHg). She was resuscitated by being given high flow oxygen and epinephrine (1:1000 solution 0.5 ml) and then she was given intravenous fluids and hydrocortisone (100 mg). She did not lose consciousness or require intubation but did stay in critical care over night before being discharged after 24 h without any further events.</p> <p>Case two¹⁷: a 49-year-old woman with a 10-year history of bilateral leg varicoses, history of arterial hypertension (treated with cilazapril), but no drug allergy or personal or family history of allergic disease.</p> <p>Intervention: 1% STD</p> <p>Effects: within 10 min of injection, she developed a generalised itch with a urticarial rash and nausea. She did not faint but had tachycardia (150 beats/min) and a weak pulse (blood pressure 60/30 mmHg). Bronchospasm and laboratory abnormalities were not found and a chest X-ray and electrocardiogram were normal. She was treated with epinephrine, hydrocortisone, phenazoline, and intravenous fluids and had a full recovery with no further events.</p> <p>(The authors noted that a skin test was not done before the procedure; they did state that the patient could have had a reaction to the benzyl alcohol but a skin test proved negative.)</p> | <p>No allergic reactions to foam were reported in the systematic review.</p> <p>One author highlighted that there have been reports of allergic reactions in sclerosants previously (a German study reported an incidence of 0.2% of allergic reactions with sclerosing agents).</p> <p>The authors of the first case report state that those performing the procedure should be trained in resuscitation techniques and have appropriate resuscitation equipment available.</p> <p>The authors from both studies highlight that allergic reactions are potentially life threatening.</p> | |

Validity and generalisability of the studies

- The literature was searched for publications that have emerged since the previously commissioned systematic review and the literature in this overview is only from that published after the review (the previous decisions were made based on this systematic review). This is significantly different to the IP Programme's normal reviewing process, which involves selecting from the entire literature (including the literature previously viewed by the Committee).
- As stated in the IP Programme methods guide, the Committee may be presented with safety data from abstracts, manufacturers' or Specialist Advisers' reports, and other miscellaneous sources if these relate to serious adverse events. Consequently, a number of sources have been included in this overview for presentation to the Committee. We have also included abstracts of minor safety events (which have already been reported in the systematic review) in appendix A.
- Because of space limitations, safety data were included on the basis that they were significantly more serious than and different from those presented in the systematic review. Consequently, appendix A includes two reports of a pulmonary embolism, a number of cases of deep vein thrombosis (DVT), and one study which reported a significantly higher rate of thrombophlebitis than the systematic review (66% versus a median rate of 4.7 across 19 studies in the systematic review).
- Some studies were selected based on their addition to the efficacy data in the systematic review. The criteria for selection of efficacy data included length of follow-up, robustness of the trial and large number of patients.
- Although varicose veins is the primary indication, safety data from the use of this procedure for other venous malformations were also searched (some of the studies included are on the use of the procedure for indications other than varicose veins). The non-English abstracts in the literature search results were

checked for significant safety events. None identified serious complications that have not already been reported in the systematic review.

- The studies used a variety of sclerosants, usually polidocanol or sodium tetradecyl sulphate, at different concentrations (ranging from 0.6 to 3%). The majority of studies prepared the foam using the Tessari method, though some used prepared foam. The use of compression following the procedure also varied in the studies.
- Most studies did not assess patient-oriented outcomes such as reduction in symptoms, cosmetic appearance or quality of life.

Specialist Advisers' opinions

Specialist advice was sought from consultants who have been nominated or ratified by their Specialist Society or Royal College. The advice received is their individual opinion and does not represent the view of the society.

Professor Andrew Bradbury, Mr Jonathan Earnshaw, Mr Tim Lees (Vascular Society of Great Britain and Ireland).

- All three Advisers perform this procedure regularly and consider it to be established practice and no longer new. All three have undertaken bibliographic research and two have undertaken clinical research on this procedure.
- The Advisers agreed that between one third and one half of all specialists perform this procedure.
- The main comparator to this procedure is surgery but radiofrequency and laser ablation are also used.
- All Advisers state that training and/or mentoring is required for this procedure, particularly when learning to cannulate veins under ultrasound imaging and using a duplex scanner.
- One Adviser stated that there is current controversy around this procedure and that there are issues relating to private insurance.

Efficacy

- The Advisers considered key efficacy outcomes to include target presence of varicose veins, vessel occlusion at 1 week, 6 months and 5 years, abolition of venous reflux, recurrence, number of treatments required, disease-specific and general quality of life improvements.
- The Advisers all agreed that long-term data on recurrence rates from RCTs show that this procedure is better than conventional surgery. One Adviser highlights that this is because the procedure is still relatively new and that other newer comparators, radiofrequency and laser ablation, also lack longer-term follow-up (longer than 2 or 3 years). Two Advisers suspect that effectiveness will not be different than for conventional surgery.
- Another Adviser states that variation in occlusion rates may be dependent on technique and experience.

Safety

- The Specialist Advisers stated that anecdotal events include skin pigmentation, and, rarely, skin ulceration, visual disturbance and migraine. Other anecdotal events include superficial thrombophlebitis, and deep vein thrombosis (although rare and stated by one Adviser to occur less frequently than with surgery).
- Two Advisers noted that there had been one case report of stroke and another of other neurological problems in two patients. They commented that this must be viewed in the context of the large number of treatments given and the relatively higher volumes of foam used in these patients.
- All Advisers noted the disagreement about the cause of the visual disturbances. The cause has been theorised to be from migrating microbubbles travelling out of the superficial venous system. Two Advisers noted that most symptoms disappear within 30 minutes, suggesting that they are not occlusive and are likely to be due to nitrogen from the air injection. Another Adviser highlighted the uncertainty about whether visual disturbance only occurs in patients with a patent foramen ovale.

- An Adviser noted that the incidence of stroke among all reported cases is extremely low and no higher than the incidence of other serious complications in other procedures used to treat varicose veins.
- They stated that additional theoretical adverse events include arterial thrombosis and allergic reaction.

Patient Commentators' opinions

NICE's Patient and Public Involvement Programme sent questionnaires to six trusts for distribution to patients who had the procedure (or their carers). NICE received no completed questionnaires.

Issues for consideration by IPAC

- The Advisers noted that the National Collaborating Centre for Health Technology Assessment have commissioned an RCT comparing foam sclerotherapy (with and without endovenous laser ablation) with standard surgery. This started in June 2008 at the University of Aberdeen with an expected publication in mid 2012 (<http://www.hta.ac.uk/1728>).
- The European Consensus on Foam Sclerotherapy was updated in 2008².
- There have been two case reports of allergic reaction to foam since the systematic review was completed (the review did not report any cases of allergic reaction). Both of these case reports occurred in patients treated with sodium tetradecyl sulfate (both at 1% and 3% concentrations).
- Whether a higher concentration of foam will increase the risk of adverse events.
- A number of foam sclerosant products are licensed for use in the UK.

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Appendix A: Additional papers on ultrasound-guided foam sclerotherapy for varicose veins

The following table outlines the studies that are considered potentially relevant to the overview but were not included in the main data extraction table (table 2). It is by no means an exhaustive list of potentially relevant studies.

| Article | Number of patients/follow-up | Direction of conclusions | Reasons for non-inclusion in table 2 |
|--|---|--|--|
| Abela A, Liamis A, Prionidis I et al. (2008) Reverse foam sclerotherapy of the great saphenous vein with sapheno-femoral ligation compared to standard and invagination stripping: a prospective clinical series. <i>European Journal of Vascular & Endovascular Surgery</i> 36: 485–90 | RCT n = 82 (90 limbs) (SFJ ligation plus reverse foam sclerotherapy [group 1], standard stripping [group 2] or invagination stripping of the GSV [group 3]) follow-up: 3 weeks | Significantly less blood loss, bruising and postoperative discomfort than stripping techniques in group 1 (foam) ($p < 0.001$). 26/27 of those treated by foam had complete destruction of the GSV at 15-day follow-up (one was patent because of incompetent perforators at the knee). No clinically detected adverse events postoperatively or at follow-up. | Studies with longer follow-up of efficacy are included in table 2. No significantly new serious safety concerns. |
| Bergan J, Cheng V (2007) Foam sclerotherapy of venous malformations. <i>Phlebology</i> 22: 299–302 | Case series n = 14 mean follow-up: 36 months | Pain-free healing in 3 patients with non-healing, painful ulcerations. Cosmetic improvement in 11 patients in the follow-up. One complication of cutaneous ulcer following injection for reticular telangiectasias. | Studies with longer follow-up of efficacy are included in table 2. No significantly new serious safety concerns. |
| Ceulen RPM, Bullens-Goessens IJM, Pi-van de Venne SJ et al. (2007) Outcomes and side effects of duplex-guided sclerotherapy in the treatment of great saphenous veins with 1% versus 3% polidocanol foam: results of a randomized controlled trial with 1-year follow-up. <i>Dermatologic Surgery</i> 33: 276–81 | RCT n = 80 follow-up: 1 year | 69.5% in 1% foam group had occlusion of treated GSV and 80.1% in 3% foam group (but not significant). 32.1% in 1% group and 50% in 3% group had thrombophlebitis (most cases resolved at 1 year). No serious adverse events (such as DVT). In 3% group, there was a pulmonary embolism 4 weeks after therapy (successfully treated with anticoagulants; after ultrasound investigation, no relationship was | Studies with longer follow-up of efficacy are included in table 2. No significantly new serious safety concerns. |

| | | | |
|---|---|--|--|
| | | found between the pulmonary embolism and the foam treatment). | |
| Creton D, Uhl JF (2007) Foam sclerotherapy combined with surgical treatment for recurrent varicose veins: short term results. <i>European Journal of Vascular & Endovascular Surgery</i> 33: 619–24 | Case series n = 129 limbs follow-up: 40 days | 93% (123) of patients showed complete destruction of saphenous trunks, junctions and varices. Two asymptomatic DVTs were detected 3 days after surgery. | Studies with longer follow-up of efficacy are included in table 2. No significantly new serious safety concerns. |
| Darke SG, Baker SJ (2006) Ultrasound-guided foam sclerotherapy for the treatment of varicose veins. <i>British Journal of Surgery</i> 93: 969–74 | Case series n = 192 (4 lost to follow-up) follow-up: 6 weeks | 163 had immediate occlusion after one intervention; 32 after two and 1 after a third ^t intervention (overall 91%). 2 transient visual disturbances for 5 min; 1 case of chest discomfort (all 3 received 1% POL); 1 further visual disturbance, probably a migraine; 1 ulcer in the thigh which healed within a few weeks on warfarin therapy. | Studies with longer follow-up of efficacy are included in table 2. No significantly new serious safety concerns. |
| Gonzalez-Zeh R, Armisen R, Barahona S (2008) Endovenous laser and echo-guided foam ablation in great saphenous vein reflux: one-year follow-up results. <i>Journal of Vascular Surgery</i> 48: 940–6 | Non-randomised controlled trial n = 53 foam, 45 laser follow-up: 1 year | Occlusion of GSV at 1 year in 77% (41/53) in foam group and 93% (42/45) in laser group. Procedure-related pain was higher in laser group. | Studies with longer follow-up of efficacy are included in table 2. No significantly new serious safety concerns. |
| Hahn M, Schulz T, Junger M (2007) Sonographically guided, transcatheter foam sclerotherapy of the great saphenous vein: medical and economic aspects. <i>Phlebologie</i> 36: 309–12 | Case series n = 20 follow-up: 1 year | After 1 year, reflux in the saphenofemoral junction in 7 patients (32%) (and 1 recurrent GSV varicosis). 4 cases of bruising, no venous thrombosis, headache or neurological complications, 1 local inflammation | Studies with longer follow-up of efficacy are included in table 2. No significantly new serious safety concerns. |
| Hertzman PA, Owens R (2006) Rapid healing of chronic venous ulcers following ultrasound-guided foam sclerotherapy. <i>Phlebology</i> 22: 34–9 | Case series n = 9 follow-up: 1 week | | This was for treating venous ulcers (not varicose veins); no safety events introduced. |
| Kalodiki E, Azzam M, Geroulakos G (2006) Trichophyia and hypertrichosis: a side | Case report n = 1 follow-up: 9 months later | Case report of hypertrichosis 9 months following surgery. | Not considered a serious safety event. |

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| effect of foam sclerotherapy. Journal of Vascular Surgery 44: 1377 | | | |
| Kolbel T, Hinchliffe RJ, Lindblad B (2007) Catheter-directed foam sclerotherapy of axial saphenous reflux: early results. Phlebology 22: 219–22 | Case series n = 53 follow-up: 1 week | Delivery of foam along the length of veins in 94% (50/53) of limbs. All GSVs were blocked at 1 week. 3 thrombophlebitis; no DVT; 1 pulmonary embolism (uneventful recovery following heparin treatment; patient had suffered DVT 40 years previously). | Studies with longer follow-up of efficacy are included in table 2. No significantly new serious safety concerns. |
| Luebke T, Brunkwall J (2008) Systematic review and meta-analysis of endovenous radiofrequency obliteration, endovenous laser therapy, and foam sclerotherapy for primary varicosis. Journal of Cardiovascular Surgery 49: 213–33 | Systematic review including 22 trials on foam sclerotherapy Follow-up:= usually more than 30 days (in four studies, more than 3 years) | No anaphylaxis; 1 pulmonary embolism from 6 studies (1/1753); 58/9294 visual disturbance in 11 studies; 4/611 transient confusion in 3 studies; 57/7122 headaches in 3 studies; 23/9740 DVTs in 14 studies; 8/7221 cutaneous necroses in 6 studies. | No significantly new information from NICE-commissioned systematic review. |
| Myers KA, Jolley D (2008) Factors affecting the risk of deep venous occlusion after ultrasound-guided sclerotherapy for varicose veins. European Journal of Vascular & Endovascular Surgery 36: 602–5 | Case series n = 852 (1931 treatment sessions) follow-up: 3 and 7 days | DVT was observed after 28 treatment sessions. | No significantly new safety data. |
| Nael R, Rathbun S, Kirkpatrick A, Whitsett T (2007) Effectiveness of endovenous foam sclerotherapy for treatment of varicose veins. Vascular Medicine 12: 154 [abstract] | Case series published as an abstract n = 156 follow-up:= ranging from 2 weeks to 2 years | 6 patients with thrombophlebitis; 3 with calf-vein thrombosis; 4 with transient neurological symptoms; 2 with chest tightness; 5 with trapped anticoagulum requiring aspiration; 1 with skin necrosis. | No significantly new serious safety concerns. |
| Nitecki S, Bass A. (2007) Ultrasound-guided foam sclerotherapy in patients with Klippel-Trenaunay syndrome. Israel Medical Association Journal: Imaj 9: 72–5 | Case series n = 7 | No major complications. All seven patients reported improvement in signs and symptoms. Five of the 7 patients (71%) were very satisfied with the cosmetic result. | Small numbers, no new safety data. |
| O'Hare, Parkin D, Vandebroek CP, | Case series n = 165 (185 veins) | At 6 months, truncal vein remained blocked in | Studies with longer follow-up of efficacy are |

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| Earnshaw JJ (2008) Mid term results of ultrasound guided foam sclerotherapy for complicated and uncomplicated varicose veins. <i>European Journal of Vascular & Endovascular Surgery</i> 36: 109–13 | follow-up: 6 months | 74% (68/92), partially blocked in 10% (9/92) and fully patent in 16% (15/92). No DVT but 10% (9) had de novo segmental deep venous reflux. | included in table 2. No significantly new serious safety concerns. |
| Pascarella L, Bergan JJ, Mekenas LV (2006) Severe chronic venous insufficiency treated by foamed sclerosant. <i>Annals of Vascular Surgery</i> 20: 83–91 | Case series n = 44 (60 limbs) (group 1: compression, group 2: failed compression had foam, group 3: foam) follow-up: up to 30 days | Limbs treated with foam had significantly better outcome than those without foam. | Studies with longer follow-up of efficacy are included in table 2. No significantly new serious safety concerns. |
| Rabe E, Otto J, Schliephake D, Pannier F (2008) Efficacy and safety of great saphenous vein sclerotherapy using standardised polidocanol foam (ESAF): a randomised controlled multicentre clinical trial. <i>European Journal of Vascular & Endovascular Surgery</i> 35: 238–45 | Multicentre RCT n = 106 follow-up: 3 months | 69% elimination of reflux in foam and 27% with liquid (rate of reflux elimination varied between centres: 96% at 6 centres and 39% at 4 centres). Reported adverse drug reactions (not otherwise defined) in 39 patients, 17 from foam and 22 from liquid group. | Studies with longer follow-up of efficacy are included in table 2. |
| Ragg JC (2007) Contrast-controlled microfoam sclerotherapy as an alternative surgery of recurrent saphenous veins reflux. <i>The American Journal of Cardiology</i> . TCT Abstracts: 203L. | Case series n = 98 follow-up: 12 months | Abstract stating no serious adverse events or DVT. | No significantly new serious safety concerns. |
| Shadid N, Frank J, Sommer A (2008) Superficial thrombophlebitis of the venous dorsal arch of the foot and deep venous thrombosis after foam sclerotherapy. <i>International Journal of Dermatology</i> 47 (Suppl 31) | Case report n = 1 | DVT occurring 6 weeks after treatment with 4 ml 3% POL foam. This followed a diagnosis of superficial thrombophlebitis. | This event has been reported in the literature. |
| Subramonia, Lees TA (2007) The treatment of varicose veins. <i>Annals of the Royal College of Surgeons of England</i> 89: 96–100 | Systematic review | 80–90% occlusions remained at 3-year follow-up | Has not introduced information not already included in the NICE-commissioned systematic review. |
| Uuorto I, Hannukainen J, Aarnio P (2007) Single-center experience with foam sclerotherapy | Case series n = 25 (27 legs) follow-up = 3 months | 66% had postoperative thrombophlebitis. At 3 months, saphenofemoral reflux | Studies with longer follow-up of efficacy are included in table 2. No new serious safety |

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| without ultrasound guidance for treatment of varicose veins. Dermatologic Surgery 33: 1334–9 | | occurred in 63% and saphenopopliteal reflux in 40%. | concerns. |
| van Neer P, Veraart JC, Neumann H (2006) Posterolateral thigh perforator varicosities in 12 patients: a normal deep venous system and successful treatment with ultrasound-guided sclerotherapy. Dermatologic Surgery 32: 1346–52 | Case series n = 12 | No DVT. Posterolateral thigh perforator diameter reduced from mean 4.06 mm to 1.97 mm. | Studies with larger numbers included in table 2. No new safety data reported. |
| Yamaki T, Nozaki M, Sakurai H et al. (2008) Prospective randomized efficacy of ultrasound-guided foam sclerotherapy compared with ultrasound-guided liquid sclerotherapy in the treatment of symptomatic venous malformations. Journal of Vascular Surgery 47: 578–84 | RCT n = 89 follow-up = 6 months | No major complications. Proportion of venous malformations that had disappeared was significantly higher in the foam group than the liquid group. | Studies with longer follow-up of efficacy are included in table 2. No significantly new serious safety concerns. |

Appendix B: Related NICE guidance for ultrasound-guided foam sclerotherapy for varicose veins

| Guidance | Recommendations |
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| Interventional procedures | <p>Ultrasound-guided foam sclerotherapy for varicose veins. NICE interventional procedures guidance 217 (2007) (this was an update of IPG182 published in June 2006)</p> <p>1.1 Current evidence on ultrasound-guided foam sclerotherapy for varicose veins shows that it is efficacious in the short term. The evidence on safety includes transient side effects in a small proportion of patients such that the procedure should be used with special arrangements for consent, and for audit or research.</p> <p>1.2 Clinicians wishing to undertake ultrasound-guided foam sclerotherapy for varicose veins should take the following actions.</p> <ul style="list-style-type: none"> • Inform the clinical governance leads in their Trusts. • Patients should be fully informed of the potential side effects associated with the procedure. Clinicians should provide patients with clear written information including other treatment options. In addition, use of the Institute's information for patients ('Understanding NICE guidance') is recommended (available from www.nice.org.uk/IPG244apublicinfo). • Audit and review clinical outcomes of all patients having ultrasound-guided foam sclerotherapy for varicose veins (see section 3.1). <p>1.3 The procedure should only be undertaken using pharmaceuticals licensed for sclerotherapy of varicose veins. Current practice includes mixing of liquid sclerosant with air with the intention of improving efficacy, and this constitutes off-label use.</p> <p>1.4 Current evidence of long-term efficacy is limited and clinicians are encouraged to collect longer-term follow-up data.</p> <p><i>Efficacy</i></p> <p>2.3.1 A systematic review of the published evidence on these procedures was commissioned by the Institute. A total of 67 studies were reviewed including nine randomised controlled trials, one registry report, eight non-randomised comparative studies, 43 case series and six case reports.</p> <p>2.3.2 Across the randomised controlled trials, the median rate of successful venous occlusion was 84% (range 67–94%), with rates greater than 60% across all studies. Meta-analysis of five randomised controlled trials, three comparing foam (n = 274) with liquid sclerotherapy (n = 266) and two comparing foam sclerotherapy (n = 207) with surgery (stripping) (n = 117) did not</p> |

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| | <p>identify significant efficacy differences between foam sclerotherapy and the two comparator treatments. The relative likelihood of complete occlusion was 1.39 (95% CI 0.91–2.11) in favour of foam over liquid sclerotherapy, and 0.86 (95% 0.67–1.10) in favour of surgery over foam sclerotherapy. Neither of these was considered significant.</p> <p>2.3.3 The rates of varicose vein recurrence and development of new veins varied across the studies, ranging from 1–15% of patients at follow-up intervals ranging from six weeks to six years. In one randomised controlled trial with a ten year follow-up, recurrence was 51%.</p> <p><i>Safety</i></p> <p>2.4.1 Adverse events reported after foam sclerotherapy included skin pigmentation, thrombophlebitis and thrombosis; chest tightness, visual disturbance, backache, confusion and migraine were also reported.</p> <p>2.4.2 Skin pigmentation occurred at a median rate of 32% in four randomised controlled trials (n = 517) at up to a year follow-up. Cutaneous necrosis occurred at a median rate of 1.3% in four case series (n = 781) at up to a year follow-up. The occurrence of local neurological injury was less than 1% across all studies. Other complications including allergic reaction, haematoma, extravasation and lower back pain occurred at a median of 4.2% in four randomised controlled trials (n = 511).</p> <p>2.4.3 Rates of visual disturbance following foam sclerotherapy ranged from 0–6%. None lasted for longer than two hours and no long-term or permanent visual impairment was reported. Headache occurred at various rates across the studies ranging from 0–23% at 60 day follow-up. Transient confusion occurred at a median rate of 0.5% (range 0–1.2%). Other complications reported included coughing, chest tightness/heaviness, panic attack, malaise and vasovagal fainting occurring at a rate of 0–3%.</p> <p>2.4.4 In a case series of 89 patients there was one report of a patient suffering a stroke following foam sclerotherapy. One case of myocardial infarction and an epileptic event were also reported (unpublished).</p> <p>2.4.5 In a case series of 290 patients, there was a single report of a patient developing a pulmonary embolism 4 months after treatment. Arterial events including deep vein thrombosis (DVT) occurred at rates of 0–6%. In 13 case series (n = 2828) there were 11 reports of DVT (a median rate of 0.4%).</p> <p><i>Other comments</i></p> <p>2.5.1 The volume and concentration of foam varied among the studies, and it is unclear whether these factors influenced efficacy outcomes and/or the rate of reported complications.</p> <p>2.5.2 Currently, only liquid sclerosants (not mixed with air or gas) are licensed for the treatment of varicose veins. It was noted that there was insufficient evidence to draw conclusions on the relative</p> |
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| | <p>safety of different types and strengths of sclerosing agents, volume of foam and foam-producing techniques.</p> <p>Radiofrequency ablation for varicose veins. NICE interventional procedures guidance 8 (2003)</p> <p>1.1 Current evidence on the safety and efficacy of radiofrequency ablation of varicose veins appears adequate to support the use of this procedure as an alternative to saphenofemoral ligation and stripping, provided that the normal arrangements are in place for consent, audit and clinical governance.</p> <p>Transilluminated powered phlebectomy for varicose veins. NICE interventional procedures guidance 37 (2004)</p> <p>1.1 Current evidence on the safety and efficacy of transilluminated powered phlebectomy for varicose veins includes small numbers of patients and is of limited quality. It does not appear adequate to support the use of this procedure without special arrangements for consent and for audit or research. Clinicians wishing to undertake transilluminated powered phlebectomy for varicose veins should inform the clinical governance leads in their Trusts. They should ensure that patients offered it understand the uncertainty about the procedure's safety and efficacy and should provide them with clear written information. Use of the Institute's Information for the Public is recommended. Clinicians should ensure that appropriate arrangements are in place for audit or research. Publication of safety and efficacy outcomes will be useful in reducing the current uncertainty. NICE is not undertaking further investigation at present.</p> |
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Appendix C: Literature search for ultrasound-guided foam sclerotherapy for varicose veins

| Database | Date searched | Version/files | No. retrieved |
|---|---------------|------------------------------|---------------|
| Cochrane Database of Systematic Reviews – CDSR (Cochrane Library) | 09/12/2008 | Issue 4, 2008 | 1 |
| Database of Abstracts of Reviews of Effects – DARE (CRD website) | 09/12/2008 | N/A | 2 |
| HTA database (CRD website) | 09/12/2008 | N/A | 0 |
| Cochrane Central Database of Controlled Trials – CENTRAL (Cochrane Library) | 09/12/2008 | Issue 4, 2008 | 4 |
| MEDLINE (Ovid) | 09/12/2008 | 1950 to November Week 3 2008 | 27 |
| MEDLINE In-Process (Ovid) | 09/12/2008 | December 08, 2008 | 17 |
| EMBASE (Ovid) | 09/12/2008 | 1980 to 2008 Week 49 | 41 |

The following search strategy was used to identify papers in MEDLINE. A similar strategy was used to identify papers in other databases.

| | | |
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| 1 | Telangiectasis/ | 6556 |
| 2 | Venous Insufficiency/ use mesz | 4517 |
| 3 | exp vein insufficiency/ use emez | 4034 |
| 4 | ((venous or vein?) adj3 (incomp\$ or insuffic\$)).tw. | 7902 |
| 5 | ((venous or vein?) adj3 ulcer\$).tw. | 4856 |
| 6 | telangiect\$.tw. | 14640 |
| 7 | ((reticular or thread or spider) adj3 (vein? or venous)).tw. | 275 |
| 8 | or/1-7 | 32837 |
| 9 | exp Lower Extremity/ use mesz | 108141 |
| 10 | exp leg/ use emez | 46869 |

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| 11 | (lower limb\$ or lower extremit\$ or leg? or calf or valves or thigh?).tw. | 289299 |
| 12 | or/9-11 | 390363 |
| 13 | 8 and 12 | 8948 |
| 14 | saphenous vein/ | 16819 |
| 15 | ((saphenous or perforator) adj3 (vein? or incompet\$ or insuffic\$)).tw. | 19195 |
| 16 | exp varicose veins/ use mesz | 13459 |
| 17 | varicosis/ or leg varicosis/ use emez | 6774 |
| 18 | (varicos\$ adj3 vein?).tw. | 7889 |
| 19 | or/13-18 | 49433 |
| 20 | Sclerotherapy/ | 7968 |
| 21 | Sclerosing Solutions/ | 5498 |
| 22 | (sclerotherap\$ or sclerosing\$ or sclerosant\$).tw. | 26831 |
| 23 | or/20-22 | 31525 |
| 24 | 9002-92-0.m. | 2949 |
| 25 | sodium tetradecyl sulfate.tw. | 325 |
| 26 | sodium tetradecyl sulphate.tw. | 89 |
| 27 | hypertonic saline.tw. | 7101 |
| 28 | ethanolamine oleate.tw. | 444 |
| 29 | 3282-75-5.m. | 222 |
| 30 | 2272-11-9.m. | 644 |
| 31 | (polydocanol or polidocanol).tw. | 893 |
| 32 | sodium morrhuate.tw. | 200 |
| 33 | 8031-09-2.m. | 488 |
| 34 | sotradecol.tw. | 164 |
| 35 | 1191-50-0.m. | 1094 |
| 36 | (aet?oxysclerol or aethoxyskerol).tw. | 191 |

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| 37 | or/24-36 | 12198 |
| 38 | foam/ use emez | 1469 |
| 39 | (foam\$ or microfoam\$).tw. | 22329 |
| 40 | (tessari or monfreux or double syringe).tw. | 69 |
| 41 | or/38-40 | 22556 |
| 42 | 41 and (19 or 23 or 37) | 594 |
| 43 | varisolve.tw. | 9 |
| 44 | 42 or 43 | 595 |
| 45 | 19 and (23 or 37) | 3196 |
| 46 | ae.fs. | 1551162 |
| 47 | exp Venous Thrombosis/ | 78485 |
| 48 | exp embolism/ | 83165 |
| 49 | Ischemic Attack, Transient/ | 25366 |
| 50 | cerebrovascular accident/ | 51814 |
| 51 | exp Migraine Disorders/ use mesz | 18612 |
| 52 | exp migraine/ use emez | 20770 |
| 53 | (dvt or thrombo\$ or embolism).tw. | 414279 |
| 54 | isch?em\$.tw. | 385043 |
| 55 | stroke?.tw. | 184782 |
| 56 | migraine?.tw. | 36125 |
| 57 | (visual or vision).tw. | 408354 |
| 58 | or/46-57 | 2798995 |
| 59 | 45 and 58 | 968 |
| 60 | 44 or 59 | 1413 |
| 61 | remove duplicates from 60 | 1096 |
| 62 | 200807*.ed. | 63324 |
| 63 | 200808*.ed. | 81735 |

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| 64 | 200809*.ed. | 66715 |
| 65 | 200810*.ed. | 89884 |
| 66 | 200811*.ed. | 42328 |
| 67 | 200812*.ed. | 0 |
| 68 | or/62-67 | 343986 |
| 69 | 2008*.em. | 1294319 |
| 70 | from 61 keep 1-17 | 17 |
| 71 | from 61 keep 18-696 | 679 |
| 72 | from 61 keep 697-1096 | 400 |
| 73 | 71 and 68 | 27 |
| 74 | 72 and 69 | 41 |