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(1) Title: Systematic review of the safety and efficacy of foam sclerotherapy for venous disease of the lower limbs

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Running title: Foam sclerotherapy for venous disease of the lower limbs

Abstract

Background: Foam sclerotherapy is a potential treatment for lower limb venous disease.

Methods: A systematic review, with no restriction on study design, to assess the safety and efficacy of foam sclerotherapy.

Results: 69 studies were included. For serious adverse events including pulmonary embolism and deep vein thrombosis, the median event rates were less than 1%. Median rate for visual disturbance was 1.4%. Median rates for some other adverse events were more common, including headache (4.2%), thrombophlebitis (4.7%), matting/skin staining/pigmentation (17.8%) and pain at the site of injection (25.6%). Median rate for complete occlusion of treated veins was 87.0% and for recurrence or development of new veins was 8.1%. Evidence from meta-analysis for complete occlusion suggests that foam sclerotherapy is associated with a lower rate compared with surgery (RR 0.86, 95% CI 0.67 to 1.10) and a higher rate compared with liquid sclerotherapy (RR 1.39, 95% CI 0.91 to 2.11). However, there was substantial heterogeneity across the studies in the meta-analysis.

Conclusion: Serious adverse events were rare. There is insufficient evidence to reliably compare the effectiveness of foam sclerotherapy with other minimally invasive therapies or surgery. Evidence from high quality randomised controlled trials is required

Introduction

Venous disease of the lower limbs includes varicose veins, reticular veins, telangiectasiae and all of the skin changes of advanced venous dysfunction including oedema, eczema, pigmentation, lipodermatosclerosis and ulceration. Current treatment options include compression hosiery, endovenous laser ablation treatment, radiofrequency ablation, open surgery (ligation, stripping and phlebectomies), and subfascial endoscopic perforator surgery alone or in combination, and sclerotherapy, which is mostly carried out as an outpatient procedure with no anaesthesia required. Sclerotherapy techniques in current use are liquid and foam sclerotherapy. Liquid sclerotherapy involves the injection of sclerosing liquid into affected veins leading to an inflammatory reaction and consequent venous occlusion[1]. Foam sclerotherapy is a modification of liquid sclerotherapy but instead of injecting liquid, the liquid is transformed into foam by forcibly mixing it with air[2-4] or other type of gas such as oxygen or carbon dioxide.

Foam sclerotherapy may be a potential treatment for all categories of venous disease, although currently, its use in the UK is 'off licence'. Anaphylaxis, vascular events such as cerebrovascular accident, myocardial infarction, and thromboembolism are serious potential complications of foam sclerotherapy. Other adverse events associated with foam sclerotherapy include transient visual disturbance, cutaneous necrosis or ulceration, and local effects such as 'minor' vein thrombosis, thrombophlebitis, local neurological injury, and skin pigmentation.

The objective of this study was to systematically review the safety and efficacy of foam sclerotherapy for treating venous disease of the lower limbs.

Methods

Search strategy

Extensive electronic searches were conducted to identify reports of published, unpublished and ongoing studies and included abstracts from conference proceedings and other grey literature sources. There were no restrictions in terms of language or publication year. The search strategies were designed to be highly sensitive, including both appropriate subject heading and text word terms. Full details of the search strategies used are available from the authors. Databases searched included Medline (1966 – May Week 2 2006), Embase (1980 – Week 20 2006), Medline in-process (23rd May 2006), Biosis (1969 – 19th May 2006), Science Citation Index (1981 – 20th May 2006), ISI proceedings (1990-23rd June 2006), Cochrane Controlled Trials Register (The Cochrane Library, Issue 2, 2006), Conference Papers Index (2000- June 2006), Cochrane Database of Systematic Reviews (The Cochrane Library, Issue 2, 2006), Database of Abstracts of Reviews of Effectiveness (April 2006), HTA Database (April 2006), National Research Register (Issue 2, 2006), Clinical Trials (June 2006) and Current Controlled Trials (June 2006). Electronic and hand searching of conference proceedings of phlebology and vascular organisations was undertaken. The table of contents of two phlebology journals (Phlebologie (1970-2005) and Australasian Journal of Phlebology (1999-2004)), not consistently indexed in the major databases, were also checked. Relevant professional and commercial websites were searched and the reference lists of all included studies were scanned.

Inclusion and exclusion criteria

Randomised controlled trials (RCTs), non-randomised comparative studies (NRCS), case series, case reports, and prospective population-based registry reports of foam

sclerotherapy for treating venous disease of the lower limbs in adults aged 16 years and above were sought. Treatment of cutaneous venous malformations was excluded.

Safety outcomes were classified into serious adverse events and adverse events. Serious adverse events assessed included anaphylaxis, arterial events, venous thromboembolism, cutaneous necrosis and ulceration, and other serious adverse events such as epileptic fits; adverse events included visual disturbance, central nervous system disturbance (such as confusion, migraine and other type of headache), other systemic symptoms (such as coughing, chest tightness, and vasovagal), local effects (such as 'minor' vein thrombosis, thrombophlebitis, matting/skin staining/pigmentation, local neurological injury, pain provoked on injection and pain persisting at the sclerosed area), and other adverse events (such as allergic reaction (local or systemic) and haematoma).

Efficacy outcomes assessed included complete occlusion of treated veins, healing of venous ulceration, recurrence of varicose veins and development of new veins, quality of life (such as time to return to normal activity, patient satisfaction, symptom relief, and change of venous disease severity measured by Venous Clinical Severity Score[5]) and procedure time. For quality of life and procedure time only outcomes from comparative studies were considered.

Complete occlusion of treated veins included outcomes reported as complete venous occlusion, elimination of reflux (if complete venous occlusion was not reported) and success rate (if complete venous occlusion or elimination of reflux were not reported). Veins remaining patent, partial occlusion, partial occlusion with minimal retrograde flow, and having residual segments not occluded were classed as treatment failure.

Where data were available, immediate (≤24 hours), short-term (≤30 days) and longer-term (>30 days) adverse events, and short-term (≤30 days) and longer-term (>30 days) efficacy were assessed. Where data on longer-term outcomes were reported for several time points later than 30 days then the data for the longest follow-up period was used.

Quality assessment

Two reviewers independently assessed the quality of the included English language full text studies. Any disagreements were resolved by consensus or arbitration by a third party.

Data analysis

Median event rates (and ranges) were tabulated by study design. Studies reporting the number of limbs or veins but not patient level data (22 studies) were not included when calculating the medians and ranges but were reported separately.

A random effects meta-analysis of RCTs was conducted to compare foam versus liquid sclerotherapy and foam sclerotherapy versus surgery where two or more studies were available. Within-patient studies were not considered. Review Manager (RevMan 4.2.8) software was used. We assessed heterogeneity between studies using the I-squared statistic.

Results

Number, type and quality of included studies

69 studies[6-73] (in 104 reports) were included (***Table 1,*** available on BJS website). 28 of the included studies were English full text studies[6-31] (eight RCTs[6-12], one registry[13], one non-randomised comparative study[14], 14 case series[15-27] and four case reports[28-31]). 24 studies were English conference abstracts[32-56] (two RCTs[32,33], five non-randomised comparative studies[34-38] and 17 case series[39-56]). 16 studies were non-English full text studies or conference abstracts[57-72] (two non-randomised comparative studies[57,58], 13 case series[59-71] and one case report[72]). One study was unpublished[73]. The follow-up time of eight studies was over three years[7,17,18,25,37,38,45,53]. The sample size in 36 studies was over 100[6,7,10,12,13,15-19,21,22,25,32,34,35,38,39,46,49,50,52-55,58-60,62-67,70,71]. ***Figure 1*** shows the screening process.

In the included studies over 9000 patients were treated with foam sclerotherapy. The most common indications for foam sclerotherapy were truncal vein (great and/or small saphenous vein) incompetence or varicosities. The most frequently used sclerosing agent was polidocanol, with a strength ranging from 0.25 to 3%. The most commonly used foam-producing technique was the Tessari technique, in which two syringes are connected by a three-way valve and fluid sclerosant is forcibly mixed with air and frothed into foam by a pumping action. Most studies used ultrasound guidance for identifying treated veins and monitoring foam injection and/or foam flow. ***Table 2*** (available on BJS website) shows the demographic details and indication for treatment for the included English language full text studies and studies in English language conference abstracts (these data were not extracted for non-English language studies).

The methodological quality of the included RCTs was generally low. The treatment allocation was adequately concealed in only one of seven RCTs[7] and three studies conducted an intention to treat analysis[7,9,11]. The methodological quality of conference abstracts and non-English language studies was not assessed. The sample sizes of most studies were more than 100. Length of follow-up in most studies, irrespective of study design, was more than 30 days. No studies reported methods of follow-up. The completeness of follow-up ranged from 70 to 100%.

Safety

Serious adverse events

Table 3 summarises the serious adverse events associated with foam sclerotherapy. In the included studies serious adverse events associated with foam sclerotherapy occurred in 0 to 5.7% of treatments. Studies including anaphylaxis[13,21,26] or intra-arterial injections[13,66] as outcomes reported that no events occurred. Although no arterial events occurred in a single large case series[21] involving 808 patients, they did occur, at a median rate of 2.1% (range 1.4 to 2.8) in two conference abstracts[39,43] involving 253 patients. The events were reported as stroke (n=1, for details see below)[43] and transient 'embolic' events (no details provided)[39]. Five English language case series[16-18,20,23] involving 1316 patients reported one patient suffering a pulmonary embolism. Deep vein thrombosis occurred at a rate of 0.02% in the French registry[13] and at a median rate of 0.6% (range 0 to 5.7%) in 25 other studies[8,10,12,16-24,26,35,40,42,46,49,55,60,63,65,71]. Cutaneous necrosis occurred at a median rate of 1.3% (range 0.3 to 2.6%) in four English language case series[16,22-24] involving 781 patients and at a median rate of 0% (range 0 to 0.2%) in five studies available as conference abstracts[50,56] or non-English language studies[57,61,71] and involving 766 patients. No

cutaneous ulceration occurred in three English language studies[8,10,26] reporting on this outcome, although one small non-English language study[69] involving 28 patients reported an event.

The stroke reported in the case series[43] was further detailed in a case report[44]. This occurred in a 61 year old man who underwent foam sclerotherapy to the great saphenous vein. The patient was reported as having fully recovered. A carotid duplex scan, performed immediately, showed normal arteries with rapidly moving echogenic particles within the left carotid lumen. This was similar to the duplex appearance of foam in the great saphenous vein. A transoesophageal echocardiogram revealed an 18 mm Patent Foramen Ovale (PFO) with an associated atrial septal aneurysm. A right-to-left shunt was demonstrated with a colour flow duplex scan and the bubble test on the transoesophageal echocardiogram.

An unpublished case report[73] recorded one case of myocardial infarction occurring 30 minutes following injection. This occurred in a 70 year old, otherwise healthy woman who underwent foam sclerotherapy to the incompetent left great saphenous vein. An echocardiogram (type of echocardiogram not specified) showed no right-to-left shunt. The patient had reported scotomas following a previous treatment.

A grand mal epileptic fit was reported in an unpublished case report[73]. Forty minutes after injection, a 70 year old man experienced scintillating scotomas, followed by confusion, stupor, and then a grand mal seizure. Subsequent investigations found no evidence of myocardial infarction, cardiovascular accident, septal defects (right-to-left shunt), deep vein thrombosis, pulmonary embolism or sepsis. It was unclear whether he had a history of epilepsy.

Adverse events

Table 4 summarises the adverse events associated with foam sclerotherapy.

Visual disturbance occurred at rate of 0.3% in the French registry[13] and a median rate of 1.4% (range 0 to 5.9%) in 14 other studies[10,16-23,27,35,58,66]. There were no reports of visual disturbance lasting longer than two hours or long-term or permanent visual impairment. Transient confusion occurred at a median rate of 0.5% (range 0 to 1.2%)[20,22,23]. Headache occurred at rate of 0% in the French registry and a median rate of 4.2% in four other studies[12,13,16,35]. Other systemic symptoms, including coughing, chest tightness/heaviness, panic attack and malaise, and vasovagal events ranged from 0 to 2.8%[13,16,17,19,22,24]. The French registry[13] reported a rate of 0.2% for coughing and vasovagal events.

'Minor' vein thrombosis occurred at a rate of 17.6% (9/51) in an English language RCT[10], 0.1% in the French registry[13], and a median rate of 1.2% (range 0 to 4.2%) in seven other studies[9,13,21,23,42,59,71]. Thrombophlebitis occurred at a rate of 45.8% (11/24) in a conference abstract[42], 0.05% in the French registry[13], and a median rate of 4.7% (range 0 to 25.0%) in 19 other studies[8-10,17,20-23,27,35,40,51,52,59,64-66,69,71].

Across studies, long-term (>30 days) matting/skin staining/pigmentation occurred at a median rate of 17.8% (range 0 to 66.7%). The median (range) rate was 31.6% (7.8 to 55.1%) in four English language RCTs[8,10,12] involving 517 patients, 2.3% (0 to 19.8%) in five English language case series[17,21-23,26] involving 759 patients, and 19.2% (in seven studies available as conference abstracts[34,42,51,52,56] or non-English language studies[57,66] involving 484 patients.

The occurrence of local neurological injury was less than 1% across all studies[8,13,16-17,21,23,26]. Pain provoked by injection or persisting in the limbs varied across studies[12,26,34,35,48,59,63] with a median rate of 25.6% (range 0.6 to 41.0%). Other

adverse events reported included allergic reaction, haematoma, extravasation, and lower back pain. Haematoma occurred at a rate of 11.2% (29/259) in an English language RCT[12] and the rates in seven other studies[8,9,12,19,23,58,63] reporting other adverse events ranged from 0% to 6.2%.

Comparative studies

In the comparative studies, the relative risks associated with foam sclerotherapy compared with other treatments for most adverse events did not reach statistical significance. However, in the French registry[13] the risk of visual disturbance was significantly higher for the foam compared with the liquid sclerotherapy group (relative risk 16.1; 95% CI 2.2-120.6).

In a meta-analysis of RCTs, the relative risk (RR) of two studies[8,12] comparing foam with surgery, involving stripping, for the outcome of skin pigmentation, was not significantly different (RR 2.02, 95% CI 0.42 to 9.86) (***Fig. 2***). There was substantial heterogeneity between studies.

Efficacy

The follow-up period of the majority of studies reporting efficacy was less than three years. ***Table 5*** summarises the efficacy outcomes.

Complete occlusion of treated veins and healing of venous ulcers

The median rate of venous occlusion was 84.4% (range 67.4 to 93.8%) in the English language RCTs[7-9,12] and 84.4% (60.0 to 98.2%) in the English language case series[19,20,25,26], with a median rate of 87.0% (range 60.0 to 98.2%) across all studies[7-

[9,12,14,19,20,25,26,32,35,38,40,48,50,53,54,59,63,64,66,70,71]. The median rate of ulcer healing was 80.5% (range 75.4 to 100%)[16-18,33].

In a meta-analysis of RCTs, the RR of three studies[7,9,32] comparing foam with liquid sclerotherapy for the outcome of complete occlusion of treated veins tended to favour foam sclerotherapy (RR 1.39, 95% CI 0.91 to 2.11) (***Fig. 3***), while the RR in two studies[8,12] comparing foam sclerotherapy with surgery involving stripping tended to favour surgery (RR 0.86, 95% CI 0.67 to 1.10) (***Fig. 3***). However neither result was statistically significant and both meta-analyses demonstrated high heterogeneity across studies.

Recurrence of venous disease and development of new veins

Across studies[7,9,14,17,25,32,48,51,54,59,63], the median rate of recurrence or development of new veins was 8.1% (range 10.1 to 27.8%). The highest rate was 51.2% which was reported in an RCT with a ten year follow-up[7].

In comparative studies, the risk of recurrence or development of new veins following foam sclerotherapy was not significantly different to that of comparator treatments[9,14], other than in the RCT[7] with the ten-year follow-up. In this study the risk of developing new veins was significantly higher for foam sclerotherapy compared with surgery (ligation only: RR 1.4, 95% CI 1.02 to 1.8; ligation combined with liquid sclerotherapy: RR 1.4, 95% CI 1.1 to 1.9).

Quality of life, disappearance of varicosities and changes of disease severity

One RCT[12] involving 272 patients reported that following foam sclerotherapy, patients required a median of two days to return to normal activity, significantly less than the 13 days following surgery. Compared with liquid sclerotherapy or surgery,

there were no statistically significant differences in patient satisfaction[6,10,38], disappearance of varicosities[10,11] and change of disease severity as measured by the Venous Clinical Severity Score[8]. The follow-up of the above studies ranged from one month to one year.

Procedure time and surgeon experience

Only one study[8] reported data on operation time (foam sclerotherapy plus ligation was 45 minutes versus 85 minutes for ligation plus stripping plus avulsion). The foam sclerotherapy was combined with sapheno-femoral junction ligation. Few studies reported surgeon experience.

On-going studies

Three ongoing comparative studies[63,74] (J Earnshaw, consultant Surgeon, Gloucestershire Royal Hospital) and two case series (K Darvall, Birmingham Heartlands Hospital; G Geroulakas, Ealing Hospital NHS Trust) were also identified. One RCT[74] with 450 patients and two-year follow-up comparing foam sclerotherapy with surgery is currently in progress in the Netherlands. Another RCT[63] with 158 patients and about two-year follow-up comparing 3% and 1% polidocanol foam is currently in progress in France. The sample sizes of the other three studies are all less than 200. The five ongoing studies, all with lengths of follow-up of less than three years, are due to be completed by 2009.

Discussion

Concerning safety, serious adverse events including arterial events, pulmonary embolism, deep vein thrombosis, cutaneous necrosis and ulceration were statistically rare. The most common adverse events associated with foam sclerotherapy were thrombophlebitis, matting/skin staining/pigmentation, and pain provoked at injection or pain persisting at the sclerosed area. Few studies reported that the risk of adverse events associated with foam sclerotherapy was significantly different to that of liquid sclerotherapy or open surgery. Generally, the comparative studies were too small to reliably detect differences in statistically rare adverse events at the level of the reported rates.

Categorising the safety outcomes was problematic. One reason for this is that the terminology for some outcomes was not used consistently across the included studies, for example 'minor' vein thrombosis was reported variously as microthrombi or sclerothrombus at superficial vein, and thrombophlebitis was reported as cutaneous inflammation or varicophlebitis. Also, some authors might argue that thrombophlebitis should not be considered as an adverse event as it is part of the sclerosing effects. It would also be argued that cutaneous necrosis or ulceration would be more appropriately grouped under adverse events rather than serious adverse events.

Some adverse events, such as stroke, myocardial infarction, other arterial events, visual disturbance, and headache, may be more likely in people with a PFO. The prevalence of PFO has been reported as around 10%[75]. However only two included studies (both case reports involving four patients in total) examined the existence of PFO[44,73]. When considering the occurrence of post-procedural events of low or very low frequency, the potential of chance occurrence (i.e. due to

"background" incidence) due to pathogenic mechanisms unrelated to foam sclerotherapy treatment should not be discounted. This is difficult to quantify, but overall, events such as stroke and myocardial infarction are relatively common in the general population. As a whole, the reported associations with adverse events do not elucidate the underlying pathophysiological mechanisms, and some of the reported adverse events might not have been caused by the treatment. However as these adverse events occurred within around 30 minutes of the procedure, a causal effect cannot be ruled out.

Concerning efficacy, foam sclerotherapy appears to be an efficacious treatment both for main trunk and minor vein disease. The results from the studies reporting the number of limbs or veins, but not patients, were similar to those of the studies reporting patient-level data. However, there was insufficient evidence to reliably compare the efficacy of foam versus surgery or other minimally invasive therapies such as compression hosiery, endovenous laser ablation treatment and radiofrequency ablation. Only six RCTs[6-9,12,32] reporting venous occlusion were identified, with a follow-up of mostly less than three years.

Concerning the foam sclerotherapy techniques, the strength of polidocanol and STS used ranged from 0.25 – 3%, with the foam dose increasing as the size of vein increased. No studies compared polidocanol with STS. Few studies treated 'minor' vein related venous disease only or recurrent venous disease only. Despite an extensive review there were insufficient data to determine the optimal volume of foam, concentration, and foam-producing methods to minimise the risks associated with the procedure and maintain efficacy.

The evolution of foam sclerotherapy technique to include physically resolvable gas may have improved its safety and efficacy. Four studies[12,40,42,48] used

oxygen and carbon dioxide based foam, one of which was an English language full text study[12], but these limited data were insufficient to fully assess the impact of using oxygen and carbon dioxide based foam, and there were also limited data to assess the effects of adding low molecular weight heparin injections[46], elevating legs prior to treatment or increasing the pressure at the sapheno-femoral junction.

Foam sclerotherapy requires a certain level of skill and training, which may impact on the safety and efficacy of the procedure. However only one prospective case series[21] gave details of the clinical experience and skill of the practitioner and two RCTs in one report[12] suggested surgeons' lack of foam sclerotherapy experience for large veins may cause higher adverse event rates such as deep vein thrombosis, headache, 'minor' vein thrombosis and haemotoma.

There are no established guidelines in the UK for foam sclerotherapy concerning indications for treatment, use of off-licence foam sclerosants, foam-producing technique, type and strength of fluid sclerosant, and the experience required by the practitioner to undertake the procedure. However, the Australian College of Phlebology has produced guidance for the use of foam sclerotherapy[76] and the German Society of Phlebology has also issued guidance[77] on the concentration and volume of foam for sclerotherapy, based on a consensus meeting of European experts on foam sclerotherapy in 2003[78]. The upper limits for volume of foam injected are 20ml and 8ml respectively.

Foam sclerotherapy is conducted as an outpatient procedure, does not require general anaesthesia and compared with surgery results in an earlier return to normal activities. However, for foam treatment several sessions may be required.

In conclusion, the available data suggested that serious adverse events were rare. Some other adverse events, including headache, 'minor' vein thrombosis,

matting/skin staining/pigmentation, and pain at the site of injection, were more common. There is insufficient evidence to reliably compare the effectiveness of foam sclerotherapy with other minimally invasive therapies or surgery. High quality RCTs of foam sclerotherapy compared with surgery and with alternative minimally invasive treatments, and with a follow-up period of at least three years, are required to determine the comparative efficacy of foam sclerotherapy and its optimal place in clinical practice.

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Table 1 Characteristics of included studies for safety and efficacy of foam sclerotherapy for venous disease of the lower limbs

Reference	Country	Follow-up	Sample size
English language full text studies			
RCT, n=8			
*Alos 2006[6]	Spain	1 year	(a) 75 foam (b) 75 liquid
Belcaro 2003[7]	Italy	10 years	(a) 150 foam (b) 148 liquid (c) 136 liquid (high dose) (d) 155 surgery (ligation) (e) 144 surgery (stab avulsion) (f) 154 surgery (ligation) + liquid (high dose)
Bountouroglou 2006[8]	UK	3 months	(a) 30 foam+ surgery (ligation) (b) 30 surgery (ligatin + stripping + avulsion)
Hamel-Desnos 2003[9]	France	1 year	(a) 45 foam (b) 43 liquid
Kern 2004[10]	Switzerland	2 months	(a) 51 foam (b) 45 liquid (polidocanol) (c) 51 liquid (chromated glycerine)
Rao 2005[11]	US	3 months	(a) 10 foam (b) 19 liquid (c) 15 liquid (high strength)
†Wright 2006[12]	Multi-centre	3 months	Centre 1: (a) 259 foam (O_2 or CO_2 based) (b) 125 foam (air based) or liquid Centre 2: (a) 176 foam (O_2 or CO_2 based) (b) 94 surgery (ligation, stripping or avulsion)
Registries, n=1			
Guex 2005[13]	France	1 month	(a) 6395 (sessions) foam (b) 5434 (sessions) liquid (c) 344 (sessions) foam + liquid
Non-randomised comparative studies, n=1			
Yamaki 2004[14]	Japan	1 year	(a) 37 foam (b) 40 liquid
Case series, n=14			
Barrett 2004[15]	US	2 years	116 (limbs)
Bergan 2006[16]	US	6 weeks	290
Cabrera 2004[17]	Spain	6 months to over 4 years	116
Cabrera 2001[18]	Spain	415 patients 4 to 6y 72 patients mean 2.5y	752
Cavezzi 2002[19]	Italy	1 month	194
Cavezzi 1999[20]	Italy	Mean 21 weeks	98
Coleridge-Smith 2006[21]	UK	6 months	808
‡Frullini 2002[22]	Italy	20 to 180 days	257
Hamada 2006[23]	Egypt	1 year	60
Kakkos 2006[24]	UK	3 weeks	38
McDonagh 2002[25]	US	2 to 6 years	162
Padbury 2004[26]	Australia	6 months	14
Tessari 2001[27]	Italy	1 month	77
Case reports, n=4			
De Waard 2005[28]	Netherlands	3 weeks	1
Lloret 2006[29]	Spain	2 years	1
Van Neer 2004[30]	Netherlands	6 weeks	1
Weaver 2004[31]	Netherlands	6 months	1
English language conference abstracts			
RCT, n=2			
Martimbeau 2003[32]	US	1 year	(a) 100 foam (b) 100 liquid
Rybak 2003[33]	Poland	Not stated	(a) 20 foam (b) 20 liquid
Non-randomised comparative studies, n=5			
Chung 2003[34]	South Korea	Not stated	(a) 52 foam (b) 76 liquid
Gobin 2003[35]	France	3 months	(a) foam

Reference	Country	Follow-up	Sample size
			(b) liquid
Gonzalez 2003[36]	Chilli	1 month	(a) 10 foam (b) 10 foam + heparin
Grondin 2003[37]	Canada	5 years	(a) (number not stated) foam 1 shot (b) (number not stated) foam 1-3 sessions (c) (number not stated) surgery (d) (number not stated) liquid
Grondin 2003[38]	Canada	(a) 10 months (b) 10 years	(a) 150 foam (O_2 or CO_2 based) (b) 150 liquid
Case series, n=17			
Baker 2006[39]	UK	Not stated	181
Bhowmick 2001[40]	UK	3 months	35 (O_2 or CO_2 based foam)
Cavezzi 2003[41]	Italy	2 years	Nearly 100 (limbs)
Coleridge-Smith 2003[42]	UK	Not stated	24
Forlee 2006[43,44]	Ireland	0 to 24 months	89
Frullini 2001[45]	Italy	5 years	21
Gonzalez 2005[46]	Chilli	2 years	143
Mackay 2002[47]	Not stated	1 year	13
McCollum 2001[48]	UK	3 months	41
Morrison 2003[49]	US	Not stated	100
Nitechki 2005[50]	Israel	Mean 10 months	423
Sadoun 2003[51]	France	2 years	20
Schadeck 2001[52]	France	Not stated	318
Sierra 2002[53]	Not reported	5 years	360
Tessari 2004[54]	Italy	Not stated	532
Vin 2005[55]	France	1 year	280 (limbs)
Weiss 2002[56]	Not stated	6 months	60
Non-English language full text studies or conference abstracts			
Non-randomised comparative studies, n=2			
Benigni 1999[57]	France	75 days	(a) 10 foam (b) 10 liquid
Demagny 2002[58]	France	6 months	(a) 200 (veins) foam (b) 200 (venis) liquid
Case series, n=13			
Breu 2004[59]	Germany	1 to 3 years	342
Creton 2005[60]	Not stated	Not stated	130
Ferrarra 2005[61]	France	3 months	50
Frullini 2000[62]	Italy	Not stated	167 veins
Hamel-Desnos 2005[63]	France	2 years	158
Lucchi 2003[64]	Italy	6 months	114
Milleret 2004[65]	Unclear	1 month	764
Schadeck 2004[66]	France	Mean 14.7 months	108
Sica 2005[67]	France	1 year	148
Sica 2003[68]	France	2 years	52
Stucker 2005[69]	German	Not stated	28
Uhl 2005[70]	Not stated	Not stated	140
Wildenhues 2005[71]	Not stated	2 years	213
Case reports, n=1			
Benigni 2005[72]	France	Not stated	5
Unpublished studies			
Case report, n=1			
Krizinger 2006[73]	Not stated	Not stated	3

*The RCT is a within-patient study
†The report consisted of two studies (RCTs)
‡the report consisted of two studies (case series)

Table 2 Patient details, indication for foam sclerotherapy and technique used

	English language full text studies (n=24)*	English language conference abstracts (n=21)†
Patients	3935	2921
Sex		
Male	410 (10.4%)	408 (14.0%)
Female	1558 (39.6%)	1067 (36.5%)
Not recorded	1967 (50.0%)	1446 (49.5%)
Age group		
≥ 16 years	2616 (66.5%)	1656 (56.7%)
Not recorded	1319 (33.5%)	1265 (43.3%)
Indication for foam sclerotherapy		
'Major' vein (SFJ/GSV, SPJ/SSV) incompetence and/or varicosities	2735 (69.5%)	2073 (71.0%)
'Minor' vein venous disease‡	131 (3.3%)	312 (10.7%)
Both major veins and minor veins	676 (17.2%)	0
Recurrent venous disease after prevous treatment	0	373 (12.8)
Venous ulcers	83 (2.1%)	20 (0.7%)
Not recorded	310 (7.9%)	143 (4.9%)
Foam sclerotherapy technique		
Used STS as sclerosing solutions	668 (17.0%)	714 (24.4%)
Used POL as sclerosing solutions	1838 (46.7%)	1805 (61.8%)
Used either STS or POL (not reported separately)	1369 (34.8%)	352 (12.1%)
Used ethanolamine oleate	60 (1.5%)	0
Not recorded	0	50 (1.7%)
Tessari method for producing foam	1848 (50.0%)	1349 (46.2%)
Monfreux method for producing foam	406 (10.3%)	0
Other methods for producing foam	367 (9.3%)	150 (5.1%)
Not recorded	1314 (33.4%)	1422 (48.7%)
Used ultrasound guidance to identify treated veins, monitor foam injection or foam flow	3935 (100%)	1558 (53.3%)
Use of ultrasound guidance not recorded		1363 (46.7%)
One treatment session required	676 (92.6%)¶	N/a§
≥ 2 treatment sessions required	54 (7.4%)¶	N/a§

SFJ, saphenofemoral junction; GSV, great saphenous vein; SFJ, saphenopopliteal junction; SSV, small saphenous vein; STS, sodium tetradecyl sulphate; POL, polidocanol

*Another study by Barrett *et al*[15] reported number of limbs (n 116) but not number of patients. The French registry[13] reported number of treatment sessions but not number of patients. The details of the study were not listed in the table as it was not possible to calculate the number of patients.

†One non-randomised comparative study by Grondin[37] did not report number of patients or limbs. One case series by Cavezzi[41] reported number of limbs (nearly 100) but not number of patients. One case series by Vin[55] reported number of limbs (280) but not number of patients. The details of the study were not listed in the table.

‡'Minor' venous disease includes reticular vein, telangiectasia, tributaries vein varicosities and perforator vein incompetence.

¶Treatment sessions required were calculated based on patient-level data. The data given in the table are from seven studies[6,12,14,21,29-31] that provided details of the number of treatment sessions. Another 11 studies[8,15-20,22,24,26,27] reported mean treatment sessions, with the means ranging from 1.1 to 3.6 sessions. One study[22] reported smaller veins (reticular veins and telangiectasias) separately, with a mean of 5 treatment sessions.

§ No studies provided details of the number of treatment sessions at patient-level. Four studies[32,34,41,56] provided details of the mean of treatment sessions at patient-level. The means ranged from 1.1 sessions to 2.3 sessions. One study[53] treated recurrent veins after surgery and reported a mean of 5 sessions.

Table 3 Summary of serious adverse events associated with foam sclerotherapy for venous disease*†

	No. of studies‡	n/N	Median rate (%) (range)
Anaphylaxis			
Registry	1[13]	0/6395¶	0
Case series (English language full text studies)	2[21,26]	0/822	0
Arterial events			
Case series (English language full text studies)	1[21]	0/808	0
Studies in conference abstracts and non-English language	2[39,43]	6/253	2.1 (1.4, 2.8)
Venous thromboembolism: pulmonary embolism			
RCT (English language full text studies)	2[12]	0/437	0
Case series (English languagefull text studies)	5[16-18,20,23]	1/1316	0 (0, 0.3)
Case series (non-English language studies)	2[62,71]	0/977	0
Venous thromboembolism: deep vein thrombosis			
RCT (English language full text studies)	4[8,10,12]	11/517	0.4 (0, 5.1)
Registry (English language full text studies)	1[13]	1/6395¶	0.02
Case series (English language full text studies)	11[16-24,26]	11/2828	0.4 (0, 1.0)
Studies in conference abstracts and non-English language	10 [35,40,42,46,49,55,60,63,65,71]	16/2076	0.7 (0, 5.7)
Cutaneous: necrosis			
RCT (English language full text studies)	1[9]	0/45	0
Registry (English language full text studies)	1[13]	0/6395¶	0
Case series (English language full text studies)	4[16,22-24]	8/781	1.3 (0.3, 2.6)
Studies in conference abstracts and non-English language	5[50,56,57,61,71]	1/766	0 (0, 0.2)
Cutaneous: ulceration			
RCT (English language full text studies)	2[8,10]	0/80	0
Case series (English language full text studies)	1[26]	0/14	0
Studies in conference abstracts and non-English language	1[69]	1/28	3.6
Other serious adverse events: intra-arterial injection			
Registry	1[13]	0/6395¶	0
Studies in conference abstracts and non-English language	1[66]	0/108	0

*****Results from case reports were not in the table. Their results were: one case each of myocardial infarction and grand mal epileptic fit were reported by Kritizinger[73]

†The RCT by Alos *et al*[6] is a within-patient study, therefore was not listed in the table. A non-English language study by Frullini & Cavezzi[62], n 167 veins, did not report results at the patient level either, hence was not listed in the table.

‡The report by Wright *et al*[12] consisted of two studies (RCTs); the report by Frullini & Cavezzi[22] consisted of two studies (case series).

¶Guex 2005[13]: adverse events were presented by number of treatment sessions rather than by number of patients.

Table 4 Summary of adverse events associated with foam sclerotherapy for venous disease*†

	No. of studies‡	n/N	Median rate (%) (range)
Visual disturbance			
RCT (English language studies)	1[10]	3/51	5.9
Registry	1[13]	19/6395¶	0.3
Case series (English language studies)	10[16-23,27]	36/2848	1.1 (0, 2.6)
Studies in conference abstracts and non-English language	3[35,58,66]	7/591	1.5 (0.9, 2.0)
Central nervous system disturbance: transient confusion			
Case series (English language studies)	4[20,22,23]	4/611	0.5 (0, 1.2)
Central nervous system disturbance: headache			
RCT (English language studies)	2[12]	55/437	14.2 (5.4, 23.0)
Registry	1[13]	0/6395¶	0
Case series (English language studies)	1[16]	2/290	0.7
Studies in conference abstracts and non-English language	1[35]	7/229	3.1
Other systemic symptoms: coughing, chest tightness/heaviness, panic attack and malaise, and vasovagal			
Registry	1[13]	10/6395¶	0.2
Case series (English language studies)	6[16,17,19,22,24]	12/1091	0.5 (0, 2.8)
Local effect: 'minor' vein thrombosis			
RCT (English language studies)	2[9,10]	9/96	8.8 (0, 17.6)
Registry	1[13]	5/6395¶	0.1
Case series (English language studies)	2[21,23]	11/868	1.5 (1.2, 1.7)
Studies in conference abstracts and non-English language	3[42,59,71]	5/579	0.9 (0.6, 4.2)
Local effect: thrombophlebitis			
RCT (English language studies)	3[8-10]	5/125	4.4 (0, 10.3)
Registry	1[13]	3/6395¶	0.05
Case series (English language studies)	7[17,20-23,27]	71/1612	3.3 (1.3, 10.3)
Studies in conference abstracts and non-English language	10[35,40,42,51,52,59,64,66,69,71]	81/1235	9.2 (0, 45.8)
Local effect: matting/skin staining/pigmentation			
RCT (English language studies)	4[8,10,12]	226/517	31.6 (7.8, 55.1)
Case series (English language studies)	5[17,21-23,26]	42/759	2.3 (0, 19.8)
Studies in conference abstracts and non-English language	7[34,42,51,52,56,57,66]	74/484	19.2 (0, 66.7)
Local effect: local neurological injury			
RCT (English language studies)	1[8]	0/29	0
Registry	1[13]	1/6395¶	0.02
Case series (English language studies)	6[16-18,21,23,26]	2/2040	0 (0, 0.7)
Local effect: pain at the site of injection			
RCT (English language studies)	2[12]	150/437	35.7 (29.7, 41.0)
Case series (English language studies)	1[26]	3/14	21.4
Studies in conference abstracts and non-English language	5[34,35,48,59,63]	113/822	7.7 (0.6, 34.1)
Others: local allergic reaction, haematoma, extravasations, lower back pain			
RCT (English language studies)	4[8,9,12]	41/511	4.2 (0, 11.2)
Case series (English language studies)	2[19,23]	1/254	0.3 (0, 0.5)
Studies in conference abstracts and non-English language	2[58,63]	1/412	0.3 (0, 0.6)

*****Results from case reports were not in the table. Their results were: six cases of visual disturbance and one case of chest heaviness were reported by Benigni & Ratinahirana[72], Weaver[31] and the unpublished case reports by Kritzinger[73].

†The RCT by Alos *et al*[6] is a within-patient study, therefore was not listed in the table. Another four studies not reporting results at the patient level were not listed in the table either. Their results were:

(1) Case series in English language full text study by Kakkos *et al*[24], n=73 sessions/45 limbs, reported 8.2% thrombophlebitis and 6.6% matting/skin staining/pigmentation;

(2) Case series in conference abstract by Forlee *et al*[44] n=86 limbs, reported 1/86 limbs 'minor' vein thrombosis, 11/86 limbs thrombophlebitis, and 33/86 limbs skin matting;

(3) Case series in conference abstract by Vin[55] n=280 limbs, reported 9/280 limbs thrombophlebitis;

(4) Case series in non-English language study by Frullini & Cavezzi[62], n=167 veins, 0.6% 'minor' vein thrombosis, 5/167 veins thrombophlebitis, 3.6% skin matting, and 0% allergic reaction;

‡The report by Wright *et al*[12] consisted of two studies (RCTs); the report by Frullini & Cavezzi[22] consisted of two studies (case series).

¶Guex 2005[13]: adverse events were presented by number of treatment sessions rather than by number of patients.

Table 5 Summary of efficacy outcomes of foam sclerotherapy for venous disease*

	No. of studies†	n/N	Median rate (%) (range)
Complete occlusion of treated veins			
RCT (English language studies)	5[7-9,12]	543/640	84.4 (67.4, 93.8)
Non-randomised comparative studies (English language studies)	1[14]	25/37	67.6
Case series (English language studies)	4[19,20,25,26]	336/372	84.4 (60.0, 98.2)
Studies in conference abstracts and non-English language	14[32,35,38,40,48,50,53,54,59,63,64,66,70,71]	2488/2858	87.8 (74.1, 97.1)
Healing of venous ulcers			
Case series (English language studies)	3[16-18]	181/216	84.5 (76.4, 100.0)
Studies in conference abstracts and non-English language	1[33]	15/20	75.0
Recurrence or developed new veins			
RCT (English language studies)	2[7,9]	68/174	27.8 (4.4, 51.2)
Non-randomised comparative studies (English languages studies)	1[14]	3/37	8.1
Case series (English language studies)	2[17,25]	7/291	3.1 (0.5, 5.7)
Studies in conference abstracts and non-English language	6[32,48,51,54,59,63]	52/693	10.1 (1.0, 15.0)

GSV, great saphenous vein; SSV, small saphenous vein

*Another 18 studies not reporting results at the patient level were not listed in the table. Their results were:

(1) Complete occlusion of treated veins:

Case series in English language full text study:

By Barrett *et al.*[15], 68/99 limbs (vein diameter <10mm) (68.7%); 13/17 limbs (vein diameter ≥10mm) (75.5%);

By Bergan *et al.*[16], 259/328 limbs (79.0%);

By Cabrera *et al.*[18], 400/500 veins (GSV) (80.0%); 215/265 veins (recurrent) (81.1%);

By Coleridge-Smith[21], 318/365 veins (GSV) (87.6%); 116/141 veins (SSV) (82.3%);

By Hamada [et al.23], 88/112 veins (78.6%);

Non-randomised comparative study in English language conference abstract:

By Grondin[37], not reported number of patients or limbs,
foam group (1 session), GSV 85%, SSV 80%; foam group (1-3 sessions), GSV 88%, SSV 89%;
surgery group, GSV 85%, SSV 73%; liquid group, GSV 75%, SSV 82%;

Case series in English language conference abstract:

By Baker & Darke[39], 196/229 limbs (85.6%);

By Cavezzi[41], 100/100 limbs (100%);

By Coleridge-Smith[42], 23/25 veins (GSV) (92.0%); 5/10 veins (SSV) (50.0%);

By Forlee *et al.*[43], 42/86 limbs (48.8%);

By Gonzalez & Barahona-Cruz[46], 91/106 veins (GSV) (85.8%); 62/69 veins (SSV) (89.9%);

By Mackay[47], 14/14 limbs (100%);

By Schadeck[52], 114/118 veins (saphenous/great collateral vein) (96.6%); 99/100 veins (recurrent) (99%); 92/100 veins (telangiectatic) (92.0%);

By Vin[55], 207/280 limbs (73.9%);

Non-randomised comparative study in non-English language:

By Demagny[58],
GSV: foam group, 101/150 veins (67.3%); liquid group, 71/150 veins (47.3%); RR (95% CI), 1.4 (1.2, 1.7)
SSV: foam group, 42/50 veins (84.0%); liquid group, 32/50 veins (64.0%); RR (95% CI), 1.3 (1.0, 1.7);

Case series in non-English language:

By Sica[67], 93/107 veins (GSV) (86.9%); 39/41 veins (SSV) (90.2%);

By Sica[68], 79/97 veins (GSV) (81.0%); 25/29 veins (SSV) (87.0%);

(2) Recurrence or developed new veins:

Case series in English language full text study:

By Barrett *et al.*[15], 4/99 limbs (vein diameter <10mm) (4.0%); 1/17 limbs (vein diameter ≥10mm) (5.9%);

Case series in English language conference abstract:

By Coleridge-Smith[42], 2/25 veins (GSV) (8.0%); 5/10 veins (SSV) (50.0%);

By Forlee *et al.*[43], 7/86 limbs (8.1%).

Non-randomised comparative study in non-English language:

By Demagny[58],
GSV: foam group, 16/150 veins (0.7%); liquid group, 33/150 veins (22.0%)
SSV: foam group, 2/50 veins (4.0%); liquid group, 7/50 veins (14.0%);

†The report by Wright *et al*[12] consisted of two studies (RCTs).

Figure 1 Flow diagram for screening process

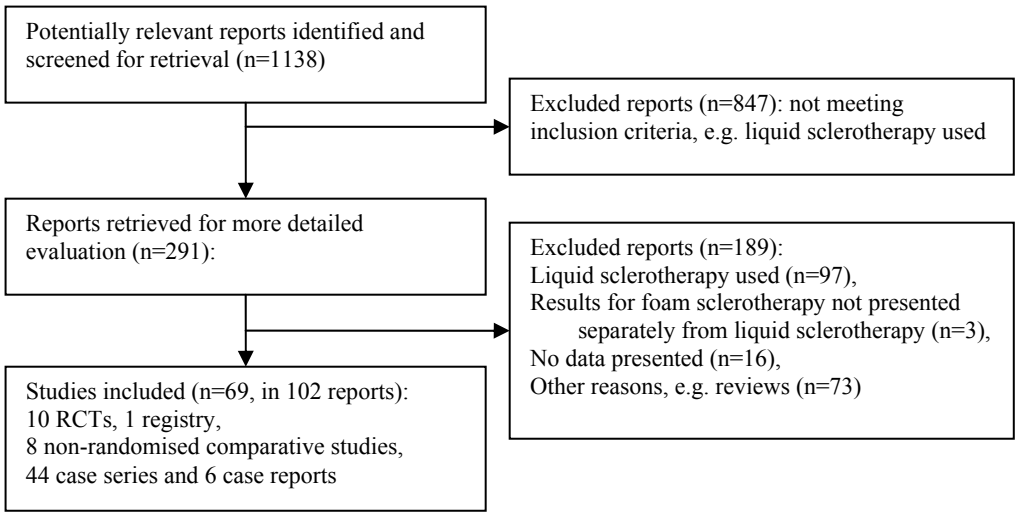

Figure 2 Meta-analysis of foam sclerotherapy versus surgery involving stripping, for skin pigmentation

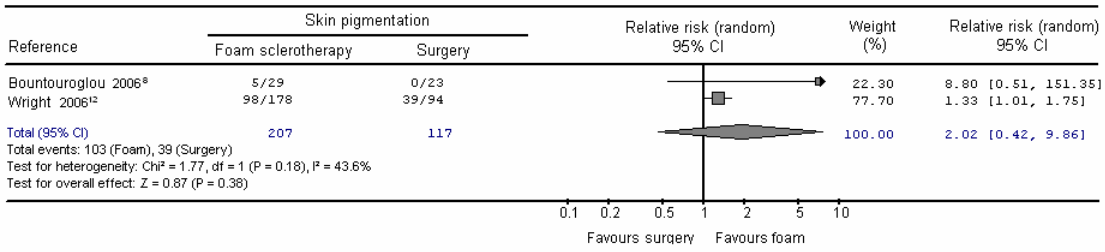

Figure 3 Meta-analysis of foam versus liquid sclerotherapy, and foam sclerotherapy versus surgery, for complete occlusion of treated veins