Original article

# Side-effects and complications of foam sclerotherapy of the great and small saphenous veins: a controlled multicentre prospective study including 1025 patients

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## Abstract

***Objectives*:** Increasing interest in foam sclerotherapy (FS) for saphenous insufficiency has highlighted the need to study the side-effects and complications of this treatment. The aim of this study is to better assess their nature and incidence.

***Methods*:** A multicentre, prospective and controlled study was carried out in which patients treated with FS for great (GSV) and small saphenous veins (SSV) trunk incompetence were included. Immediate untoward events were reported. Duplex ultrasound (DUS) examination was carried out to assess all patients between the eighth and 30th day. In addition, 20% of patients were called by an external auditor.

***Results*:** In total, 818 GSV and 207 SSV were treated in 1025 patients in 20 phlebology clinics. Ninety-nine percent of patients were controlled with DUS and non-duplex-checked patients were all called. The saphenous trunk was occluded in 90.3% of patients. Twenty-seven (2.6%) side-effects were reported: migraine ($n = 8$, 4 with visual disturbance); visual disturbance alone ($n = 7$); chest pressure alone ($n = 7$); and chest pressure associated with visual disturbance ($n = 5$). Eleven thrombo-embolic events occurred: 10 deep vein thrombosis (DVT) but only five in symptomatic patients, and one pulmonary embolism that occurred 19 days following the FS without DVT identified by DUS. One transient ischaemic stroke, with complete clinical recovery in 30 minutes, and one septicaemia with satisfactory outcome were reported as well.

***Conclusion*:** This study demonstrates in a large sample of patients a low rate of adverse reactions after FS of great and small saphenous trunks. However, but the eventuality of exceptional but more serious complications has to be taken into account in the management of patients. A multicentre study like this one takes into account different practices and reports all possible complications, thus demonstrating the need for a common validated protocol.

**Keywords:** foam sclerotherapy; venous insufficiency; side-effect; complication

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## Introduction

Ultrasound-guided foam sclerotherapy (FS), also called endovenous chemical ablation, has become a common treatment for patients with saphenous insufficiency. Sclerotherapy has been used satisfactorily for decades. Ultrasound guidance and

injection of foam have revolutionized the method. The efficacy of FS has been demonstrated in many publications.[1–17] If the nature of the side-effects and complications of FS is known and has been reported in several studies,[1,9,10,18–33] the precise incidence of adverse events of FS is still unclear.

The objective of this study was to assess the side-effects and complications of FS of the great saphenous vein (GSV) and the small saphenous vein (SSV).

## Patients and methods

A multicentre, prospective and controlled study was carried out in which patients treated with FS for GSV and SSV trunk incompetence were included. All patients had been previously assessed with clinical and duplex ultrasound (DUS) examinations. The criteria for inclusion were: (1) a reflux into the GSV trunk identified from the terminal valve, the preterminal valve[34] or below, at the groin level and fed by the pelvic veins; (2) a reflux into the SSV trunk starting at the terminal valve; (3) a reflux whose duration was greater than one second; (4) a saphenous trunk with a diameter greater than 4 mm, measured at 15 cm below the groin (GSV)[34] or at the median third of the calf (SSV); and (5) patients with a clinical, aetiological, anatomical and pathophysiological classification (CEAP) clinical class[35,36] from C2 to C6.

Patients with (1) a personal history of deep vein thrombosis (DVT) – Es of the CEAP – or pulmonary embolism (PE); (2) previously identified thrombophilia; (3) symptomatic patent foramen ovale (PFO) – a screening to detect asymptomatic PFO was not performed prior to FS;[37] and (4) a history of migraine with aura were excluded from the study. Patients with official contraindication, according to the French Vidal® dictionary (Vidal, Issy-les Moulineaux, France), for the sclerosing agents polidocanol, also known as lauromacrogol 400 (DCI), or sodium tetradecyl sulphate (DCI), also known as sotradecol, were also excluded.

The patients received information according to the French legislation and their informed consent for participation in the survey was recorded.

The reporting form was divided into two parts (Figure 1). At inclusion, the first part was faxed by the investigators to the principal investigator and coordinator (JLG). The patient's features, the FS features and a possible immediate complication or side-effect were noted. The patients then were questioned and a DUS examination was performed between the eighth and the 30th day. All deep veins of both lower extremities, including calf muscular veins, were examined from the vena cava to the calf veins in order to detect a DVT. At the time of this examination, it was indicated whether a complication occurred and whether the saphenous trunk was occluded. Then the second form was also faxed to the principal investigator. If an adverse event occurred, a specific form was filled out and was sent as well. In addition, 20% of patients, randomly selected, were called by an external auditor.

The complications and side-effects were all discussed with a Committee of Validation of Critical Events including a neurologist (Professor M Hommel, University of Grenoble, France), a specialist

**INCLUSION**

Date: Form N°:
Doctor: Name: Centre N°:
Patient: Name: Surname: Age: years Sex F [ ] M [ ]
Phone number: Relative's phone number:

The patient has the whole inclusion criteria and none exclusion criterion Yes [ ] No [ ]
The patient has given his consent for participation to the survey Yes [ ] No [ ]

| **Patient's history** | Yes | No | |
|---|---|---|---|
| Migraine (without aura) | [ ] | [ ] | |
| Family history of thrombo-embolic event | [ ] | [ ] | If yes, specify: |
| Family history of thrombophilia | [ ] | [ ] | If yes, specify: |

Clinical class (CEAP): C__ S [ ] A [ ]

**Foam Sclerotherapy features**
GSV [ ] SSV [ ] Right [ ] Left [ ]
*If GSV*: reflux from the terminal valve [ ] preterminal valve [ ] from pelvic veins [ ]
Diameter: mm
Sclerosing agent: Polidocanol [ ] Sodium Tetradecyl Sulfate [ ]
Concentration : 0.5% [ ] 1% [ ] 1.5% [ ] 2% [ ] 3% [ ]
Gas : air [ ] other [ ] specify :
Ratio liquid/gas : Injected volume of foam : mL
Direct puncture [ ] Short catheter or Butterfly [ ]
Elastic compression : Yes [ ] No [ ]

| **Immediate complication** | Yes | No |
|---|---|---|
| Death | [ ] | [ ] |
| Anaphylactic shock | [ ] | [ ] |
| Visual disturbance | [ ] | [ ] |
| Chest pressure | [ ] | [ ] |
| Neurological disorder | [ ] | [ ] |
| Intra-arterial injection | [ ] | [ ] |

Responsibility of sclerotherapy: Excluded [ ] Unlikely [ ] Likely [ ]
If a complication occurred, fill out the specific form

**From the inclusion, fax this form to the coordinator**

**CHECK-UP EXAMINATION INCLUDING SYSTEMATIC DUPLEX ULTRASOUND EXAMINATION**

Date: Day +____ Patient lost to follow-up: [ ] Death [ ]

| **Occluded saphenous Vein** | Yes [ ] | No [ ] |
|---|---|---|
| **Complication** | Yes [ ] | No [ ] |
| If yes : | | |
| Visual disturbance | [ ] | [ ] |
| Chest pressure | [ ] | [ ] |
| Neurological disorder | [ ] | [ ] |
| Clinical suspicion of PE | [ ] | [ ] |
| If yes, is the PE confirmed? | [ ] | [ ] |
| Skin necrosis | [ ] | [ ] |
| Deep vein thrombosis | [ ] | [ ] |
| Other | [ ] | [ ] |

Responsibility of sclerotherapy: Excluded [ ] Unlikely [ ] Likely [ ]
If a complication occurred, fill out the specific form

**Fax the form from the end of the examination to the coordinator**

**Figure 1** English translation of the reporting form

in venous thrombosis (Professor P Mismetti, University of Saint-Etienne, France) and a vascular surgeon (Dr M Perrin, Lyon, France).

Data analysis was performed using the SAS 8.2 software (SAS Institute, Cary, NC, USA). Quantitative variables were expressed as means ± standard deviation and were compared using the analysis of variance test. The proportions of qualitative variables were tested with non-parametric tests (Fisher's exact test) and a $P < 0.05$ was considered significant.

**Table 2** Distribution of the diameter of the great and small saphenous veins

| Diameter | Number of GSV (%) | Number of SSV (%) |
|---|---|---|
| 4–4.9 mm | 111 (13.57 %) | 60 (28.99 %) |
| 5–5.9 mm | 203 (24.82 %) | 56 (27.05 %) |
| 6–6.9 mm | 196 (23.96 %) | 43 (20.77 %) |
| 7–7.9 mm | 140 (17.11 %) | 20 (6.66 %) |
| 8–8.9 mm | 89 (10.88 %) | 28 (13.58 %) |
| ≥9 mm | 79 (9.66 %) | |

GVS, great saphenous vein; SSV, small saphenous vein; mm, millimetre

## Results

### Population

In total, 1025 patients were included in 20 French phlebology outpatient clinics. Eight hundred and eighteen (79.8%) GSV and 207 (20.2%) SSV were treated in 781 (76.2%) female and 244 (23.8%) male patients. The distribution between the right (500; 48.8%) and the left (525; 51.2%) leg was similar. The average age was 54 ± 13.8 years (median, 55; range, 18–90 years). The distribution of the patient's clinical classes is described in Table 1. If most of the patients (660 = 65%) were C2, 35% of the patients presented a chronic venous insufficiency (C3 and up) and 13 (1.3%) an active ulcer. Seventy percent of patients were symptomatic. In patients with GSV insufficiency, the terminal valve was incompetent in 515 patients (63%), the top of the reflux was identified at the preterminal valve in 211 (25.8%), and at the groin level from pelvic varicosities in 92 (11.2%).

The average GSV diameter was 6.3 ± 1.79 mm (median, 6; range, 4–16 mm), while the SSV diameter was 5.66 ± 1.59 mm (median, 5; range, 4–12 mm) (Table 2).

### FS features

Various procedures were used. The foam was always prepared with Tessari's method[18] or the Tessari/double-syringe system.[37] Polidocanol was used in 931 (90.83%) patients and sodium tetradecyl sulphate in 94 (9.17%). The concentration of the sclerosing agent used to prepare the foam ranged from 0.5% to 3%; the most commonly used concentration (mode, 40% of patients) was 1%. Air was used to prepare foam in 953 (93%) of patients and oxygen ($O_2$) in 72 (7%). The ratio of liquid and gas ranged from 1 + 1 (one part of liquid plus one part of gas) to 1 + 5 (one part of liquid plus five parts of gas); the most commonly used ratio (mode, 60% of patients) was 1 + 4. The average injected volume was 4.5 ± 2.5 $cc^3$ (median, 4; range, 1–18 $cc^3$). Direct puncture, or a closed needle technique, was used in 87.5% of patients and a short catheter or a butterfly in 12.5%. Elastic compression, exerting at least a 15 mmHg ankle pressure, was applied in 72.3% of patients at the end of the procedure.

**Table 1** Distribution of the patient's clinical classes according the CEAP classification

| Clinical class | Number | % |
|---|---|---|
| 2 | 660 | 64.39 |
| 3 | 257 | 25.07 |
| 4 | 83 | 8.10 |
| 5 | 12 | 1.17 |
| 6 | 13 | 1.27 |
| | 1025 | 100.00 |

### Follow-up

One thousand and fifteen (99%) patients were checked with DUS according to the protocol and the 10 non-checked patients were all called by the phlebologist who had performed the FS. Thus, no patient was completely lost to follow-up. DUS was performed between the eighth and 30th day in 941 patients (91.8%) and between one and three months in 74 (7.2%). The median follow-up was 20 days. According to the protocol, 205 patients (20%) were called by an external auditor, which revealed no significant event.

*A vein sclerosis*, which is a complete occlusion of the treated saphenous trunk with elimination of reflux,[3,4,8,13–17] was observed in 917 (90.3%) patients.

### Side-effects and complications

No death or anaphylactic shock or intra-arterial injection was reported. One infectious complication (septicaemia) occurred in a 42-year-old woman

following an injection with a direct puncture into the GSV of 2 $cc^3$ of foam prepared with polidocanol 3% mixed with air. The patient had a myxoid heart valve disease. A *Staphylococcus aureus* was identified as being the germ likely responsible. The patient's outcome was satisfactory.

One transient ischaemic attack (TIA) occurred in a 52-year-old woman following an injection with a short catheter of 10 $cc^3$ of foam into her SSV. The foam was prepared with polidocanol 0.5% mixed with $O_2$. She presented a dysarthria for 30 seconds and paresthesia of her left hand for 30 minutes. The clinical recovery was complete within 30 minutes. An extended screening was carried out, including cardiological and neurological examinations. It revealed the existence of a PFO combined with an interatrial septal aneurysm (IASA). A brain computed tomography scan was normal. A brain magnetic resonance imaging showed the existence of two hypersignals on T2-weighted images in the right hemisphere, but its association with the injection of foam was not established. In fact, neurologists consider that such lesions may occur spontaneously in patients with PFO associated with IASA.

Eleven ($11/1025 = 1.07\%$) venous thromboembolic events (VTEs) were reported. They were shared out in five symptomatic DVT ($5/1025 = 0.5\%$), all distal; five (0.5%) asymptomatic DVT, all not completely occlusive; and one PE. The features of the DVT, treatment and outcome are described in Table 3. A compression therapy had been applied after FS in all patients but one. Except from two asymptomatic and not completely occlusive thrombosis of the femoral common vein, all DVT were distal. DVT were more frequent ($P = 0.032$) with FS of SSV ($5/205 = 2.42\%$) than with FS of GSV ($5/818 = 0.61\%$). DVT complicating FS of SSV were, in all patients, medial gastrocnemius veins (MGV) thrombosis. MGV thrombosis was more frequent ($P = 0.002$) with FS of SSV ($5/207 = 2.47$) than with FS of GSV ($1/818 = 0.12\%$). When a DUS examination was performed at the end of anticoagulation treatment (AT), a complete recanalization of the deep veins was observed in six out of seven patients.

One PE occurred in a 66-year-old woman. It was diagnosed with a helical computed tomography scan. Its association with FS was not certain insofar as it arose 19 days following the treatment with FS and as repeated DUS revealed no DVT. The clinical outcome was satisfactory. The screening for risk factors was negative, showing neither thrombophilia nor neoplasm, but the patient's questioning revealed that her mother and one sister had presented a PE.

Twenty-seven ($27/1025 = 2.\ 63\%$) immediate side-effects were reported:

**Table 3** Features, treatment and outcome of the deep vein thrombosis

| | Location of DVT | Treated SV | Foam sclerotherapy features | AT | Complication | DUS examination check-up |
|---|---|---|---|---|---|---|
| Symptomatic DVT | MGV | SSV | Polidocanol 1% + air; 2.5 mL | Curative dosage; 30 days | No | Recanalization |
| | MGV | SSV | Polidocanol 2% + air; 4 mL | Curative dosage; 14 days | No | Recanalization |
| | MGV | SSV | Polidocanol 2% + air; 2 mL | No | No | No |
| | MGV | GSV | Polidocanol 3% + air; 2 mL | Curative dosage; >30 days | Septicemia | No |
| | PTV | GVS | Polidocanol 3% + air; 6 mL | Curative dosage; 10 days | No | No extension |
| Asymptomatic and not completely occlusive DVT | CFV | GSV | Polidocanol 1.5 % + air; 7 mL | Curative dosage; 14 days | No | Recanalization |
| | CFV | GSV | Polidocanol 1% + air; 8 mL | Curative dosage; 21 days | No | Recanalization |
| | MGV | SSV | Polidocanol 0.5 % + air; 3 mL | No | No | Recanalization |
| | MGV | SSV | Polidocanol 2 % + air; 2 mL | No | No | No |
| | Controlateral Fibular veins | GSV | Polidocanol 1.5 % + air; 4 mL | Prophylactic dosage 21 days | No | Recanalization |

DVT, deep vein thrombosis; SV, saphenous vein; AT, anticoagulant therapy; DUS, duplex ultrasound; MGV, medial gastrocnemius vein; SSV, small saphenous vein; GVS, great saphenous vein; PTV, posterior tibial vein; CFV, common femoral vein

- Eight cases of migraine (0.78%) were identified by the neurologist who analysed the side-effects; they always occurred in patients with a history of migraine; they were a headache combined with a visual disturbance (VD) in four patients, a headache alone in two patients, and a VD alone in two;
- Seven patients (0.68%) reported an isolated VD in the form of blurred vision ($n = 4$) or scotoma ($n = 3$); and
- Twelve patients (1.17%) described a chest pressure, isolated ($n = 7$) or combined with a blurred vision ($n = 4$) or scotoma ($n = 1$).

The average injected volume in patients who presented migraine or DV was $5.03 \pm 2.44$ mL (median, 4; range, 2–8 mL). The average injected volume in patients who presented chest pressure was $4.54 \pm 1.92$ mL (median, 4; range, 1–10 mL). The injected volumes of foam were not significantly higher in patients who presented with migraine or VD, chest pressure or at least one of these side-effects, than in patients who did not experience these disturbances: $P$ was 0.49, 0.99 and 0.51, respectively.

In patients who experienced VD ($n = 16$), the liquid + gas ratios were 1 + 4 in nine patients, 1 + 5 in six patients and 1 + 3 in one patient. In patients with chest pressure ($n = 12$), the ratios were 1 + 4 in seven patients, 1 + 5 in four patients and 1 + 3 in one patient. All patients with VD or chest pressure were treated with an air-based foam.

## Discussion

Infectious complications appear to be exceptional. A French expert's report published in 1996[38] reported two cases of septicaemia following liquid sclerotherapy over 20 years. Including the case observed in this series, we count three cases over 30 years. This figure is very low compared with the millions of sclerotherapy sessions performed every year. Furthermore, septicaemia is more a complication of venous injection rather than a specific complication of FS. However, even if FS with a direct puncture is an ambulatory and swift method, it needs to respect the precise rules of asepsis.

Regarding the risk of stroke, we should remember that millions of FS sessions have been performed and that only one case of stroke, with minimal after-effects, had been previously reported[26] after FS of saphenous veins. Recently, Bush *et al.*[32] reported one case of cerebrovascular accident, also with minimal after-effects identified at the examination two weeks following the incident, and one case of TIA, following treatment with FS of perforator veins and reticular or spider telangiectasia, respectively. Another case of stroke, occurring three days following the injection of 0.5% liquid polidocanol, has also been reported,[39] but its relationship with sclerotherapy is not established because of the period of time between the sclerotherapy session and the appearance of the problem. Volume and/or quality of foam can be discussed in most cases of stroke occurring after FS. All patients had an undiagnosed PFO. In our series, one TIA occurred following injection of 10 $cc^3$ of foam prepared with polidocanol 0.5% and $O_2$ into the SSV. It is important to notice the circumstances of the occurrence of this event: the patient lay face down for 40 minutes and the trouble arose when she got up with a Valsalva manoeuvre. As in the cases previously reported, this patient had an undiagnosed PFO associated with IASA. Considering the high prevalence of PFO, which is estimated to be around 20 to 30% in the adult population,[40] the risk of stroke following FS appears to be very low. Some authors[33] present instrumental findings and a pathophysiological hypothesis of paradoxical micro emboli, which need more evidence and pathophysiological explanations.

According to the Second European Consensus on Foam Sclerotherapy of Tegernsee[37] and the opinion of experts,[41] a preliminary screening for PFO or right-to-left shunts is not necessary. The injection of a large volume of foam[31,42] remains controversial. According to the above-mentioned consensus,[37] we consider that, in most patients, we can treat saphenous insufficiency by injecting a limited volume of foam.[1,3,4,6,13,14,16,17] Following the injection of foam, we recommend patients avoid a Valsalva manoeuvre; in particular, not to put compression stockings on themselves. Additional measures, including elevating the leg 30° during injection and remaining supine for five minutes after the injection, have been suggested.[32,37,43]

In this series, migraine or VD occurred in 2% of patients. Although these side-effects have been reported following the injection of a liquid sclerosing agent,[44] they seem more frequent with FS.[24] The frequencies of occurrence, as mentioned in the literature, vary from 0% to 14%,[1,9,10,18–25,27,29,31] with a median rate of VD and headache of 1.4% and 4.2%, respectively.[15] According to neurologists, an isolated VD is likely a migraine, but only a systematic neurological examination of all patients with VD could confirm this hypothesis. On the basis of observational studies, a link between migraine and PFO is often suggested; however, the Mist-trial[45] did not clearly confirm this relationship.

The type of gas (air or more physiological gas) to prepare foam is a controversial topic. In a recent work, Morrison *et al.*[31] did not find a significant difference in the frequency of occurrence of VD by substituting $CO_2$ for air despite using a large volume of foam. In his series, the average air and $CO_2$-based foam volumes injected were $27 \pm 10$ mL and $25 \pm 12$ mL, respectively.

Chest pressure occurred in our series in 1.1% of patients. The physiopathology of this side-effect is not clear. Patients described two different forms: a simple chest pressure or a painful chest tightness. Most often, it was a short-lasting disturbance, with recovery within five minutes. In some patients a cardiological examination was carried out and did not reveal any abnormality. According to Morrison *et al.*,[31] chest tightness is more frequent if large volumes of foam, more than 15 mL, are injected and, in this case, its frequency is reduced by substituting $CO_2$ to air. Recently, Hamel-Desnos *et al.*[46] observed no modification of troponin following FS of GSV and SSV (mean volume: 4 mL; range, 2.5–7.5 mL).

We observed a low prevalence of VTE: 1.1% and only 0.6% in symptomatic patients. No AT was prescribed following the injection of foam, but patients with a personal history of VTE were excluded. We did not take superficial thrombophlebitis into account given that this side-effect remains a minor event, after having eliminated an associated DVT with DUS examination.[47] In their systematic review of FS, Jia *et al.*[15] estimated that the median rate of VTE, including PE and DVT, was less than 1%. In our series, in symptomatic patients, DVT were all distal and most often MGV thrombosis. Bergan *et al.* [10] made a similar observation. MGV thrombosis complicated more commonly FS of SSV than GSV, likely because of the anatomy of the SSV. The high frequency of a common ending between SSV and MGV, of gastrocnemial perforator veins as well, is well known. However, we observed a rapid recanalization of the MGV and the CFV thrombosis, although we used a short duration of AT, which contrasts with the outcome of spontaneous MGV thrombosis,[48,49] and suggests that distal and not completely occlusive DVT occurring after FS do not require a long-term AT. Coleridge Smith[9] managed distal and not completely occlusive DVT without AT.

Regarding the other methods of treatment of saphenous insufficiency, there is only one study[50] with a systematic check-up of patients after surgery: a DVT was identified in 5.3% of patients. With radiofrequency[51–54] and laser,[55–58] the rates vary from 0% to 16% and 0% to 8%, respectively. Our series and the data of the literature demonstrate that FS does not lead to more VTE than the other methods of treatment of saphenous insufficiency.

## Conclusion

This study demonstrates a low rate of side-effects of FS of great and small saphenous trunks in a large sample of patients. The eventuality of exceptional but more serious complications has to be taken into account in the management of patients. A multicentre study like this one takes into account different practices and reports all possible complications, thus demonstrating the need for a common validated protocol.

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Sclerosing agents used in this study may not be licensed in all countries; it is the responsibility of physicians to comply with local regulations.

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