

Immediate and Midterm Complications of Sclerotherapy: Report of a Prospective Multicenter Registry of 12,173 Sclerotherapy Sessions

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BACKGROUND. Growing interest in sclerotherapy has emphasized the need for complete knowledge of all aspects of this method.

OBJECTIVE. To precisely delineate the actual incidence of immediate and delayed untoward events of daily sclerotherapy.

METHODS. A multicenter prospective registry was established in 22 phlebology clinics to report their activity and complications.

RESULTS. During the study period, 12,173 sessions of sclerotherapy were carried out, 5,434 with liquid, 6,395 with foam, and 344 using both. Four thousand eighty-eight (33.9%) ses-

sions were carried out with ultrasound guidance. Forty-nine incidents or accidents (0.4%) occurred, of which 12 were with liquid and 37 with foam. These were reported during the time of the study and an additional 1-month follow-up. Most numerous were 20 cases of visual disturbances (in 19 cases, foam or air block was used); all resolved shortly, without any after-effects. A femoral vein thrombosis was the only severe adverse event in this study.

CONCLUSIONS. This study demonstrates that sclerotherapy is a safe technique.

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SCLEROTHERAPY HAS been satisfactorily used for decades, and ultrasound-guided sclerotherapy with foam is thought to have revolutionized the management of varicose vein disease.¹⁻³ However, a certain reluctance remains in the minds of some physicians, and an important number are still concerned about the supposed or alleged risks of adverse events, such as deep venous thrombosis (DVT) and/or pulmonary emboli. Several studies have already analyzed the efficacy of the method⁴⁻⁷ and described the possible complications.⁸ But the precise incidence of complications of sclerotherapy is not known. Although only a small number of complications have been reported (eg, only one case of cutaneous necrosis and two cases of “residual” pain were reported in 2003 in France by the main malpractice insurance company⁹), a large-scale study was lacking.

This situation stimulated the interest of the Board of the French Society of Phlebology, which decided to sponsor a prospective multicenter registry.

The objective of the study was to assess the actual numbers of untoward events, complications, and side effects of daily sclerotherapy practice in phlebology

clinics. The study was to include most modalities of care: liquid and foam, ultrasound guidance, and sclerotherapy for telangiectasias and large varicose veins.

Materials and Methods

Twenty-two medical doctors specializing in phlebology (20 French, 1 Italian, 1 Spanish) volunteered to report their daily activity and the problems related to sclerotherapy injections. Data collection was based on a daily form to check all types of sessions and a weekly form on which all daily sessions were summarized. These included the items in Table 1, plus an indication of the mode of administration, whether by ultrasound guidance, open or closed needle, butterfly needle, or catheter. All sclerotherapy sessions had to be reported consecutively for all patients, even if the same patient was treated several times during the registry period.

All incidents or accidents were required to be reported and had to be described individually on a separate form (Figure 1). The reporting period was to include 1 month after the end of the registration period in order to include delayed incidents. Investigating centers were given a random number, and the data analysis was blinded. The weekly forms and accident

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Table 1. Number of Sessions, Sclerosing Agent, and Type of Injected Varicose Vein

Type of Varicose Vein	Number of Sessions with Liquid	Number of Sessions with Foam	Number of Sessions with Both
Reticular and spider veins	3,631	2,293	40
Great saphenous vein trunk or junction	261	1,533	130
Small saphenous vein trunk or junction	109	492	4
Main tributaries	422	714	34
Small varices or nonsaphenous	717	332	37
Perforating veins	77	199	2
Postsurgical recurrences	217	832	97
Total	5,434	6,395	344

forms were faxed weekly to the principal investigator (J.-J.G.).

All doctors were members of the French Society of Phlebology, had several years of experience in sclerotherapy, and were equipped with duplex sonograms.

To report an actual and average phlebology practice, no special advice or recommendations were given regarding the sclerosing techniques or sclerosing agents to be used and no data were collected regarding indications or the results of the procedures. Specifically, the efficacy of therapy and bad results, such as matting or pigmentation, were not assessed.

Data were analyzed with SAS software (SAS Institute Inc, Cary, NC, USA) in the Department of Epidemiology and Biostatistics of the Medical University of Dijon. Descriptions provided average \pm SD and percentage. Comparison of percentages was conducted by chi-square testing or with the Fisher exact test when required by a small sample size.

Because all treatments and recordings were obtained in private practice offices, Institutional Review Board approval was not necessary.

Results

Technique of Delivery and Sclerosing Agents

During a median of 8 (\pm 3.1) weeks, 12,173 sessions of sclerotherapy were carried out by the 22 physicians. Foamed sclerosants were used in 6,395 sessions (52.5%), 5,434 with liquid alone (44.6%) and 344 with both liquid and foam (2.8%). Three centers used only liquid sclerosants, 5 used only foam, and 14 used both. The number of sessions, choice of sclerosants, and physical form of the injected varicose veins are reported in Table 1.

Foam sclerosants were less frequently used than liquid for treatment of reticular and spider veins (2,293 vs 3,631). But foam was used significantly more ($p < .001$) in the treatment of great saphenous veins (1,533 vs 261) and small saphenous veins (492 vs 109). Ultrasound guidance was used in 4,088 sessions

(33.9%), whereas in the remaining 7,985 sessions (66.1%), it was not. It is interesting to note that injections of saphenous veins represented 17% of sclerotherapy sessions in this registry.

A closed-needle technique (needle set onto a syringe, blood reflux through a needle controlled by aspiration) was used in 3,504 ultrasound-guided injections (33.9%), and in 584 (14.3%), an open-needle technique (reflux controlled by blood dripping through a needle) was used. In the open-needle technique, the most commonly used device was the butterfly needle.

Physicians using only foam sclerosants were more prone to use ultrasound-guided sclerotherapy (36%) than those using only liquid (0.9%). Finally, an open-needle technique without ultrasound guidance was used in 90 sessions.

Incidents, Accidents, Complications

The accidents/incidents data collection form translated into English is reproduced in Figure 1. Forty-nine incidents or accidents were reported (0.40%). These are tabulated in Table 2. The incidence varies between centers from 0 in 678 (0%) to 5 in 481 (1.04%), which is not statistically significantly different (Fisher exact test, not significant). We regrouped complications and side effects according to their time of onset or recording.

Immediate Complications

Visual disturbances were the most frequently recorded adverse events. They were observed either with liquid (4 times, 20%) or with foam (16 times, 80%). A second look at physicians' files revealed that in three cases, liquid injections included injection of air (air block-derived technique). Thus, this complication occurred almost always when air was injected (19 of 20 times, 95%). Visual disturbances were observed more often after treatment of reticular and spider veins (14 cases, 70%) than after treatment of other types of veins (6 cases, 30%). All cases spontaneously regressed, without after-effects. Visual disturbances were observed in

Center #: _____	Form #: _____	Date: ____/____/2004
Type of incident – accident:		
Immediate	Delayed	
Delay of observation: _____ days	Delay of Onset: _____ min.	
<input type="checkbox"/> Deep V. Thrombosis	<input type="checkbox"/> Vaso-vagal fainting	
<input type="checkbox"/> Anaphylactic Shock	<input type="checkbox"/> Nausea, Vomiting	
<input type="checkbox"/> Headaches	<input type="checkbox"/> Visual disturbances	
<input type="checkbox"/> Paresthesias	<input type="checkbox"/> Intra-arterial Injection	
<input type="checkbox"/> Cutaneous Necrosis	<input type="checkbox"/> Other <input type="checkbox"/> Describe _____	
Responsibility of sclerotherapy regarding onset of adverse event:		
<input type="checkbox"/> Excluded <input type="checkbox"/> Unlikely <input type="checkbox"/> Likely		
Evolution of incident / accident:		
Describe evolution:		
Sequellae: no <input type="checkbox"/>		
yes <input type="checkbox"/>	describe:	
Type of sclerotherapy used:		
Type of treated varicose V. : _____		
Physical form of sclerosing agent: liquid <input type="checkbox"/> Foam <input type="checkbox"/>		
Agent Used:	Name of molecule: _____	
	Concentration: _____ %	
	Injected volume: _____ mL	
	If foam : total injected volume of foam: _____ mL	
Air/Liquid ratio: _____ mL sclerosant + _____ mL Air		
Non US Guided sclerotherapy <input type="checkbox"/>	Ultrasound Guided <input type="checkbox"/>	
Open Needle <input type="checkbox"/>	Closed Needle <input type="checkbox"/>	
Previously sclerosed patient <input type="checkbox"/>		
First session of sclerotherapy <input type="checkbox"/>		
Patient		
Male <input type="checkbox"/>	Female <input type="checkbox"/>	Age: _____ years
Weight: _____ Kg	Height: _____ cm	BMI: _____
If the accident is a DVT:		
Ipsilateral <input type="checkbox"/>	contralateral to injection	
- Personal history of DVTs ?:	yes <input type="checkbox"/>	no <input type="checkbox"/>
- Thrombophilia search:	negative <input type="checkbox"/>	positive <input type="checkbox"/>
	not done <input type="checkbox"/>	indicate abnormality: _____
Was this thrombophilia known by the physician prior to the injection(s):		
	yes <input type="checkbox"/>	no <input type="checkbox"/>
Other remarks:		

Figure 1. Incident/accident reporting form.

very different combinations of foam, with concentrations ranging from 0.1 to 3%, volumes from 1 to 10 mL, and ratios from 1 volume of liquid plus 1 volume of air to 1 of liquid plus 7 of air; both foaming sclerosants were involved. No significant correlation was observed.

All headaches were associated with visual disturbances. Nausea was rare (one case alone, three cases associated with visual disturbances).

Vasovagal fainting was observed in all modalities of care. This incident is nonspecific and benign but does represent the danger of a fall. No incident of falling was reported in this study.

Three cases of paresthesias and cramps were reported. One patient indicated a metallic taste in the mouth after the injection. Curiously, one physician observed four cases of coughing the same day after use of foam.

Delayed Complications

Delayed complications are solely thrombotic. One femoral vein thrombosis occurred in a 53-year-old male with a previous history of superficial varicose vein thrombophlebitis who was treated for great saphenous vein incompetence with 6 cm³ of polidocanol foam (air to liquid ratio: 4/1). He was treated with 1

Table 2. Number of Complications according to Sclerosant Form

	Liquid	Foam	Both
Immediate			
Anaphylactic shock	0	0	0
Intra-arterial injections	0	0	0
Vasovagal fainting alone	4	6	0
Headaches alone	0	0	0
Paresthesias alone	2	1	0
Nausea and vomiting alone	1	0	0
Visual disturbances alone	4	8	0
Visual disturbance associated with 1 or more of headache, nausea, vasovagal fainting	0	8	0
Others	1	5	0
Delayed			
Deep venous thrombosis	0	1	0
Muscular venous thrombosis	0	1	0
Muscular venous extension	0	1	0
Perforating venous thrombosis	0	3	0
Intense superficial thrombophlebitis	0	3	0
Skin necrosis	0	0	0
Total	12	37	0

week of low-molecular-weight heparin and 3 months of oral anticoagulation. There was complete recanalization of the thrombus without any residual reflux. A search for thrombophilia was carried out and proved negative.

One case of distal muscular vein thrombosis was noted, as well as an extension to the saphenogastrocnemius common trunk after sclerotherapy of the small saphenous vein. In three other cases, the sclerosis extended to an entire perforating vein, without muscular or deep vein extension.

The cases of muscular vein thrombosis and sclerosis were treated by compression only, as were the perforating vein extensions, except one, which received a prophylactic dose of low-molecular-weight heparin for 6 days. No further complication or after-effect was reported regarding these patients.

Superficial thrombophlebitis was not supposed to be reported as a "complication" in the registry because these complications belong entirely to the technique and are difficult to classify as normal or abnormal, but three cases attracted the attention of our physicians, either because of an abnormal extension along the vein or because of an excessive inflammatory reaction.

All delayed complications were observed after foam injections, with concentrations ranging from 0.5 to 3%, volumes from 1.5 to 10 mL, and ratios from 1 plus 3 to 1 plus 5 (volume of liquid plus volume of air). No significant correlation was observed.

Fortunately, we did not observe any skin necrosis, muscular necrosis, or arterial injection. These compli-

cations are known but exceptional, thanks to the progress of the technique (mainly ultrasound guidance), and their frequency has probably been reduced dramatically. The occurrence of nonspecific complications, such as allergy and anaphylaxis, was not observed either.

Discussion

General Comment

Interpretation of such a prospective multicenter registry must take into account the flaws and bias inherent in the method. Although the figures achieve a fairly significant number, they are merely the simple observation of a random phenomenon. They represent the activity of these 22 doctors during a single 8-week period. Generalization to the larger community might be erroneous. The panel was made up of professionals who were representative of an average community. Their variety ensures that all modalities of sclerotherapy were assessed. Sclerotherapy in France represents 1 to 1.5 million sessions of multiple injections each per year, carried out by approximately 1,200 physicians. Our data represent about 1% of the yearly sclerotherapy activity in sessions, not treatments or patients. The incidence of incidents or accidents was less than 1% in all centers, which confirms that the average incidence is indeed 0.40%.

There is no accounting of the number of patients treated or of those lost to follow-up. This was not feasible in this type of registry. However, most

complications are not related to a series of procedures but to a single treatment event. The overall risk is, to some extent, multiplied by the number of procedures necessary to achieve the end point of the treatment.

There are three sclerosing agents in common use in France: polidocanol (also known as Lauromacrogol 400), sodium tetradecyl sulfate (also known as Sotradecol), and chromated glycerin. Because most physicians use all three of them, sometimes in the same session, we did not take sclerosant information into account in the evaluation of the practice. It is interesting to note that on the French market, polidocanol represents 74.91% of sales by unit (all concentrations; unit = box of 5 × 2 mL single-use vials), sodium tetradecyl sulfate 13.28% (all concentrations; unit = box of 10 × 2 mL single-use vials), and chromated glycerin 11.81% (single concentration; unit = box of 6 × 5 mL single-use vials). Note that foam cannot be prepared with chromated glycerin.

Analysis of Serious Adverse Events

A serious adverse event is usually defined as an untoward outcome, which can be responsible for any of the following:

- Death
- Life-threatening event
- Hospitalization or prolongation of hospitalization
- Persistent or significant disability or incapacity
- Congenital anomaly or birth defect
- Event considered as severe by the investigator

Regarding venous thromboembolism, no pulmonary emboli were noted, and only one case of true DVT was reported (femoral vein). The other reported nonsuperficial thromboses were either located distally in muscular veins or benign extensions of the sclerosing process to muscular or perforating veins. These required minimal treatment. So, if we consider the definition of a severe adverse event, only one occurred during this registry period.

Benign Complications and Side Effects

Visual disturbances are still a concern for phlebologists. In the study, all cases have been benign, rapidly and completely reversible without treatment, and without after-effects. However, it is worthwhile to observe that the occurrence of such disorders seems to be more frequent when air is injected either with foam or an air block technique. Another interesting observation is the increased incidence after treatment of telangiectasias and reticular veins; these procedures require a slower use of the foam. Therefore, transformation of foam into bubbles with the liquid, as in the

air block technique, may cause the problem.⁴ As indicated above, in this study, no significant correlation was demonstrated between liquid and air ratios and the rate of complications.

There is no clear explanation for the observation, but an association of foam injection with migraine has been reported.¹⁰ In the present study, all headaches were associated with visual disturbances. Three patients of five presenting with visual disturbance and headache after foam injections had a previous history of ophthalmic migraine.

Conclusion

Sclerotherapy is altogether a very safe procedure, and we have demonstrated that the risks of complications are extremely low. As we said previously about DVTs after sclerotherapy: "It is important, however, to remember that the incidence of DVT in a population of patients with varicose veins is greater than in the general population and the correlation with sclerotherapy may not exist at all."¹¹

Importantly, it is necessary to emphasize that sclerotherapy requires in-depth knowledge, proper training, and adequate equipment,¹² such as a duplex scanner, when carrying out ultrasound-guided injections.

It is compulsory to inform patients of all risks, not only of severe and very rare complications but also of benign side effects, such as visual disturbances, in order to restrict immediate driving after injections, and venous inflammation, with its evolution and need for specific care (local skin cream, compression).

The very low risk of deep or muscular venous thrombosis does not remove the need for a duplex check at follow-up sessions at 1 or 2 weeks to assess the efficacy of the injection and to detect a possible DVT. The clinical signs of DVT must be carefully noted to carry out a complete duplex sonogram if necessary.

Visual disturbances appear to be possibly correlated with injection of larger air bubbles than those contained in fresh foam. Further studies should focus on this possible explanation and suggest technical solutions.

Considering the low rate of complications, the low cost of the procedure, the absence of out-of-work time, and the immediate efficacy of duplex ultrasound-guided foam injections, we should expect an important increase in the use of sclerotherapy in the management of varicose veins in the future.

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Commentary

Foam sclerotherapy is ushering in a new era of sclerotherapy.¹ It enhances treatment of telangiectasias and reticular varices and is replacing surgery for varicose veins. When foam sclerotherapy is discussed in meetings and seminars, two questions arise. The first relates to the adverse events that might occur when air is injected into the circulatory system, and the second has to do with the danger of thromboembolic events. This report documents the safety of foam sclerotherapy with regard to these theoretic problems.

The single femoral vein thrombosis in this collected experience was probably identified because of the close surveillance of this particular group of patients. The true incidence of deep venous thrombosis following varicose vein surgery is unknown but is frequently quoted as being 1%. Such surgery has never been subjected to the scrutiny that is employed by all who do foam sclerotherapy, and the 1% figure represents the best guess. The incidence of deep venous thrombosis following conventional sclerotherapy is also unknown but is certainly less than that of surgery and is probably comparable to the experience in this study.

Clearly, injection of air into the circulatory system in the form of foam produces no serious side effects and no cardiopulmonary insufficiency. Foam contains air but is not air, and experimental work reported elsewhere documents the fact that no gross or histologic pulmonary lesions are produced by high quantities of foam injected into the pulmonary arterial circulation of the experimental animal.

Finally, this study confirms the fact that physicians using foam sclerotherapy have seen in their patients a dry cough, visual disturbances, ocular migraine, true migraine, and virtually no permanent adverse events. This study points up the fact that sclerosant mixed with air is associated with adverse events and not the liquid alone. The explanation for this is probably particulate matter crossing from the right heart to the left through a patent foramen ovale (PFO). The prevalence of PFO has been stated to be 27%,² and the incidence is virtually the same for men and women. The presence of a PFO has been associated with cryptogenic stroke in young people.³ Therefore, it is quite logical that a PFO is responsible for the adverse events in foam sclerotherapy.

None of the adverse events after foam sclerotherapy appear to be permanent; therefore, it can be assumed that foam sclerotherapy is safe, as well as efficient and inexpensive.

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