REVIEW ARTICLES

Richard P. Cambria, MD, Section Editor

Neurological complications of sclerotherapy for varicose veins

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Background: **Sclerotherapy has been shown to be an effective and increasingly popular therapeutic strategy for the treatment of varicose veins. However, recent reports of serious side effects, including cerebrovascular accidents (CVA) and transient ischemic attacks (TIA), as well as speech and visual disturbances, have caused serious concern regarding its use. This review evaluated the reported incidences of neurological side effects associated with the use of sclerotherapy.**

Methods: **A systematic search of the data bases MEDLINE, OVID Embase, and Google Scholar was undertaken by two independent reviewers. Articles reporting neurological side effects in humans following foam and liquid sclerotherapy were included; animal studies, laboratory studies, and review articles were excluded. Additional references were also obtained using the related articles function.**

Results: **The search yielded 1023 articles, of which 41 studies were found to meet the inclusion criteria. A total of 10,819 patients undergoing sclerotherapy were reviewed. There were 12 case reports of CVA with confirmatory brain imaging and nine reports of TIA. There were 97 (0.90%) reports of neurological events overall, including TIA, visual and speech disturbances, and 29 cases of reported migraine (0.27%). Symptoms occurred at times ranging from minutes to several days following sclerotherapy. Eleven patients with TIA or CVA were found to have a right to left cardiac shunt, usually a patent foramen ovale.**

Conclusions: **Neurological side effects following sclerotherapy are a rare occurrence; however, CVA associated with the use of sclerotherapy is clearly documented. The pathologic mechanisms resulting in CVA are likely to be different to those leading to migraine and visual disturbances; however, care should be exercised in patient selection, particularly in those with known cardiac defects. (J Vasc Surg 2012;55:243-51.)**

Chronic venous insufficiency poses a huge burden to patients' quality of life and thus, to the economic standpoint of healthcare systems, which have helped to drive the impetus to explore effective and safe treatment strategies. In recent years, the increasing popularity of minimally invasive techniques has resulted in a shift away from traditional surgery and procedures performed under general anesthesia, toward an out-patient based approach.[1,2] The concept of treating varicose veins on an outpatient basis requiring little expense has made sclerotherapy an attractive option, in comparison to other invasive or minimally invasive techniques.[3] Although early attempts to treat varicose veins with sclerosing agents were fraught with complications, predominantly consisting of infections, phlebitis, and gangrene, such that cessation of their use was advised by a panel of experts at a surgical congress in Lyon in the 1800s, the development of newer sclerosants and techniques to improve efficacy has led to a wide acceptance of foam sclerotherapy, which is now considered by many to be a highly successful treatment strategy with minimal side effects.[4] Foam sclerotherapy is used to treat truncal incompetence, perforating veins, and primary and secondary varicosities as well as reticular and spider veins. It is also used in combination with traditional surgery or endovenous thermal ablation. However, recently highlighted serious systemic adverse events, including deep venous thrombosis, pulmonary embolism, and, particularly, neurological events such as transient ischemic attacks (TIA) and cerebrovascular accidents (CVA) have slowed the fervor that was initially observed.[5,6] In this study, we present a review of the literature of the various neurological complications observed following the use of sclerotherapy.

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METHODS

Search strategy. An electronic search was carried out using PubMed, OVID Embase, and Google Scholar to

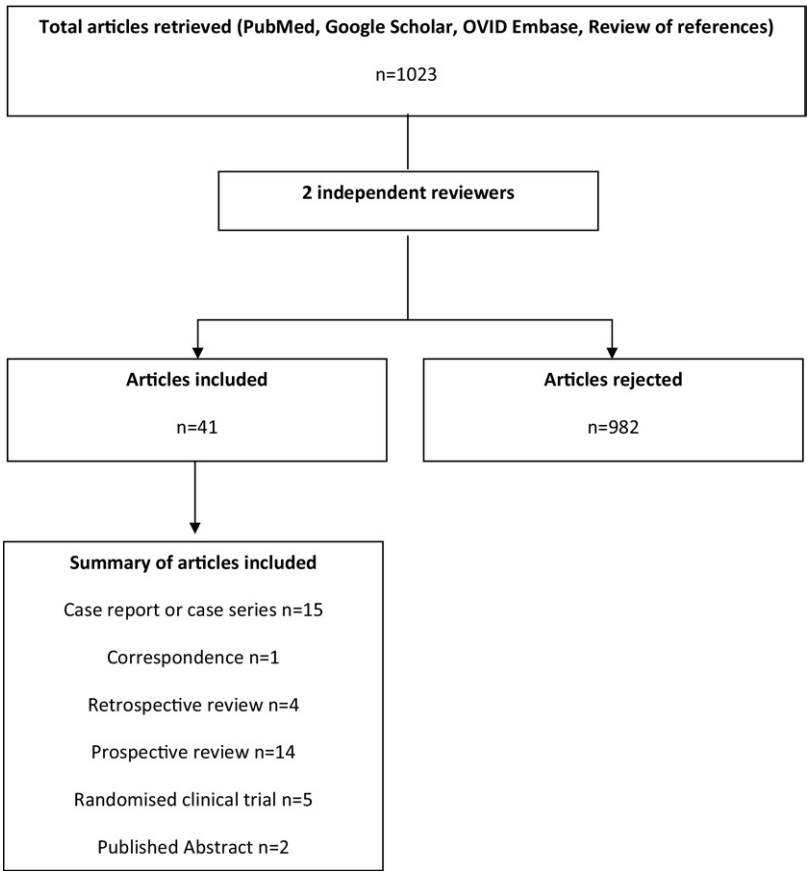

Fig. QUORUM diagram detailing the systematic search strategy.

identify all studies concerned with the use of sclerotherapy for the treatment of varicose veins that reported on neurological complications. The following search terms were used: "vein and sclerotherapy and (TIA or speech or stroke or CVA or migraine or headache or visual or complication)." Based on the title and abstract of the publication, articles containing clinical data on the neurological complications of sclerotherapy were reviewed in detail. The "related articles" function was utilized to broaden the search, and all abstracts, studies, and citations were reviewed for each selected publication. References of the articles acquired were also searched manually. No language restrictions were made. The latest date for this search was January 2011.

Inclusion and exclusion criteria. Any article that reported on neurological complications of sclerotherapy for treatment of varicose veins in humans was included. Laboratory and animal studies were excluded. Systematic reviews, questionnaires, and registries reporting on sclerotherapy were excluded to avoid duplication of data.

Data extraction and quality assessment. Two independent reviewers (A.S., T.S.) assessed the data from each accepted paper and extracted the following information: author, year of publication, type of publication, number of cases treated, the type of sclerosant used, neurological complications observed, and the presence of any detected cardiac abnormalities. The reported neurological complications were categorized as CVA, TIA, visual disturbances, or speech disturbances. CVA were diagnosed based on the presence of confirmatory cerebral imaging. Episodes were classified as TIA if they had been reported as TIA in the original publication; symptoms were otherwise reported as visual or speech disturbances. The numbers of patients reporting migraine or headache were also reported, although the authors acknowledge these may not necessarily represent neurological complications; the criteria used to differentiate between headache, migraine with aura, and visual disturbances is likely to have been different in different studies and for this reason all are included. Any discrepancy between the two independent reviewers was resolved following discussion with a third party.

RESULTS

The search yielded 1023 articles, of which 41 articles met the inclusion criteria and were subsequently included. Of these articles, there were 15 case reports, one correspondence, two published abstracts, four retrospective studies, 14 prospective studies, and five prospective randomized studies. A summary of the papers included is detailed in the Figure.

This gave a total of 10,819 patients who underwent sclerotherapy with either liquid or foam sclerosants. Sodium-tetradecyl sulfate (STS) was used in 5990 cases, polydocanol (POL) in 3999 cases, chromated glycerin (CRO) in 52 cases, and sodium morrhuate in one case.

Case reports. The majority of neurological side effects defined as TIA or CVA were reported as case reports or small case series (Table I). Nine patients were reported to have had a TIA, three of which were reported as case reports; however, the authors are unable to state whether or not all of these diagnoses were confirmed by a neurologist. CVA was reported to have occurred in 12 patients, all of which were reported as case reports. Confirmatory cerebral imaging of the presence of CVA was confirmed either by computed tomography imaging (CT) in four patients[7-10] or magnetic resonance imaging (MRI) in six patients.[11-14] One patient had normal MRI imaging but, due to persistent symptoms for 2 days, was classified as having had a CVA,[15] and one patient had thrombus in the right middle cerebral artery on autopsy.[16] The earliest case report found was in 1947, published in the British Medical Journal, of transient hemiplegia and speech disturbance in a 32-year-old female after the injection of sodium morrhuate,[16] and in 1951, a 62-year-old female patient who died shortly after injection of sodium morrhuate into varices[16] was found to have evidence of intracranial hemorrhage and thrombus in the middle cerebral artery at postmortem. The other cases included four left middle cerebral artery (MCA) territory infarcts, one right MCA infarct, two right-sided cerebellar infarcts, one right frontal infarct, and two cases of air emboli in the MCA. The timing of the onset of symptoms was highly variable. In eight cases, symptoms occurred within minutes of treatment,[7,8,12,13,16,17] in three cases this occurred at 1 to 4 hours,[14,15,18] two cases reported symptoms the following day within 24 hours,[11,13] and the remaining cases were at 2 days, 3 days, and 5 days following treatments.[9,10,13] In two cases, residual weakness was observed at the time of discharge from hospital, and there was one reported fatality in the case of the patient who suffered a hemorrhagic stroke.[16] However, in the majority of cases, symptoms completely resolved prior to discharge from the hospital. In 11 of the 16 cases of TIA or CVA, the patients were confirmed to have a patent foramen ovale (PFO) on echocardiography or transesophageal imaging; in three cases no cardiac defects were found; and in the remaining three cases, results of cardiac investigations are not mentioned. There was one reported case of an episode of transient visual and speech disturbance, not thought to be due to a TIA that occurred in a patient with a PFO. In seven cases (37%), liquid sclerosants were used resulting in one migraine, four CVAs, and two TIAs. The remaining 12 (63%) were following foam sclerotherapy and included eight CVAs, one TIA, and one migraine.

Cohort studies and randomized trials. The remaining 26 articles included prospective or retrospective studies and randomized trials and evaluated 10,801patients. There were six additional cases (0.06%) of TIA or amaurosis fugax reported, one of whom had a proven PFO. No cases of CVA were reported. Visual disturbances not considered to be a TIA or CVA were reported to have occurred in 84 of 10,801 (0.78%) patients within the cohort studies. A total of 357 treatment sessions using liquid sclerosants were identified; however, in all the mentioned studies, this was compared with foam sclerosants. In two studies, the authors specify that the visual disturbances occurred following the administration of foam rather than liquid.[19,20] In the remaining two studies, there were six episodes of transient visual disturbances where the treatment preparation was not specified, and therefore may have occurred following liquid sclerosants. There were eight cases of headache following liquid sclerosants.[21,22] One patient reported an isolated speech disturbance, and one study reported on six cases of visual disturbances, paresthesia headache, and migraine; however, numbers were unspecified (Table II).[23] An additional 76 patients in total (0.70%) reported headaches, and 29 (0.27%) reported migraine with aura (Table II). The overall incidence of neurological complications, defined as including TIA, CVA, and/or speech, visual, or motor disturbances but not including migraine, calculated from the combined data from the cohort studies and randomized trials was 97 (0.90%). Cardiac defects, including PFO, were reported in three patients with migraine; however, cardiac investigations were not carried out in all patients. Techniques used to create foam varied widely, but the Tessari[24] technique appeared to be the most frequently used (Table II). Concentrations of sclerosant used frequently depended on the type of vein treated and the sclerosant utilized, but varied from 0.25% to 5%. The volumes of sclerosant used also varied significantly, and frequently depended on the size and nature of the veins treated; however, in the majority of studies, <20 mL of foam per patient was used. In five studies, more than 20 mL was frequently used; however, no association between the volumes of foam used and the reporting of neurological side effects was identified (Table II). Air was the most frequently used gas; however, CO^2 was used in three studies, and O^2 was used in one study. The most frequently used ratio of gas to sclerosant mixture was 1:4; however, ratios ranged from 1:2 to 1:8. No association between the gas used or the ratio of gas and sclerosant and the number or type of neurological side effects was observed (Table II).

DISCUSSION

The findings of this systematic review highlight that serious neurological complications following foam sclerotherapy are rare, particularly when carried out by trained clinicians in a controlled environment. However, the occurrence of CVA and TIA is well-documented following sclerotherapy and therefore raises understandable concern. The majority of these incidences are published as case reports with confirmatory evidence of cerebral ischemia, although the majority of patients had no residual deficit when discharged from hospital. The first recorded incidence of CVA following sclerotherapy appears to have occurred in 1951 and resulted in the death of a 41-year-old woman. Intracranial hemorrhagic and thrombus in the

Table I. Overview of case report studies reporting neurological complications following foam sclerotherapy

First author	*Year*	*Type of study*	*Total patients*	*Type of vein*	*Foam used*	*Liquid used*	*Technique*	*Volume*	*Concentration of sclerosant (%)*	*Ratio of liquid:air*
Benigni[33]	2003	CR	1	RV	1	0	U	2 mL	0.2	U
Bush[7]	2008	CR	2	P, RV, T	2	0	Tessari	2-10 mL	2	U
Drai[17]	1994	CR	1	V	0	1	U	U	U	U
Forlee[8]	2006	CR	1	GSV	1	0	Tessari	20 mL	0.5	—
Gardner[34]	1947	CR	1	V	0	1	NA	0.75 mL	5	—
Hahn[1]	2010	CR	1	SSV	1	0	Tessari	3 mL	1	—
Hanish[10]	2004	CR	1	R, T	0	1	U	0.5 mL	0.5	NA
Hartmann[18]	2009	CR	1	GSV, SSV	1	0	DSS	9 mL	3	1:4
Kas[11]	2000	CR	1	T	1	1	U	1 mL	U	U
Kunzlberger[28]	2006	CR	1	T	0	1	NA	2 mL	1	NA
Leslie-Mazwi[12]	2009	CR	1	U	1	0	Benigni-Sadoun	U	U	U
Ma[13]	2011	CR	3	V	3	0	Tessari	4-16 mL	1.5-3	1:3
Peller[16]	1951	CR	1	V	0	1	NA	2 mL	5	—
Picard[14]	2010	CR	1	GSV	1	0	Tessari	4 mL	0.5	1:4
Van der Plas[15]	1994	CR	1	GSV, P	0	1	NA	2 mL	3	NA
								1 mL	1	

AASV, Anterior accessory saphenous vein; *ASD*, atrial septal defect; *CR*, case report; *CVA*, cerebrovascular accident; *GSV*, great saphenous vein; *mL*, milliliters; *NA*, not applicable; *P*, perforating vein; *PFO*, patent foramen ovale; *POL*, polydocanol; *R*, reticular vein; *SSV*, small saphenous vein; *STS*, sodium-tetradecyl sulphate; *T*, telangiectasia; *TIA*, transient ischemic attack; *U*, unknown/unspecified; *V*, varices/varicosities/tributaries.

right-middle cerebral artery was found on postmortem examination, the reasons behind which are unclear. The authors of the original paper suggested that the death was likely to have occurred as a result of anaphylaxis; they were unable to explain the intracranial thrombus and hemorrhage. The precise mechanism behind the occurrence of symptoms is poorly understood, and several different etiologies have been suggested. The authors acknowledge that the techniques used for the injection of sodium morrhate into varices in the 1940s and 1950s were considerably different from techniques used in sclerotherapy today. In the majority of patients with CVA or TIA, a PFO or other right to left cardiac shunt has been identified, and the majority of authors hypothesize that symptoms occur as a consequence of particles of sclerosant arriving in the cerebral circulation through a right to left cardiac shunt. Evidence for the theory includes the demonstration of bubbles on transcranial Doppler (TCD); however, foam bubbles in the middle cerebral artery have been observed on TCD in the absence of neurological complications[25] in up to 42% of patients undergoing foam sclerotherapy.[26] Other proposed mechanisms include the fact that symptoms occur as a result of air embolus, and confirmatory MRI images of air bubbles in the cerebral circulation of symptomatic patients suffering CVA have been reported.[12,13] Similar neurological symptoms have also been observed in divers after surfacing, whereby air bubbles have been shown to cause transient neurological symptoms.[27] It has also been suggested that an inflammatory reaction to the sclerosant may cause vasospasm resulting in symptoms.[28]

Liquid sclerotherapy was the first of its kind to be utilized, but further technical refinement has led to the development of "foam," which was formally published by Orbach.[29] Foam is a combination of sclerosant and gas and has been favored over liquid sclerotherapy due to its prolonged contact with the vein intima by its ability to displace blood from the treated vein and thus requires reduced amounts of sclerosant for treatment.[30] It has been suggested that neurological side effects appear to be more common with the use of foam,[31] with a median rate of 1.4% quoted in a previous systematic review.[6] However, the authors report four cases of CVA and seven cases of TIA following the use of liquid sclerosants in this review. This included two case reports of neurological events of likely stroke and TIA,[16,32] which were originally reported as anaphylactic reactions to sodium morrhate. Therefore, there may be a number of neurological events that were incorrectly attributed to anaphylactic reactions following liquid sclerosants that have gone unnoticed.

It has been suggested that the method for foam creation may also be an influencing factor for the development of neurological symptoms due to the varying size of bubbles produced. The Monfreux method generates foam via the use of a glass syringe that contains liquid sclerosing solution. The outlet of the syringe is sealed and the piston is pulled back drawing air into the syringe through the gap between the syringe body and the piston, creating a fluid foam with reasonably large bubbles.[24]

This method has been proposed to have higher rates of side effects such as dizziness and states of confusion,[25] thought to be due to the creation of larger air bubbles, although the true nature of these symptoms is questionable. Due to the fact that not all studies published details of the methods used to create foam, and the relatively small number of neurological side effects that were observed, the authors were unable to conclude whether the method of foam creation had any effect on the incidence of neurological side effects. However, the majority of the studies included utilized the Tessari technique, which is distinguished by creating a mixture of fine-bubbled sclerosant in

Table I. Continued

Type of gas			*Sclerosant*			*Neurological symptoms/disturbances*						*Cardiac defect*
Air	O_2	CO_2	*STS*	*POL*	*CG*	*Migraine*	*Headache*	*Visual*	*Speech*	*TIA*	*CVA*	
U	U	U	0	1	0	1	0	0	0	0	0	U
2	0	0	2	0	0	0	0	0	0	1	1	ASD + U
U	U	U	U	U	U	0	0	0	1	1	0	PFO
1	0	0	0	1	0	0	0	0	0	0	1	PFO
NA	NA	N	Sodium morrhuate			0	0	1	1	1	0	U
1	0	0	0	1	0	0	0	0	0	0	1	PFO
U	U	U	0	1	0	0	0	0	1	0	1	PFO
1	0	0	0	1	0	0	0	1	1	0	0	PFO
U	U	U	0	0	1	0	0	0	1	0	1	PFO
NA	NA	NA	0	1	0	1	0	0	0	0	0	0
U	U	U	1	0	0	0	0	0	0	0	1	0
3	0	0	3	0	0	0	0	0	0	0	3	3x PFO
NA	NA	NA	Sodium morrhuate			0	0	0	0	0	1	Not detected
1	0	0	0	1	0	0	0	0	0	0	1	PFO
NA	NA	NA	0	0	0	0	0	0	0	0	1	U

air or gas using two syringes and a three-way tap. Sclerosant is flushed back and forth between the two syringes via a three-way tap, usually in the ratio of one part sclerosant to four parts air.[26] This technique is believed to contain compact, smaller diameter air bubbles within the foam, providing further evidence that additional factors are likely to be involved. The volumes of foam sclerosant used have also been called into question. Many have suggested that the use of large amounts of foam, such as the 20 mL used in the case of ischemic stroke reported by Forlee et al,[8] is unsafe. However, this review highlighted other cases that also reported the subsequent development of CVA when using <10 mL of foam[7,14,15] and thus, the degree to which the volume of sclerosant injected contributes to the development of neurological side effects is questionable. However, the majority of studies included in this review appear to have used <20 mL of foam per patient.

It is likely that the pathologic mechanism resulting in CVA is different than that occurring in patients reporting transient visual, speech, and motor disturbances and symptoms of migraine, and it is likely that the majority of the neurological side effects seen are unrelated to true CVAs, which are very rare. The majority of symptoms occurred within minutes to hours after the injection of sclerosant; however, there are cases of symptoms occurring up to 5 days afterward.[9] It is highly implausible that this could have been caused by an air or sclerosant particle in the cerebral circulation, and the authors suggest it may have been caused by a paradoxical venous thromboembolism and although a PFO was demonstrated in this case,[9] no evidence of deep vein thrombosis was found. Indeed, there has also been a case report of a TIA following phlebectomy, which may have been a coincidental association.[27] Patients known to suffer from migraine with aura appear to be at greater risk of developing visual disturbances,[28] and it has been suggested that these visual disturbances correspond to migraines with aura.[29] An association between migraines with aura and PFO has been quoted by many observational studies and may offer a plausible explanation for the occurrence of visual disturbances after sclerotherapy. This has been strengthened by research published by Raymond-Martimbeau, whereby 71.4% of patients reporting visual disturbances, migraines with aura, or chest tightness following foam sclerotherapy were found to have PFO.[30] It has been suggested that cytokines, such as endothelin released by the action of foam sclerosants acting on the endothelium, reach the cerebral arterial circulation through right to left cardiac or intrapulmonary shunts. Endothelin has been shown to initiate one of the pathways leading to migraine with aura. Support for this theory is provided by reported incidences of migraine with aura reported following angiographic studies.[29] It is hypothesized that foam bubbles passing through a PFO may induce endothelin release, which quickly reaches the cerebral cortex, leading to cortical spreading depression, a depolarizing waveform occurring in the cerebral cortex, and shown to be associated with migraine with aura, including visual, speech, and motor disturbances.[31] Levels of endothelin measured in rats following foam sclerotherapy appear to be significantly higher than in those who have been treated with liquid sclerosants[32] in the minutes following the procedure, which may provide an explanation as to why neurological symptoms appear to occur more frequently following foam sclerotherapy. Generally, the pressure gradient between the right and the left atrium is small in most patients with PFOs, but the incidence of shunting can be increased when the pressure in the right atrium is raised, such as during valsalva maneuvers. Therefore, it has been suggested that

Table II. Overview of cohort and randomized studies reporting neurological complications following foam sclerotherapy

First Author	*Year*	*Type of study*	*Total patients*	*Type of vein*	*Foam used*	*Liquid used*	*Technique*	*Volume of foam (cm3)*	*Concentration of sclerosant (%)*
Bergan[35]	2006	PR	293	GSV, P, V	293	0	Tessari	5-10 mL	1-3
Bhogal[36]	2008	PA	112	—	112	0	U	10-17 mL	U
Bradbury[37]	2010	PR	977	GSV, SSV, AASV	1252 legs	0	Tessari	4-8 mL	1-3
Cabrera[38]	2004	RR	116	GSV, SSV, P	116	0	U	1-30 mL	0.27-1
Cabrera[39]	2001	RR	783	GSV + V	783	0	U	10-20 mL	0.25-3
Cavezzi[40]	2002	PR	194	75 V, 15 R, 11 AASV, 33 SSV, 43 GSV, 17 P	194	0	Tessari	2.9 mL	0.2
Ceulen[41]	2008	C	35	U	35	0	U	5 mL	1
Chapman[42]	2009	PR	146	146 GSV	146	0	Tessari	7.3 mL	3
Darke[43]	2006	PR	181	115 GSV, 28 SSV, 77 other	181	0	Tessari	14 mL	1
Demagny[19]	2002	PRT	254	GVS + V	200 veins	200 veins	U	2 mL	1.5-3
Frullini[44]	2002	RR	453	337 large veins 116 small varicosities	257	196	257 Monfreux 196 Tessari	U	U
Frullini[45]	2000	RR	U	GSV, SSV, V	595 veins	0	Frullini	U	U
Gillet[46]	2010	PR	20	GSV n = 7, SSV n = 2, AASV n = 4, V n = 10, R n = 5, P n = 1	20	0	DSS + Sterivein device	5.60 + 2.77 mL	0.5-3
Gillet[47]	2009	PR	1025	818 GSV 207 SSV	1025	0	Tessari/DSS	4.5 mL	0.5-3
Kern[20]	2004	PRT	150	150 RV + SV	51	99	Monfreux	10 mL	100 CRO 0.25 POL
Morrison[48]	2008	PR	177	GSV, SSV, V	177	0	Tessari	6-57 mL	1
Myers[49]	2007	PR	489	453 GSV 174 SSV		U	Tessari	3-40 mL	0.6-3 foam 3 liquid
Neuhardt[23]	2008	PA	75	U	100	0	Tessari	4-35 mL	1-3
Ouvry[21]	2008	PRT	95	95 GSV	47	48	DSS	2-2.5 mL	3
Park[50]	2009	PR	312	437 GSV/SSV	312	0	Tessari	2-13 mL	3
Raymond-Martimbeau[51]	2009	PR	3259	GSV, SSV, V	3259	0	Raymond-Martimbeau	0.5-8 mL	0.5-3
Reich-Schupke[52]	2010	PR	76	V	110 legs	0	Tessari	1-2 mL	0.5
Smith[53]	2006	PR	808	1109 GSV + SSV	808	0	Tessari	<20 mL	1-3 STD 1 POL
Tessari[54]	2001	PR	77	24 GSV/SSV 30 V 23 RV/SV	77	0	Tessari	1-8 mL	0.1-3
Wright[22]	2006	PRT	562	GSV, SSV	552	10	U	<30 mL 9.8 mL	1 0.5-3
Yamaki[55]	2009	PRT	107	107 GSV	107	0	Tessari	0.7-4 mL	1-3

AASV, Anterior accessory saphenous vein; *ASD*, atrial septal defect; *C*, correspondence; *CRO*, chromated glycerin; *CVA*, cerebrovascular accident; *GSV*, great saphenous vein; *mL*, milliliters; *NA*, not applicable; *P*, perforating vein; *PA*, published abstract; *PFO*, patent foramen ovale; *POL*, polydocanol; *PR*, prospective cohort study; *PRT*, prospective randomized trial; *R*, reticular vein; *RR*, retrospective cohort study; *SSV*, small saphenous vein; *STS*, sodium-tetradecyl sulphate; *TIA*, transient ischemic attack; *U*, unknown/unspecified; *V*, varices/varicosities/tributaries.

avoiding maneuvers such as bending over to put on shoes or compression stockings and remaining supine following injection of foam[33] for approximately 5 minutes may reduce the risk. In the majority of studies evaluated in this review, details of such activities are infrequently published, making it difficult for the authors to comment as to whether this contributed to any of the side effects reported. Further studies to support this hypothesis are awaited, although it is important to note the contrast between the relatively high prevalence of PFO in general population (up to 25%)[34] and the exceedingly low incidence of neurological complications after foam sclerotherapy. It is, therefore, highly likely that additional factors are involved, and, in view of these data, the authors feel unable to justify the routine investigation of all patients for a cardiac defect prior to sclerotherapy, which would be impractical.

Table II. Continued

Ratio of liquid: air	*Type of gas*			*Sclerosant*			*Neurological symptoms/disturbances*						*Cardiac defect*
	Air	*O_2*	*CO_2*	*STS*	*POL*	*CG*	*Migraine*	*Headache*	*Visual*	*Speech*	*TIA*	*CVA*	
1:4	293	0	0	0	34	0	0	0	3	0	0	0	U
U	U	—	U		U		0	0	1	0	0	0	U
1:4	977	0	0	977	0	0	0	3	5	0	0	0	U
U	0	0	116	0	116	0	0	0	2	0	0	0	U
U	783	0	0	Lauromacrogol 400			0	0	8	0	0	0	U
1:4/5	194	0	0	194	0	0	0	0	1	0	0	0	U
1:4	35	0	0	0	35	0	1	0	1	0	0	0	7× PFO
1:3	146	0	0	146	0	0	2	0	0	0	0	0	U
1:3	181	0	0	0	181	0	1	0	2	0	0	0	U
1:4	200	—	0	400	0	0	0	0	0	0	5	0	U
U	453	0	0	363	90	0	0	0	4	0	0	0	U
1:2	595	U	U	387	208	0	0	0	2	0	0	0	U
1:4-1:8	20	0	0	1	19	0	10	10	20	1	0	0	U
1:1-1:5	953	72	0	94	931	0	8	0	7	0	1	0	1× PFO
1:4	150	0	0	0	99	51	0	0	3	0	0	0	U
1:4	49	0	128	0	177	0	0	0	8	0	0	0	U
2:3	489	0	0	Both		0	0	0	3	0	0	0	U
U	100	0	0	0	100	0		<7% U			0	0	U
1:4	95	0	0	0	95	0	0	1	0	0	0	0	U
1:5	312	0	0	0	437	0	0	2	1	0	0	0	U
1:4	3259	0	0	3259	0	0	4	0	2	0	0	0	5× PFO
1:5	110	0	0	0	110	0	1	1	0	0	0	0	U
1:3	808	0	0	1000	149	0	0	0	14	0	0	0	U
1:4	77	0	0	77	0	0	0	0	2	0	0	0	U
U	437 Varisolve, 64 STD, 61 POL			64	498	0	0	62	6 U	0	0	U	0
1:4	107	0	0	0	112	0	2	0	0	0	0	0	2

It has also been suggested that the solubility of the gas used to create the foam may have an effect on the complications observed. The replacement of air mixture, containing high percentages of relatively insoluble nitrogen with carbon dioxide, which is highly soluble, has been shown to reduce side effects such as dizziness and chest tightness, but no statistically significant reduction was noted in the occurrence of visual disturbances or other neurological side effects.[35]

The true incidence of neurological complications following sclerotherapy remains unknown and is subject to significant reporting bias. The authors also acknowledge that in some of the articles included in this review, important details regarding the nature of treatment provision, the neurological side effects experienced, and cranial or cardiac imaging are omitted from publications, making it difficult to interpret the relationship between neurological side effects and different sclerotherapy regimes.

At present, the use of foam sclerotherapy in the UK is considered acceptable for use by the National Institute for Health Clinical Excellence, which has provided guidance for its use.[36] However, it is still "off-label," with the intention of enhancing efficacy, and the key to success appears to be appropriate patient selection and caution in certain patient groups. Obtaining informed consent as well as adequate posttreatment care with the propensity to avoid, identify, and treat complications should be routinely instituted. Sclerotherapy remains a cost-effective way of treating varicose veins particularly for recurrent veins, patients with tortuous veins, and those unable to tolerate anesthesia or sedation, and allows treatment to be performed with minimal discomfort, rapid recovery times, and high levels of patient satisfaction in many cases.[37-39] Uniformity in the reporting standards of studies using sclerotherapy, such as including details of the type and form of sclerosant used, the gas mixture, details of the preparation technique, and the volumes used would be helpful in allowing comparisons between studies, which at present is difficult due to the heterogeneity of the reported data. There is also a need for clinicians to report all major complications to the regulatory authorities so that an accurate picture of complication rates is reported, as there is often a tendency to report only positive results.[40]

CONCLUSION

When considering the treatment of varicose veins, a condition that is commonly perceived as benign, one can appreciate the enormous tumult related to the major and potentially fatal neurological complications that have recently been reported with sclerotherapy. Nonetheless, the current literature highlights their relative infrequency when considering the millions of sclerotherapy injections that have been carried out to date. However, precautions should be exercised particularly in patients with a known PFO and perhaps those known to suffer from migraine.

AUTHOR CONTRIBUTIONS

Conception and design: AS, TS, AD
Analysis and interpretation: AS, TS, TW
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Writing the article: AS, TS
Critical revision of the article: TW, AD, AS
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TS and AS contributed equally to this work.

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