

Safety Concerns for Sclerotherapy of Telangiectases, Reticular and Varicose Veins

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Key Words

Sclerotherapy · Varicose veins · Safety · Polidocanol · Sodium tetradecyl sulphate

Abstract

Background: Sclerotherapy has been extensively used in the treatment of valvular insufficiency of superficial veins. Although sclerotherapy seems safe, reports of serious adverse events (AE) have been published. This paper aims to review AE of sclerosing agents. **Methods:** Electronical databases were searched for identifying articles on local, serious and long-term AE of sclerotherapy. **Results:** Hyperpigmentation and matting are the most often local AE of sclerotherapy. Other local AE include superficial thrombophlebitis, pyoderma gangrenosum, pain, ulcer formation, and hypertrichosis. Local AE can be serious, that is, it can include cutaneous necrosis, intra-arterial injection with subsequent acute ischemia that can lead to amputation, and necrotizing fasciitis. Most data on systemic AE of sclerotherapy are extracted from case series and case reports. Systemic AE include neurological complications, such as ischemic stroke, transient ischemic attack, visual disturbances and cardiac toxicity, that is, myocardial infarction, Takotsubo cardiomyopathy, chest tightness, pulmonary embolism, deep vein thrombosis, septicemia, anaphylaxis. It is difficult to estimate the frequency

of serious systemic AE of sclerotherapy. **Conclusion:** Physicians practicing sclerotherapy should be aware of the possible local and systemic AE of sclerotherapy, inform patients accordingly and be prepared for the appropriate management of the rare but possibly lethal serious AE.

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Introduction

Treatment options for varicose veins include compression hosiery, endovenous laser ablation, radiofrequency ablation, conventional operation, subfascial endoscopic perforator surgery, and sclerotherapy [1]. Sclerotherapy involves the injection of a liquid or foam substance that interacts with the vessel lining, causing a controlled thrombophlebitic reaction. This response, if successful, leads to the production of a fibrous cord [2]. The sclerosants most commonly used worldwide include glycerin, hypertonic saline, morrhuate sodium, sodium tetradecyl sulphate (STS), and polidocanol.

Although sclerotherapy is generally considered safe, there are certain publications that reveal the presence of serious adverse events (AE) of sclerotherapy and this leads to safety issues. This paper aims at reviewing AE of sclerosing agents.

Sclerosing Agents

Sclerosants can be classified into detergents, chemical irritants, and osmotic agents [3].

Detergents destroy vein cell membrane through protein denaturation. Detergent solutions include sodium morrhuate, ethanolamine oleate, STS, and polidocanol.

STS is composed of sodium 1-isobutyl-4-ethylcoyl sulfate plus benzoyl alcohol 2% and phosphate buffered to pH 7.6. The mechanism of action of STS is based on the disruption of the intercellular cement between the endothelial cells, resulting in the desquamation of the cells in plaques. Sodium tetradecyl sulfate is a potent toxin for endothelial cells in that, brief exposure to even low concentrations are effective in stripping endothelium over a considerable distance [4–8]. Diluted sodium tetradecyl sulfate is also able to induce a hypercoagulable state, possibly by the selective inhibition of protein C, protein S and antithrombin and it can also promote platelet aggregation [6–8]. STS is commonly used in concentrations of 0.5–3% to sclerose lower limb varicose veins [4, 5]. The maximum dose for STS is 10 ml of 3% solution [4].

Polidocanol is quite popular in Europe. Polidocanol is a synthetic fatty alcohol with detergent activity causing endothelial cell death [9]. Polidocanol is used in concentrations of 0.25–5% to sclerose lower limb varicose veins and telangiectasias [4, 5].

Sodium morrhuate is a biological extract rather than synthetic compound and its composition varies from lot to lot [10]. It is FDA approved for the treatment of vascular ectasias of the lower extremity. Ethanolamine oleate is a synthetic preparation of oleic acid and ethanolamine that has weak detergent properties. The principal disadvantages of the drug are high viscosity that makes injection difficult, a tendency to cause red cell hemolysis and hemoglobinuria, the occasional production of renal failure at high doses and the possibility of pulmonary complications [5].

Chemical irritants damage the cell wall by direct caustic destruction of the epithelium. Chemical irritants include polyiodinated iodine, that is, a mixture of elemental iodine with sodium iodide, along with a small amount of benzyl alcohol, and chromated glycerin [4, 5]. Polyiodinated iodine is not FDA approved, while it is approved by Health in Canada for local injection in sclerotherapy [4, 5].

Chromated glycerin is a chemical irritant with weak sclerosing effect. Chromated glycerin has been used since 1933 for the treatment of telangiectasias [4, 5, 11].

Osmotic agents damage the cell by shifting the water balance through cellular gradient (osmotic) dehydration and cell membrane denaturation. They include hypertonic sodium chloride solution and sodium chloride solution with dextrose. The principal advantage of hypertonic saline is the fact that it is a naturally occurring agent with no molecular toxicity [4, 5].

Safety of Detergents

Local AE

Hyperpigmentation and matting are the most often local AE of sclerotherapy. Post-sclerosis dermal pigmentation is defined as the appearance of increased pigmentation that is observed within the course of an ectatic blood vessel, treated with sclerotherapy. Dermal pigmentation can be transient or permanent. The incidence of transient hyperpigmentation ranges from 10 to 30%. Its onset is gradual after treatment session with peak appearing at 6–8 weeks posttreatment. Although hyperpigmentation may persist for months, spontaneous resolution occurs in 70% of patients in 6 months with 99% resolution occurring in 1 year. Permanent pigmentation, that is, staining after 1 year affects 1–2% of patients [12]. Hyperpigmentation is caused by the migration of melanin pigment to the skin and by the deposition of hemosiderin in the dermis. Perivascular fragmentation of red blood cells occurs after fragmentation by macrophages. The intracellular fragments in the macrophage cytoplasm are further compartmentalized into hemoglobin containing globules. Since hemosiderin is an indigestible residue of hemoglobin degradation, it may appear as aggregates up to 100 μm in diameter [13–17]. Removal of post-sclerotherapy thrombi may reduce the incidence of hyperpigmentation. Persistent thrombi are thought to cause ‘perivenulitis’. The ‘perivenulitis’ favors extravasation of red blood cells through a damaged endothelium or by an increase in permeability of treated endothelium. Thus, the development of postsclerotherapy hyperpigmentation is influenced by the extent of endothelial destruction with resultant inflammation and extravasation of red blood cells [13–17]. Evidence suggests that the incidence of hyperpigmentation is greater with certain concentrations of STS, hypertonic saline and polidocanol than with chromated glycerin [17, 18]. Despite the involvement of melanin in the etiology of hyperpigmentation after sclerotherapy, no scientific evidence could be identified on the effect of sunlight on predisposition to hyperpigmentation.

Telangiectic matting or post sclerotherapy neo-vascularization refers to the appearance of tiny red telangiectasias that appear in the area of the sclerosed vein. This local AE occurs in approximately 15–20% of patients treated with sclerotherapy. Matting consists of an unpredictable individual reaction of the patient that appears after the surgical removal of the vein [12, 19]. The cause of matting remains unclear. It has been suggested that this represents either dilatation of pre-existing subclinical vessels or angiogenesis due to inflammatory processes and vascular obstruction [12]. It appears as a patchy pigmentation with onset 4–6 weeks posttreatment. Technique-related measures to prevent this complication include using the minimum sclerosant concentration, small volumes and low pressure when treating a vein. Telangiectic matting usually is transient and resolves 3–12 months posttreatment [5, 12]. Nevertheless, matting can be also permanent [12]. The first step in treating matting is to look for untreated proximal reflux from saphenous veins, perforators, tributaries, or reticular veins [5]. Glycerin has a low risk for telangiectic matting [5].

Nerve injury may infrequently occur following sclerotherapy of deeper venous segments. The nerves most commonly affected are saphenous or sural nerve, which lie close to the greater and lesser saphenous vein respectively [20]. Normally the dysfunction resolves in 3–6 months.

Superficial thrombophlebitis after sclerotherapy is reported at a frequency of 4–7.5% [1]. It occurs primarily after treatment of larger varicose veins and is manifested by an area of erythema, heat, and tenderness over an indurated venous segment. This usually develops within a few weeks of treatment and involves the treated area or a venous segment proximal or distal to the injection site [21]. In case of post sclerotherapy superficial thrombophlebitis, assessment should be made to understand the involvement of the proximal saphenous veins and concomitant deep vein thrombosis.

Pyoderma gangrenosum occurs rarely. It can develop at sites of minor trauma and in surgical wounds. It has been reported following sclerotherapy [22]. Other local AE include pain, hypotrichosis.

Serious Local AE

Cutaneous necrosis may occur with the injection of any sclerosant agent under ideal circumstances and does not necessarily represent physician error [12]. Cutaneous necrosis is infrequent; it is reported to affect 0.23% of patients. The mechanism of necrosis is not known; however, possible causes have been suggested, including extravasa-

tion of the solution into the perivascular space, injection into a dermal arteriole or arteriole feeding a varicose vein, reactive vasospasm of a vessel, passing of the sclerosant into arterial circulation through arteriovenous anastomoses [23], sludge formation and subsequent closure of arteriovenous shunts, excessive cutaneous pressure induced by compression techniques. However, it is usually reported after perivascular injection of sclerosants in higher concentrations and rarely after properly performed intravascular injections of sclerosants in various concentrations, that is, 0.5% polidocanol in the treatment of spider veins [12]. A relevant study has examined the experimental potential of liquid and foamed polidocanol in causing skin necrosis, when injected into the superficial subcutaneous tissue of rats and has showed that quantities of up to 0.5 ml of 0.5% polidocanol, as either a liquid or foam, do not induce visible skin necrosis [24]. In addition, experimental data show that the likelihood of cutaneous necrosis depends on the pressure of injection and the diameter of the vessel, that is, the greater the pressure the greater the likelihood of cutaneous necrosis and the smaller the vessel the greater the likelihood of cutaneous necrosis. According to Poiseuille's law, pressure decreases proportionally as viscosity increases and, thus, the risk of cutaneous necrosis is lower when using sclerosants with higher viscosities. Detergent sclerosants are the least viscous. On the other hand, 75% dextrose has been reported to cause minor skin necrosis when extravasated and when this occurs, it causes a superficial 1–2 mm scar that heals in 1 or 2 weeks [24].

Arterial injury causing acute ischemia has been reported in at least 18 patients after accidental intra-arterial injection of sclerosing agent with and without ultrasound guidance [25–33]. Dangerous sites for intra-arterial injection include the posterior medial malleolar region, the perforators and the saphenofemoral and the saphenopopliteal junctions. Arteries at risk at these areas include the external pudendal artery, a small vessel that can cross anterior to the greater saphenous vein as well as small superficial arteries near the short saphenous vein. Arterial injury is due to either accidental intra-arterial injection or intravenous injection and subsequent intra-arterial passage of the sclerosant due to arteriovenous anastomoses.

Sometimes there are no clinical signs until inadvertent tissue damage has already set in. Sometimes, immediate pallor, paresthesias and paralysis precede tissue necrosis. Accidental intra-arterial injection is a medical emergency and hospitalization is needed. A possible treatment is based on anticoagulation with heparin, application of fibrinolytic therapy or application of intra-arterial vasodi-

lation. Lumbar sympathectomy has also been reported as a treatment method in the case of injection in the posterior tibial artery [33].

Acute ischemia of the posterior leg compartment necessitating fasciotomy and Achilles tendon elongation has been reported in a case of accidental popliteal artery injection during sclerotherapy of external saphenous vein [27]. At least 4 patients have been submitted to partial foot or below knee amputation and at least 12 patients have been submitted to submetatarsal amputations [25, 30–32]. A case report of 3 patients treated with foam sclerotherapy revealed arterial injury causing gangrene in all 3 patients following the procedure [25]. A 16-year-old woman with Klippel-Trenaunay syndrome and associated varicosities and venous lakes, treated with foam sclerotherapy, developed dry gangrene in both toes. A 23-year-old man with varicosities and atrophie blanche reported severe pain and cold foot as a result of foam embolisation following 3% foam injection. This developed into gangrene, which required partial foot amputation and free flap muscle transfer. A 54-year-old man with varicosities developed deep pain as a result of incorrect placement of the injection needle. Duplex scanning revealed a double saphenous system with a subfascial position of the main trunk. This evolved into gangrene, which necessitated a below-knee amputation [25]. Amputation has been reported in a 36-year-old woman submitted to endovascular catheter assisted ablation of the great saphenous vein due to an arteriovenous fistula between the anterior accessory saphenous vein and the superficial femoral artery [31]. In addition, other patients have experienced extensive muscle necrosis, or variable amounts of cutaneous scarring with or without muscle damage.

A case cluster of necrotizing fasciitis (1 patient) and cellulitis (2 patients) following polidocanol varicose vein sclerotherapy has been reported. The patient with necrotizing fasciitis was submitted to debridement. Streptococcus A was isolated from specimen cultures [34].

Systemic AE

Systemic AE due to sclerosing agents include cerebrovascular AE, cardiac toxicity, pulmonary embolism, deep venous thrombosis (DVT), serious anaphylactic reactions.

Cerebrovascular AE

At least 16 cases of stroke following sclerotherapy have been published with 4 of them following liquid sclerosants and 12 cases following foam sclerotherapy [35–42]. A majority of the reported patients recovered com-

pletely with no long-term sequelae. Stroke has been reported either immediately or 3–5 days after sclerotherapy with either polidocanol [37] or STS. One case of stroke with minimal after effects has been described, identified at the examination 2 weeks after sclerotherapy [42]. Paradoxical gas emboli were observed in the brain-supplying or the intra-cranial arteries of 5 patients with an immediate onset of stroke after foam sclerotherapy. Paradoxical clot embolism was suspected in 3 patients with a delayed onset of stroke and concurrent venous thrombosis. In another 5 cases, which included 2 cases with an immediate onset after liquid sclerotherapy, no specific cause was identified.

Paradoxical gas or clot embolism from a venous source due to deep vein thrombosis has been implicated in a majority of cases. Risk factors for paradoxical embolism include a large patent foramen ovale opening, an associated atrial septal aneurysm, a large right-to-left-shunt and a right-to-left-shunt at rest. Patent foramen ovale is the most common risk factor for paradoxical embolism. A patent foramen ovale persists when fusion of the septum primum and septum secundum is inadequate and its prevalence in the general population ranges between 16 and 34% [37]. However, a majority of the studies attributing the systemic AE of sclerotherapy to patent foramen ovale have not assessed the existence of patent foramen ovale.

In addition, neurologic complications including transient ischemic attacks, transient visual disturbance and transient confusional state and migraine have been described [40, 42]. Gillet et al. [40], in a multicenter prospective study of foam sclerotherapy of great and small saphenous veins including 1,025 patients, reported a case of transient ischemic attack in a 52-year-old woman presenting with dysarthria for 30 s and paresthesia of the left hand for 30 min and clinical recovery within 30 min. In the same series, 7 cases of isolated visual disturbance as well as 5 cases of chest pressure combined with visual disturbance were reported. In another series of 453 patients, 7 events of visual disturbance were reported [43].

The frequency of occurrence of visual disturbance varies in the literature between 1.4 and 14% of patients and is probably dose-related [40]. This occurs following both liquid and foam sclerotherapy, but is more frequent after foam sclerotherapy [44]. It often occurs in patients who have a previous history of migraine, but may occur in anyone. According to neurologists, isolated visual disturbance is nothing more than a migraine, but this cannot be confirmed unless all patients with symptomatic visual disturbance are submitted to systemic neurological ex-

aminations, that is, neurological consultation and brain-weighted diffusion MRI [40]. Visual disturbance has been described in the form of blurred vision or scotoma. Scotoma resolves within 30 min in most patients. It is highly likely to return in subsequent sessions of treatment.

Cardiac Toxicity

Sclerotherapy with STS has been associated with both myocardial infarction and Takotsubo cardiomyopathy [1, 45]. Myocardial infarction has been reported 30 min after foam sclerotherapy with STS. This occurred in a 70-year-old, otherwise healthy woman who underwent foam sclerotherapy to correct the incompetent left great saphenous vein [1]. Cardiac enzyme elevation in a patient 30 days following sclerotherapy has been reported in a retrospective case series of 325 patients [46]. The authors have not associated the cardiac enzyme elevation with treatment, although it is difficult to exclude it.

One case of Takotsubo cardiomyopathy has been reported in a 70-year-old woman after cosmetic sclerotherapy for varicose veins of the legs with STS injections. A few minutes after treatment, the patient experienced severe chest pain of sudden onset and the electrocardiogram suggested an ST elevation myocardial infarction. However, subsequent coronary angiography was normal, while ventriculography was diagnostic of Takotsubo cardiomyopathy. Cardiac function of the patient returned to normal within 3 days of presentation [45].

Six cases of cardiac toxicity of polidocanol have been reported, although 4 of them were used outside licensed indications [47, 48]. Sylvoz et al. [47] reported respiratory and cardiac arrest a few minutes after polidocanol foam sclerotherapy in a 48-year-old woman. Initial ST segment elevation and negativity of anaphylaxis markers suggest direct myocardial toxicity. Cardiac toxicity of polidocanol can be attributed to negative inotropic, negative chronotropic, negative dromotropic effect of polidocanol as well as to reduction of automaticity of sinus node [49].

Pulmonary Embolism

Several cases of pulmonary embolism with or without DVT have been reported after sclerotherapy including intradermal venectasies [50, 51]. There is not much clarity on the true incidence of pulmonary embolism following sclerotherapy. A fatal case has also been reported. The fa-

tal case concerns compression sclerotherapy with STS in a 36-year-old woman. The woman died 10 days following sclerotherapy and postmortem examination demonstrated pulmonary embolism. Evidence of deep vein thrombosis in the calf was also identified [52].

Deep Vein Thrombosis

The rate of DVT after sclerotherapy has been reported to range between 1/1,000 and 6%. The frequency of DVT depends on the operator, on the procedure, patient history, that is, thrombophilia, smoking, and the drug, that is, after polidocanol treatment, the frequency of deep vein thrombosis is reported to range between 0 and 0.14% in large groups. Gillet et al. [40] reported that 1.07% of their patients developed DVTs as diagnosed by routinely performed duplex ultrasound on follow-up. However, an even lower rate of 0.2% has been reported by a French registry that performed duplex ultrasound on symptomatic patients [44]. Myers and Jolley [53] reported a study of deep veins examined by ultrasound within 7 days after foam sclerotherapy, which detected deep venous occlusion in 28 of 1,931 procedures. On the other hand, no case of DVT was reported in a study of 165 patients submitted to ultrasound-guided foam sclerotherapy for truncal varicose veins.

However, deep vein thrombosis following sclerotherapy may be under-reported, especially in case of silent DVT. Sclerotherapy may affect all components of Virchow's triad, that is, endothelial damage, venous stasis, and coagulation. In addition, anatomical variation may be the cause of deep vein thrombosis following sclerotherapy. It has been demonstrated by venography, that venae communicantes exist, that connect intradermal venectasies to the deep veins. DVT has occurred even after sclerotherapy of telangiectasias. According to Myers and Jolley [53], the risk of DVT after sclerotherapy is lower when using highly diluted or undiluted sclerosant, when treating veins less than 5 mm in diameter and when restricting the volume of foam injected to less than 10 ml.

Epileptic Seizure

A case of grand mal epileptic seizure following sclerotherapy has been reported [1]. A 70-year-old man was injected with 5 ml of 1% STS foam to a large lateral thigh perforator vein. Forty minutes later, he experienced scintillating scotomas, followed by confusion, stupor, and then a grand mal seizure [1].

Allergic Reactions

The incidence of non-fatal allergic reactions to STS is estimated to be approximately 0.3% [54, 55]. Four cases of anaphylactic shock leading to death have been reported in patients who received STS. One of these 4 patients reported a history of asthma and this is a contraindication to the administration of STS. A fatality has been reported after a test dose of 0.5 ml STS 0.5% in a 64-year-old woman.

One death due to anaphylactic shock has been reported 5 min after injection with 1 ml polidocanol. Seven non-fatal cases of anaphylactic shock due to polidocanol have been reported. Three of these have been reported in detail from the Netherlands. These patients have been anaphylactic within 15 min after polidocanol injection. Two of them had taken the drug for the first time.

Infectious Complications

One case of septicaemia has been reported in a multicenter prospective study of foam sclerotherapy of great and small saphenous veins including 1,025 patients [24]. The case occurred in a 42-year-old woman following an injection with a direct puncture into the great saphenous vein 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 that was likely responsible to cause this disease. The patient's outcome was satisfactory [40]. Another 2 cases of septicaemia following liquid sclerotherapy have been reported in a French expert's report [56].

Safety of Osmotic Agents

Hypertonic saline is not widely accepted as a sclerosing agent because it can cause pain, burning, and leg cramps upon injections, and in case of extravasation, it is likely to cause significant tissue necrosis.

Safety of Chemical Irritants

Chromated glycerin can cause posttreatment hyperpigmentation, telangiectatic matting, or tissue necrosis if extravasated. On the other hand, it is highly allergenic due to chromium, and could lead to ureteral colic and

hematuria especially after high doses. Chromium is among the 10 most important sensitizers. Chromium allergy is chronic with a poor prognosis. The risk is not only to provoke a severe allergic reaction in patients sensitive to chromium but also to induce sensitization in patients who were not allergic to chromium before sclerotherapy. A rare transient visual disturbance has been reported after sclerotherapy with chromated glycerin.

Discussion

This paper highlights that sclerotherapy of varicose veins is associated with common AE. In addition, sclerotherapy is associated with rare but serious AE and even death. As expected, most data on systemic AE associated with sclerotherapy, come from case reports and voluntary reporting systems. Since these reactions are reported voluntarily from a population of uncertain size and without a control group, it is difficult to estimate their frequency reliably or to establish a casual relationship to drug exposure. However, statistical modeling suggests that more than 1–3 spontaneously reported cases of AE are very unlikely to be coincidental. However, when assessing the occurrence of rare events, the potential of chance occurrence due to pathogenic mechanisms unrelated to sclerotherapy should also be taken into consideration.

Moreover, it is extremely difficult to estimate the frequency of AE of sclerosants due to significant under-reporting worldwide. On the other hand, it is well known, that the hierarchy of clinical evidence used in the evaluation of clinical efficacy is not the most appropriate hierarchy of evidence in the evaluation of drug safety. Thus, randomized controlled trials, that are considered to provide the highest level of evidence for assessing the therapeutic efficacy of the drugs, have limited ability to assess drug toxicity. They are generally not powered to detect rare AE.

In conclusion, physicians should be aware of the possible serious and even life-threatening AE of sclerotherapy, inform patients accordingly and be prepared for the appropriate management of these AE. Future research efforts should focus not only on the development of sclerosant agents with better safety profile but also more importantly on the understanding of the pathophysiology of venous hypertension and on the development of alternative treatment modalities that target the etiology of venous hypertension.

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