Sclerotherapy

12

Kathleen Gibson

Clinical Pearls

1. Hypertonic saline is the sclerosant that causes most pain.
2. Physician-compounded foam is produced by the Tessari method and combining 1:3 or 1:4 mixture of sclerosant and gas.
3. Propriety foam has smaller bubbles with narrower distribution of sizes than physician-compounded foam and is therefore more stable.

Overview

Venous insufficiency is one of the most common vascular disorders, with a prevalence of up to 63.9% in a survey of over 91,500 patients [1]. As outlined by a multidisciplinary consensus committee on chronic venous disease, the clinical severity of venous disease is wide, and patients may present with manifestations ranging from cosmetically bothersome telangiectasias to advanced disease with ulceration [2]. The use of sclerotherapy, whether liquid or foam, has a role in treating venous disease at every stage. Sclerotherapy is one of the most widely used treatments for improving the appearance of spider veins. It can be used to treat truncal saphenous incompetence, as well as incompetent tributary veins. In more advanced disease, it has been used in the treatment of pathologic perforator veins and in treating nests of abnormal dermal and subdermal veins associated with active and healed ulcers. In addition to these more common uses, sclerotherapy is also an important treatment for vascular malformations and the treatment of pelvic venous insufficiency. With the transition of venous care from the hospital to the office and the increase in the use of minimally invasive ultrasound-guided techniques, the breadth of applications of sclerotherapy in the treatment of venous disorders makes it an integral part of a vein physician's armamentarium.

History

Sclerotherapy refers to the destruction of a vein by injecting it with a substance to induce vessel injury followed by obliteration of the vessel. Zollikofer, in Switzerland, reported the first documented use of sclerotherapy in the treatment of veins in 1682. He injected a vein with acid to induce thrombosis. Since that time, multiple

K. Gibson, MD, FACS (✉)
Lake Washington Vascular Surgeons,
1135 116th Ave NE, Suite 305, Bellevue,
WA 98004, USA
e-mail: drgibson@lkwv.com

C.I. Ochoa Chaar (ed.), *Current Management of Venous Diseases*,
https://doi.org/10.1007/978-3-319-65226-9_12

different sclerosing agents have been used including absolute alcohol, mercury compounds, sugar complexes, and hypertonic electrolyte solutions. The most commonly used sclerosing agents in use today, hypertonic saline, sodium tetradecyl sulfate (STS), and polidocanol (POL), were first described in 1926, 1946, and 1966, respectively [3].

Foam sclerotherapy is a technique that is in wide use in the United States and throughout the world [4]. Foam sclerosants are produced by mixing sclerosants in the detergent class with a gas (typically room air, CO2, O2, or a CO2/O2 mixture). The first published description of mixing air with a sclerosant was in 1944, by Orbach [5]. This technique did not become popular until some 50 years later. In 1997 two papers were published regarding the use of foam sclerosants. Juan Cabrera of Spain described his technique, utilized since the early 1990s of the creation of sclerosant foam to treat varicose veins [6]. Monfreux of France in the same year published a technique for creating a foam sclerosant using a glass syringe and a sterile plug [7]. The method of foam production that is most widely used today (the double syringe technique) was described by Lorenzo Tessari of Italy in 2000 [8].

Physician-compounded foams (PCFs) are not standardized and vary widely according to sclerosant used, gas used, and technique of production. This variability leads to differences in the physical characteristics of the foam including variation in bubble size, as well as foam stability [9]. In 2013, after 14 years of systematic pharmaceutical development, the FDA approved a standardized proprietary foam sclerosant. Marketed as Varithena™ (BTG West Conshohocken, PA), it is an injectable 1% POL foam with specific indication for treatment of incompetent great saphenous veins, accessory saphenous veins, and their branches above and below the knee [10]. Standardized commercial products provide more consistent foam characteristics (bubble size, sclerosant strength) and assured sterility [9].

Sclerosants

Destruction of the target vessel is the intended action for all sclerosing agents, but the mechanism of action differs depending on sclerosant class. Table 12.1 lists the most commonly used sclerosing agents worldwide. The main sclerosant classes are hyperosmolar agents, detergents, and corrosives. Hyperosmolar agents cause diffusion of water from the intracellular space to the extracellular, causing nonspecific cell destruction as well as hemolysis. In contrast, detergent sclerosants cause protein theft denaturation. This causes lysis of the cell wall, without hemolysis. Corrosive sclerosants have a direct cytotoxic effect on the endothelium. All sclerosants stimulate platelet aggregation. This in turn induces a dense network of platelets and fibrin that occlude the vessel, which is eventually replaced with fibrotic tissue [11].

The most widely used sclerosants in the United States are hypertonic saline, STS, and POL [4]. Both STS and POL are approved by the FDA for

Table 12.1 Sclerosing agents

Agent	Class	Trade name	Distributor	FDA/US status
Hypertonic saline	Hyperosmolar	N/A	Multiple	Off-label
Saline/propylene glycol	Hyperosmolar	Sclerodex	Omega Laboratories (Canada)	Not available
Sodium tetradecyl sulfate	Detergent	Sotradecol	Mylan	Approved
Polidocanol	Detergent	Asclera	Merz	Approved
Sodium morrhuate	Detergent	Scleromate	Glenwood, LLC	Approved
Chromated glycerin	Corrosive	Sclermo	Omega Laboratories (Canada)	Not available
Polyiodinated iodine	Corrosive	Sclerodine	Omega Laboratories (Canada)	Not available

Table 12.2 Advantages and disadvantages of sclerosing agents

Agent	Advantages	Disadvantages
Hypertonic saline	Inexpensive No real allergy potential	Painful Ulceration with extravasation Can cause hyperpigmentation
Sodium tetradecyl sulfate	Minimally painful Able to treat larger veins	Allergy less rare Ulceration more common than with POL Contraindicated with severe asthma Can cause hyperpigmentation
Polidocanol	Nearly painless Ulceration rare Allergy very rare	Limited in size of veins to treat Can cause hyperpigmentation

venous injection, but the use of hypertonic saline is considered "off-label." Specifically, STS is approved for treatment of "veins of the lower extremity," whereas POL is approved for the treatment of reticular and spider veins. Each sclerosant has different dosing, different advantages, and disadvantages as shown in Table 12.2. STS is a synthetic surfactant (soap), while POL is a non-ester local anesthetic [12]. Hypertonic saline has only a local effect and then is rapidly diluted. Detergent sclerosants are quickly deactivated by binding to circulating blood proteins, which may be a factor in the low incidence of thrombotic complications with sclerotherapy [13].

In general, while it is less expensive than other agents, hypertonic saline is more painful and has more adverse effects than detergent sclerosants [14]. STS is available in higher concentrations (stronger potency) in the United States than POL and therefore may be the agent of choice in the treatment of larger veins, venous malformations, and in the treatment of pelvic congestion syndrome [15, 16]. In other parts of the world, higher concentrations of POL are available. Most sclerotherapists would advise injecting larger vessels prior to moving on to smaller vessels: injecting feeding reticular veins, for example, prior to spider telangiectasias.

Liquid vs. Foam Sclerotherapy

Sclerosants from the detergent class can be mixed with gases to produce foam sclerosants. Upon injection, foam sclerosants displace the blood in the vessel, forming a "vapor lock," keeping the drug in contact with the vessel wall and delaying deactivation by circulated plasma proteins. The injected foam sclerosant is in contact with the vessel wall for a longer period of time, which increases the efficacy in comparison to liquid sclerotherapy. Volume and concentration of the sclerosing agent can therefore be decreased, as the active contact time is increased [17].

Advantages of foam over liquid sclerotherapy include its echogenicity with ultrasound, allowing the user to perform sclerotherapy in a precise and controlled manner. In general, foam sclerotherapy is not used for spider vein injections but is utilized for larger veins. Foam sclerotherapy is superior to liquid sclerotherapy in terms of closure rates of varicose veins and truncal veins such as the great saphenous vein (GSV). A prospective randomized trial by Hamel-Desnos and colleagues in 2003 compared foam sclerotherapy to liquid sclerotherapy (using POL) in the treatment of GSV reflux. This demonstrated that foam sclerotherapy eliminated GSV reflux in 84% and 80% of limbs at 3 weeks and 6 months, whereas liquid sclerotherapy had the same effect in 40% and 26% of limbs during the same time points [18].

Physician-Compounded Foam

Physician-compounded foam (PCF) is considered an "off-label" use of FDA-approved liquid sclerosants as the drug is fundamentally changed by mixing it with a gas. Despite the lack of

specific FDA approval, the use of PCFs in the United States, and indeed worldwide, is widespread [4]. PCFs are an effective tool in the treatment of truncal veins, tributaries/branches (replacing microphlebectomy in many cases), venous malformations, and pelvic source varicosities. Treatment is readily performed in an outpatient clinic setting and requires no procedural sedation, and patients return to normal activity levels very quickly with minimal discomfort. PCFs are produced by forcibly mixing a sclerosant of the detergent case with a gas through a small aperture, producing small sclerosant encapsulated gas bubbles. The aperture used is typically either a three-way stopcock or a "female to female" stopcock (double syringe technique). Air or physiologic gases (CO2, O2, or a mixture of both) are typical gases, while the most common choices of sclerosant include POL and STS. Figure 12.1 shows the technique as described by Tessari [19]. Typically the ratio of liquid to gas is 1:3 or 1:4 depending on whether "wet" versus "dry" foam is preferred. The stability of the foam and the size of gas bubbles in the circulation are dependent on the method of foam production, the gas chosen for use (O2 vs. CO2 vs. room air), and other factors including atmospheric pressure and temperature [20]. As the amount of nitrogen in the gas used to create foam increases, the foam is more stable, but the bubbles are also less soluble in the blood [21].

In terms of the use of PCF in the treatment of GSV incompetence, duplex closure rates are highly variable in the literature, ranging from 69 to 91%, depending on the agent used, the concentration, and the number of treatment sessions administered before assessing closure [22–26]. These variables, as well as differing patient populations and disease severities, make comparisons between studies difficult. Additionally, the evaluation of outcome assessments including venous clinical severity scores (VCSS) and quality of life (QOL) instruments is not consistent or uniform. Two more recently randomized trials did assess QOL after ablation of the GSV with ultrasound-guided PCF vs. comparator treatments. Rasmussen and colleagues randomized patients to surgical stripping, endothermal laser ablation (EVLT), radio-frequency ablation (RF), or ultrasound-guided foam sclerotherapy (UGFS). Recanalization and retreatment were most common in the UGFS group, but at 3 years, all groups showed similar improvements in VCSS and QOL [27]. A second randomized trial by van der Velden and colleagues compared EVLT and conventional surgery to UGFS. At 5 years, the GSV was obliterated in 85%, 77%, and 23% in the surgical, EVLT, and UGFS groups, respectively. In contrast to the Rasmussen study, QOL scores in the UGFS groups were inferior compared to the other groups [28]. Other studies suggest that UGFS is a cost-effective treatment for GSV reflux, especially when compared to conventional surgery [29].

Venous tributaries associated with saphenous reflux can be treated in either a staged or concomitant fashion. Choices for tributary treatment

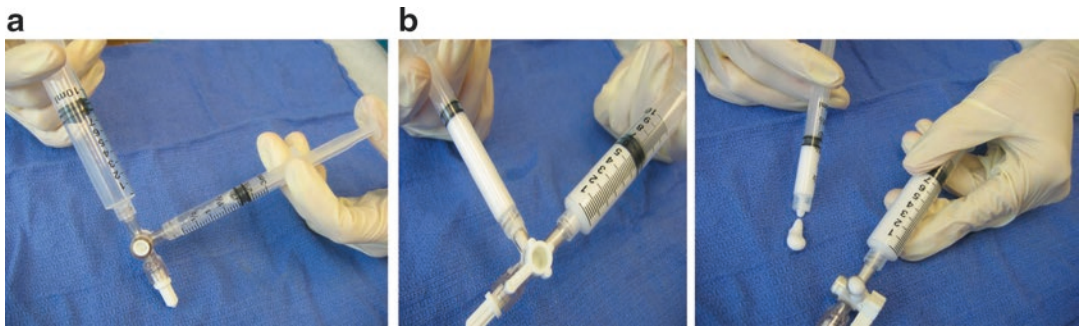

Fig. 12.1 Tessari technique for the production of physician-compounded foam. (**a**) 8 cc gas, 2 cc liquid. (**b**) Mix with three-way stopcock

include stab phlebectomy and UGFS. Recent clinical practice guidelines from the Society of Vascular Surgery and the American Venous Forum recommend either approach as an acceptable treatment (Grade 1B) [30]. Data comparing stab phlebectomy to UGFS in the treatment of tributaries is sparse, and both treatments have proponents. Considerations in treatment choice include vein size, depth, extent, and history of hypertrophic scarring or hyperpigmentation.

The use of PCF is in general thought to be safe and well tolerated; however, serious adverse events can occur. In particular, neurologic complications such as strokes and transient ischemic attacks, while rare, have been reported. In most of these reported cases, air was the gas used to produce the foam, and the patients were often found to have a structural defect such as a patent foramen ovale (PFO) or atrial septal aneurysm [31–34]. These cases have led some to advocate the use of physiologic gases (CO2 or CO2/O2) rather than air-based foams for the production of PCF [35]. While there is no firm data to support this position in terms of prevention of strokes and TIAs, there is data demonstrating fewer visual disturbances and other side effects when physiologic gases are used [36]. Physiologic gases, which have minimal nitrogen content, are biocompatible and as such are rapidly absorbed. Other than gas canister cost, there is little downside to their use. While there is minimal risk of cerebral embolization in patients without a PFO or large pulmonary shunt, a study of 221 varicose vein patients showed that 58.5% of the individuals had a right to left shunt with bubble testing: much higher than the prevalence of such shunts in the general population (est. 26%) [37]. Although individuals with right to left shunts are ostensibly at higher risk of cerebral embolization with foam sclerotherapy, the overall rarity of these events and the high prevalence of such shunts in this population make screening for shunts prior to foam sclerotherapy impractical and unnecessary. Nonetheless, foam sclerotherapy should be used with caution in patients with a known right to left defect, particularly if the patient has a history of previous events that led to the detection of the defect. The use of good quality foam (no grossly visible bubbles) and limiting injection volumes is recommended. In the case of neurologic symptoms during or after foam sclerotherapy, hyperbaric oxygen therapy has been reported to resolve intracerebral gas in the vasculature [34].

Proprietary Foam

An alternative to the use of PCF for the treatment of incompetence of the GSV, accessory saphenous veins (ASV), and their tributaries is proprietary endovenous microfoam (PEM), marketed as Varithena™. There are no head-to-head studies comparing PCF to PEM, and extrapolating results from studies of PCF are difficult due to varying study designs, endpoints, and the lack of a standard production method or technique for PCF. The sclerosant drug in PEM is 1%POL, but it is produced with a proprietary canister system containing a very low nitrogen physiologic gas. With in vitro testing in a benchtop vein model, PEM gas bubbles are overall smaller, with a narrower distribution of sizes when compared to PCF bubbles, and the stability of PEM foam is superior to PCF. Theoretically increased stability should improve foam performance in vivo, and smaller circulating bubbles could theoretically improve patient safety [37].

The neurologic safety of the use of PEM for the treatment of GSV incompetence was demonstrated in a Phase II clinical trial published in 2011. Patients with symptomatic GSV incompetence were tested with a transcranial Doppler (TCD) bubble testing for the presence of a right to left shunt. Patients who qualified for the study by virtue of a positive bubble test were then treated with PEM. During treatment, TCD monitoring showed middle cerebral artery bubbles in 61 patients. These patients had diffusion-weighted MRI testing (very sensitive to the presence of edema formation) at baseline and at 24 h and 1 month posttreatment. Patients additionally underwent visual field and neurologic testing.

None of the patients were found to have changes in MRI, visual fields, or neurologic examinations after PEM treatment [38].

In the development of PEM, following the Phase II trial, pilot studies were performed to develop a patient-reported outcome tool (PRO) and to test methods of patient blinding leading up to the pivotal Phase III trials in the United States [39]. The reliance of surrogate markers such as duplex closure of veins was deemed by the FDA to be insufficient for approval of PEM, and they required a validated PRO assessing varicose vein symptoms to be the pivotal study endpoint [40]. The VVSymQ® is the PRO instrument used in the trials. It assesses the severity of the five symptoms (heaviness, aching, throbbing, swelling, and itching) shown to be most relevant to patients with varicose veins.

The two pivotal trials, VANISH-1 (275 patients) [41] and VANISH-2 (230 patients) [42], utilized the VVSymQ® as the primary study endpoint and change in appearance of the leg as assessed by both an independent physician reviewer and the patients themselves. Patients with symptomatic GSV or ASV reflux were enrolled in the prospective single-blind randomized trials. Duplex closure was assessed, as was patient safety. Both studies compared PEM to placebo, but the VANISH-1 study randomized patients to three differing doses of POL (0.5, 1.0, and 2.0%), while VANISH-2 randomized patients to 0.5 or 1.0% POL. VANISH-2 patients were allowed to have a two treatment sessions, separated by 1 week. At 8 weeks the primary endpoint (improvement in the patient PRO) and the secondary endpoints (including improvement in appearance) were assessed. Both studies showed significant improvement in both PRO scores and appearance, and compared to placebo, these improvements were highly statistically significant ($p < 0.0001$ for both endpoints). One-year follow-up was reported for the VANISH-2 group, and symptom improvement was sustained [43]. The duplex closure rates at 8 weeks in the 1% POL groups were 80.4% for the VANISH-1 trial [41] and 86.2% for the VANISH-2 trial [42]. There were no significant adverse neurologic events in the trials, other than headache, but 5.4% of patients had superficial thrombophlebitis following the procedure, and 4.7% had a deep vein thrombosis (DVT) on follow-up duplex examination. The majority of these events were asymptomatic and detected because of study protocols requiring detailed post-procedure duplex evaluation, including imaging of all tibial vessels. There were no symptomatic pulmonary emboli, and none of the patients with a DVT later showed signs or symptoms of post-thrombotic syndrome.

Following the pivotal trials, the FDA approved Varithena for use in November of 2013 [44]. The product was released for commercial release in August of 2014. Advantages over traditional endothermal ablation techniques for truncal saphenous ablation include the avoidance of tumescent anesthesia with its attendant pain and bruising [45, 46] and the ability to treat side branch tributaries quite simply in a concomitant fashion. It can be used to treat tortuous veins and in this way can treat a broader spectrum of anatomic presentations compared to EVLT and RF. As such, it provides an attractive option for treating recurrent varicose veins and neovascularization. It does not have an indication for treatment of the small saphenous vein (SSV), so its use in this disease pattern would be considered off-label. Primary disadvantages compared to endothermal ablation include dosing limitations which may limit the number of veins that can be treated in a single session, a lower rate of duplex closure, and a higher rate of thrombotic events (DVT and superficial thrombophlebitis), when compared to historic endothermal ablation data. While data to support the safety and efficacy of PEM is robust compared to data for PCF, it is significantly more expensive.

One of the main barriers to the use of PEM at the time of this publication is the lack of a dedicated current procedural technology (CPT) code for billing. Payor coverage and reimbursement rates are variable and regional, with some insurers still considering PEM “investigational.” Over time, carrier coverage has become more widespread,

and issues of coverage and reimbursement should become more certain when a CPT code specific to PEM is approved.

Patient Workup Prior to Sclerotherapy

A thorough history and physical examination should be taken prior to treatment of either varicose veins or telangiectasias with sclerotherapy. Patients should be queried about previous treatments and response to those treatments including any adverse events they may have encountered. Special attention should be paid to the patient's goals—are they being treated for cosmetic reasons, for symptoms, or for both? It is imperative that the risks and benefits of the procedure be addressed, and the pretreatment consultation is key to avoid unrealistic expectations on the part of the patient. Multiple sclerotherapy sessions may be required for the patient to achieve their goals.

Special considerations in the pretreatment consultation include review of medications and medical history. Sclerotherapy should not be performed in pregnant women or women who are breast-feeding unless the benefit clearly outweighs the risk, which is seldom if ever the case for venous treatment. Patients who are taking minocycline should not be treated with sclerotherapy as permanent hyperpigmentation can occur [47]. If a patient has had a previous reaction to a sclerosing agent, they should not receive that agent again. Small dose skin testing with subsequent in-clinic observation can be performed and would be recommended in any patient in whom there is concern for allergic reaction. STS is contraindicated in patients with asthma. All locations where sclerotherapy is performed should have a readily available and up-to-date emergency kit in the event of an anaphylactic reaction to a sclerosant.

Prior to foam sclerotherapy with PCF or PEM, patients are queried about a known history of a structural heart defect (such as an atrial septal defect or a PFO), and if present, alternative therapies may be suggested. As sclerotherapy may cause visual disturbances or migraine headache [48], patients with a history of migraine (especially migraine with aura) are cautioned that therapy could possibly trigger symptoms. They are advised to bring any medications that they would usually take in the event of a migraine with them to their sclerotherapy session.

Techniques

STS is available in 1 and 3% concentrations, and POL is available as 1 and 0.5%. Both STS and POL have a maximum volume per session of 10 cc. Small volumes should be injected, and the concentration of sclerosant injected will depend on the vein size. Table 12.3 lists suggested sclerosant concentration by vein diameter. The lowest effective dose and concentration that will reliably achieve vessel occlusion should be used in order to minimize adverse effects such as matting, ulceration, and venous thrombosis.

Prior to sclerotherapy of either telangiectasias or varicose veins, photo documentation of the intended treatment area(s) is recommended. Photographs of the same area(s) should be repeated in follow-up to assess results and progress. Injection sites, type, and volumes of sclerosants should be documented at the time of treatment. In the author's practice, "before and after" photos are shared with the patient at every visit. With the treatment of telangiectasias in particular, the main reason for treatment may be the patient's dissatisfaction with visual appearance of the limb, making photography a necessary tool. The widespread availability of digital

Table 12.3 Sclerotherapy concentration by vein diameter

Vein diameter	Detergent	Hypertonic saline
<1 mm	STS 0.1–0.3% POL 0.3–0.5%	11.7%
1–3 mm	STS 0.5–1.0% POL 1.0%	23.4%
>3 mm	STS 1.0–3.0% POL 1.0% (or foam)	–

cameras and software programs to store medical images has simplified the use of photography in a vein practice.

Telangiectasias

Sclerotherapy of spider telangiectasias, while both safe and effective, can take a great deal of practice before mastery is obtained. The sclerotherapist should position themselves in a favorable ergonomic position in relation to the target vein. As the target vein may be a millimeter in diameter or less, any extraneous movement will dislodge the needle from the vein. When performing sclerotherapy, bracing the elbow, wrist, and hypothenar eminence of the dominant hand against a solid surface will ensure stability. The non-dominant hand is used to stretch and stabilize the skin. Such positioning is shown in Fig. 12.2. A small needle (30 or 32 gauge) and a small volume (3 cc) syringe are typically used. During injection the needle angle is very shallow with the bevel is up. Bending the needle can be helpful to facilitate shallow vein entry. The sclerosant is "dripped" into the vein with a minimal amount of pressure to avoid extravasation. There are many options to improve visualization of small veins from simple (magnification lenses, loupes) to more complex. The Syris™ system, Veinlite®, and Venoscope® are all transillumination aids, while the Veinviewer® utilizes projected near infrared light to visualize subdermal veins.

Aftercare following sclerotherapy is not standardized, and most practitioners follow nonevidence-based guidelines. There is very little data regarding exercise, bathing, and sun exposure following sclerotherapy. Compression stockings or bandaging is routinely recommended, but the level of compression and length of time stockings should be worn is highly variable. A randomized trial of 100 by Kern et al. in 2007 compared results in women treated with 3 weeks of 23–32 mm Hg compression stockings versus no stockings following sclerotherapy of telangiectasias and reticular veins. The study found no difference in adverse events between the two groups but did find a significant difference ($p = 0.026$) in favor of compression in terms of improvement in appearance as rated by blinded observers [49].

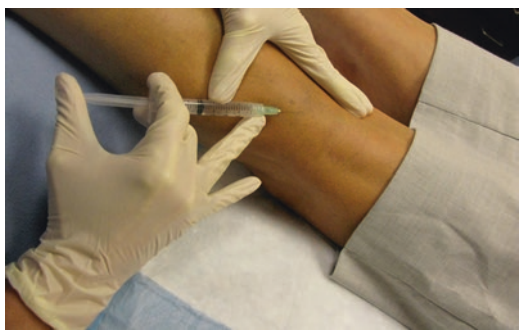

Fig. 12.2 Positioning for sclerotherapy of telangiectasias

Superficial Venous Insufficiency

PCF is commonly used for treating varicose veins [4] and is most commonly performed with UGFS. If ultrasound is not available, sclerotherapy can be performed with confirmation of needle placement with blood return. The author prefers UGFS as the ultrasound can confirm intravenous needle placement, show spasm in the treated vein, and follow the PCF as it travels through the vein. It is imperative for treating varicose veins that may be too deep to easily see. Marking the veins to be treated with an indelible pen with the patient in the standing position prior to treatment is helpful. The author typically uses a 23- or 25-gauge butterfly needle when treating varicose veins, but a standard needle can also be used. Multiple injections with small volumes are recommended, to avoid inadvertent boluses of foam into the deep system. Transit of the PCF is followed with ultrasound, and successfully treated veins should appear small, bright, and in spasm. The use of compression following treatment of PCF is not standardized in terms of strength of compression, type of compression (bandaging versus stockings), and length of time compression should be worn. The author's practice places patients in a 20–30 mm Hg stocking with or without underlying pressure pads for 2 weeks after treatment. Patients walk for 10 min

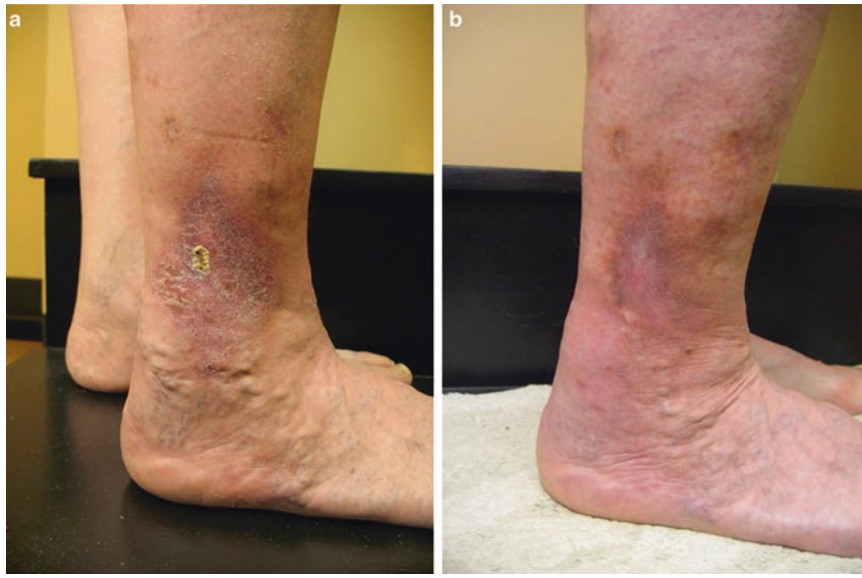

Fig. 12.3 Ultrasound-guided foam sclerotherapy in the treatment of advanced venous disease: before and after photos. (**a**) Baseline. (**b**) Three months posttreatment

post-procedure and are encouraged to walk/be physically active hourly during the first 2 weeks after treatment.

PCF has applicability in the treatment of advanced venous disease [50] as it can be readily used to inject and close nests of abnormal subdermal veins in patients with venous ulceration and lipodermatosclerosis. UGFS in these advanced cases is typically used as an adjunct to truncal ablation and compression therapy. Figure 12.3 shows before and after pictures of a patient with a lateral leg ulcer treated with UGFS and compression therapy. According to recent SVS/AVF guidelines, treatment of pathologic perforator veins (those greater than 3.5 mm in diameter with >500 ms of reflux near an open or healed ulceration) is suggested to aid in ulcer healing and prevent recurrence in patients with CEAP clinical class 5 or 6 disease [51]. UGFS can be used to treat pathologic perforator veins, and Masuda and colleagues showed a 75% improvement in patients' VCSS and venous disability scores [52]. When treating perforator veins with foam, the author recommends injection of small volumes, dorsiflexion of the foot, and pumping of the calf muscle after injection to potentially decrease volumes of foam in the deep veins.

In the author's practice, UGFS is commonly used to treat pelvic source varicose veins presenting with vulvar and inner or posterior thigh varicose veins. Pelvic venous insufficiency is a frequent source of recurrent or missed varicose veins [53]. The author uses a standard technique for treatment of veins in this region but typically has an assistant, so that one hand performs the injection, one hand holds the ultrasound probe, and two hands stretch and flatten the skin to pin the underlying veins as they tend to roll away from the needle. In the author's experience, the technique is quite successful with a low incidence of side effects; however, some patients may need multiple treatment sessions, and recurrence is not uncommon, particularly if the underlying pelvic varices are untreated. Figure 12.4 shows before and after photos of a patient with pelvic venous insufficiency manifesting as vulvar and medial thigh varices before and 3 months after UGFS.

PCF has been used extensively for both treatment of pelvic venous insufficiency on its own or as an adjunct to coil embolization of the gonadal veins [54]. It also is an essential tool for the treatment of vascular malformations [55]. Discussion of these techniques is beyond the scope of this chapter.

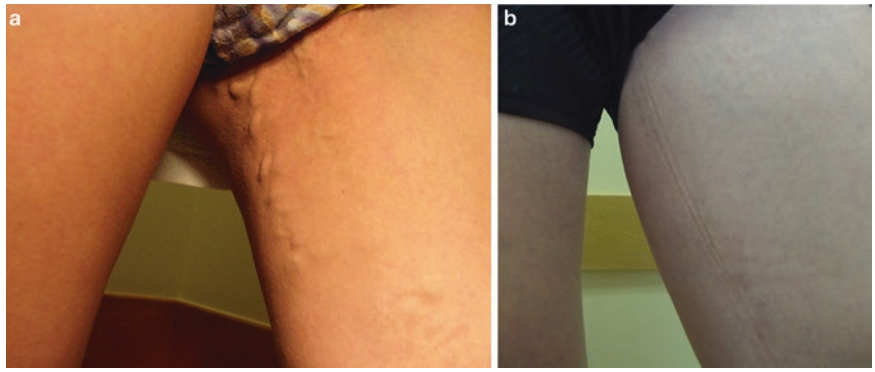

Fig. 12.4 Pelvic source varicose veins before and 3 months after ultrasound-guided foam sclerotherapy. (**a**) Baseline. (**b**) Three months

PEM

The technique for GSV or ASV ablation with PEM is standardized and outlined in its instructions for use (IFU) [56]. The technique requires two individuals—one to image the saphenofemoral junction and one to compress the SFJ once the PEM reaches this area and a second to inject PEM and hold pressure caudal to the access site. The GSV or ASV is accessed in a typical fashion with ultrasound guidance in a transverse or longitudinal view with either an angiocatheter or a micropuncture sheath with the tip of the access catheter usually positioned in the midthigh. Once venous access has been confirmed with blood return, the catheter is flushed with saline, and the limb is elevated approximately 45 degrees. The PEM is produced according to the IFU and is injected into the vein using a silicon-free syringe. During injection, the GSV or ASV caudal to the access site is compressed digitally, and an ultrasound probe is held in longitudinal view over the SFJ to await arrival of the PEM. The PEM will appear as a bright white column traveling forward through the vein as shown in Fig. 12.5. As soon as this column reaches about 2–3 cm from the SFJ, the ultrasound probe is turned into the transverse position, and the GSV or ASV is compressed to keep the PEM from entering the common femoral vein. Simultaneously, the digital pressure being held beyond the access site is released. The SFJ is compressed until the GSV or ASV is visualized with ultrasound and found to be in complete spasm along the treatment length, with no areas of patency. This may take up to 5 min. In the author's experience, a typical GSV can be treated with 4–7 cc of PEM.

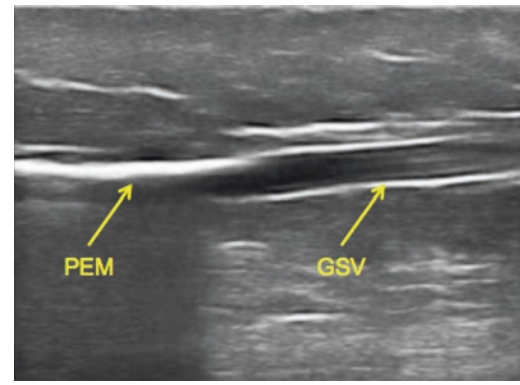

Fig. 12.5 Column of PEM in the GSV

Following treatment of the truncal vein in the thigh, it can be treated more caudally by either pulling the access catheter back slightly, compressing above the tip of the catheter and injecting retrograde through the catheter, or by accessing the vein in another location. Side branches are then accessed using a butterfly or other needle and injecting small volumes of PEM (1–2 cc per injection) while compressing any large perforator veins in associated with the side branches being treated. Up to 15 cc of PEM may be used in a treatment session. Following completion of treatment, the leg is wrapped with a short-stretch bandage, a compression pad, and a compression stocking. Patients are instructed to

walk or be active for 5–10 min out of every waking hour for the first 2 weeks after the procedure. More than one treatment session may be required for optimal results in patients with extensive branch varicosities.

Side Effects and Complications

Allergic reactions may occur with injection of any substance; however, allergy to hypertonic saline would only occur if the patient had an allergy to any additives in the solution. Allergy to both POL [57] and STS [58] has been reported, but in general, allergy is felt to be more common with STS. As stated earlier in this chapter, emergency kits should be readily available in all clinics performing sclerotherapy, with all appropriate staff trained in the treatment of anaphylaxis.

Cutaneous necrosis can occur following sclerotherapy and can be disfiguring. Ulceration is felt to be more common with hypertonic saline and STS compared to POL but can occur with any sclerosant [59]. It is more common in patients with dense telangiectasias, especially in areas of thin skin or bony prominences. Mechanisms of cutaneous necrosis include extravasation of contrast and inadvertent injection into a small arteriole or arteriovenous fistula. Figure 12.6 shows ulceration on a patient's skin following liquid sclerotherapy treatment for telangiectasias. Patient reassurance is important, as most ulcerations are small and will heal over time, although scarring may result. Large areas of cutaneous necrosis may require referral to a wound care specialist.

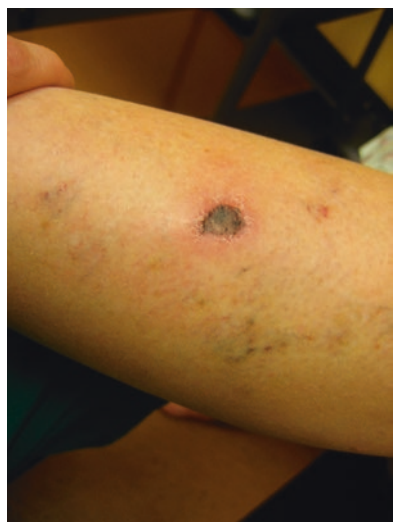

Fig. 12.6 Skin ulceration following sclerotherapy

Telangiectatic matting can occur after sclerotherapy in 10–30% of patients [59]. The etiology is not known but may be due to angiogenesis as a response to inflammation. Retrospective studies have shown a possible link to the use of oral contraceptives and increased risk of matting [60]. Compression therapy does not decrease the incidence of matting [49], and it can occur with any sclerosing agent. As with hyperpigmentation, patients should be reassured that resolution with time is typical.

Hyperpigmentation is common following sclerotherapy and will generally gradually lighten and improve over time. Spontaneous resolution will typically occur in 70% of patients by 6 months and 99% of patients by 1 year [59]. Conservative therapy with observation should be the first approach to the patient with hyperpigmentation after sclerotherapy. In the case of persistent hyperpigmentation, bleaching agents [61], topical lasers [62], and intense pulse light (IPL) therapy [63] have been suggested for treatment.

Deep vein thrombosis can occur following sclerotherapy and as referenced earlier in this chapter occurred in 4.7% of patients treated with PEM in the VANISH trials [41, 42]. Most of these patients were asymptomatic. A review of nearly 1 million subjects undergoing venous procedures from a nationwide healthcare database comprised of 40 million patients showed that the prevalence of reported DVT and PE after sclerotherapy was 0.8% and 0.2%, respectively. These rates were lower than reported rates for endothermal ablation (RFA and EVLT) and surgery [64]. Superficial phlebitis after sclerotherapy is not uncommon but is rarely dangerous. Early drainage of trapped coagula using an 18-gauge needle or a number 11 blade may provide quick relief of discomfort and decrease the extent of hyperpigmentation following sclerotherapy.

As described earlier, strokes have been reported in rare circumstances with the use of foam sclerosants. Visual disturbances and migraines are more commonly reported and can occur with the use of either liquid or foam sclerotherapy. A recent literature review estimated that the prevalence of transient visual disturbance with sclerotherapy ranged from 0.09 to 2% [65]. Proposed mechanisms for visual disturbance and migraine with sclerotherapy include gas and particle microemboli or the release of endothelin from the treated veins. Endothelin is a potent vasoconstrictor and bronchoconstrictor, and increases in endothelin-1 with foam sclerotherapy in a rat model give support to the concept that endothelin release may be responsible for side effects of migraine, visual disturbance, and cough following sclerotherapy [66].

In general, sclerotherapy is safe and well tolerated, and it is likely that the most common "adverse event" following treatment is failure to meet the patient's expectations in terms of cosmesis. One of the most important considerations in terms of patient satisfaction is educating patients in regards to realistic outcomes. Patients should be counseled that immediate improvement in appearance is not likely and that improvement is usually gradual and incremental. Multiple treatment sessions, especially for telangiectasias, may be necessary for the patient to achieve their desired results. Pre-procedural counseling should be thorough and include showing patients photographic examples of both ideal and nonideal outcomes.

Conclusions

Sclerotherapy is a versatile tool for the treatment of superficial venous insufficiency: from the treatment of unsightly telangiectasias to advanced venous disease. The availability in the United States of proprietary foam may broaden the indications for the use of sclerotherapy. Familiarity with therapeutic agents and proper techniques are imperative to for both patient safety and for obtaining good results.

References

1. Rabe E, Guex JJ, Puskas A, Scuderi A, Fernandez Quesada F, Coordinators VCP. Epidemiology of chronic venous disorders in geographically diverse populations: results from the Vein Consult Program. Int Angiol. 2012;31:105–15.
2. Porter JM, Moneta GL. Reporting standards in venous disease: an update. International Consensus Committee on chronic venous disease. J Vasc Surg. 1995;21(4):635–45.
3. Goldman MP, Guex JJ, Weiss RA. Sclerotherapy. In: Treatment of varicose and telangectatic leg veins. 5th ed. Amsterdam: Saunders/Elsevier; 2011. p. ix–xi.
4. Rathbun S, Norris A, Morrison N, Gibson K, Hohenwalter E, Lohr J, Raymond-Martimbeau P, Worthington-Kirsch R, Stoner J. Performance of the endovenous foam sclerotherapy in the USA. Phlebology. 2012;27(2):59–66.
5. Orbach EJ. Sclerotherapy of varicose veins: utilization of an intravenous air block. Am J Surg. 1944;66:362–6.
6. Cabrera Garrido JR, Cabrera Garcia-Olmedo JR, Garcia-Olmedo Dominguez MA. Elargissement des limites de la schlerotherapie: nouveaux produirs sclerosants. Phlebolgie. 1997;50:181–8.
7. Monfreux A. Traitement sclerosant des troncs saphenies et leurs collaterals de gros caliber par le methode MUS. Phlebologie. 1997;50:355–60.
8. Tessari L. Nouvelle technique d'obtention de la sclero-mousse. Phlebologie. 2000;53:129.
9. Carugo D, Ankrett DN, O'Byrne V, et al. The role of clinically-relevant parameters on the cohesiveness of sclerosing foams in a biomimetic vein model. J Mater Sci Med. 2015;26(11):258.
10. Varithena (prescribing information) in: https://www.btgplc.com/media/1266/varithena-media-fact-sheet-us-var-2013-0835-3.pdf, Provensis LTD, a BTG International Group Company, December 2013.
11. Worthington-Kirsch R. Injection sclerotherapy. Semin Intervent Radiol. 2005;22(3):209–17.
12. Feied CF. Sclerosing solutions. In: Fronek H, editor. The fundamentals of phlebology, venous disease for clinicians. 2nd ed. San Leandro: American College of Phlebology; 2007. p. 23.
13. Parsi K, Exner T, Connor DE, et al. Lytic effects of detergent sclerosants on erytrocytes, platelets, endothelial cells and microparticles are attenuated by albumin and other plasma components in vitro. Eur J Vasc Endovasc Surg. 2008;36(2):216–32.
14. Peterson JD, Goldman MP, Weiss RA, et al. Treatment of reticular and telangectatic leg veins: double-blind prospective randomized comparative trial of polidocanol and hypertonic saline. Dermatol Surg. 2012;38(8):1322–30.
15. Park HS, Do YS, Park KB, et al. Clinical outcome and predictors of treatment response in foam sodium tetradecyl sulfate sclerotherapy of venous malformations. Eur Radiol. 2016;26(5):1301–10.

16. Pieri S, Agresti P, Morucci M, de' Medici L. Percutaneous treatment of pelvic congestion syndrome. Radiol Med. 2003;105(1–2):76–82.
17. Gibson K, Ferris B, Pepper D. Foam sclerotherapy for the treatment of superficial venous insufficiency. Surg Clin North Am. 2007;87(5):1285–95.
18. Hamel-Desnos C, Desnos P, Wollmann JC, et al. Evaluation of the efficacy of polidocanol in the form of foam compared with liquid form in sclerotherapy of the greater saphenous vein: initial results. Dermatol Surg. 2003;29(12):1170–5.
19. Tessari L, Cavezzi A, Frullini A. Preliminary experience with a new sclerosing foam in the treatment of varicose veins. Dermatol Surg. 2001;27(1):58–60.
20. Patel SB, Ostler AE, Dos Santos SJ, et al. Effects of environmental and compositional manipulation on the longevity of Tessari-made foam for sclerotherapy. J Vasc Surg Venous Lymphat Disord. 2015;3(3):312–8.
21. Carugo D, Ankrett D, Zhao X, et al. Benefits of Polidocanol endovenous microfoam (Varithena®) compared to physician compounded foams. Phlebology. 2016;31(4):283–95.
22. Bergan J, Pascarella L, Mekenas L. Venous disorders: treatment with sclerosant foam. J Cardiovasc Surg. 2006;47(1):9–18.
23. Darke SG, Baker SJ. Ultrasound-guided foam sclerotherapy for the treatment of varicose veins. Br J Surg. 2006;68(2):182–3.
24. Darvall KA, Bae GR, Adam DJ, et al. Duplex ultrasound outcomes following ultrasound-guided foam sclerotherapy of symptomatic recurrent great saphenous varicose veins. Eur J Vasc Endovasc Surg. 2011;42(1):107–14.
25. Blaise S, Bosson JL, Diamond JL. Ultrasound-guided sclerotherapy of the great saphenous vein with 1% vs. 3% polidocanol foam: a multicentre double-blind randomised trial with 3-year follow-up. Eur J Vasc Endovasc Surg. 2010;39(6):779–86.
26. Gonzalez-Zeh R, Armisen R, Barahona S. Endovenous laser and echo-guided foam ablation in great saphenous vein reflux: one-year follow-up results. J Vasc Surg. 2008;48(4):940–6.
27. Rasmussen L, Lawaetz M, Serup J, et al. Randomized clinical trial comparing endovenous laser ablation, radiofrequency ablation, foam sclerotherapy, and surgical stripping for great saphenous varicose veins with 3-year follow-up. J Vasc Surg Venous Lymphat Disord. 2013;1(4):349–56.
28. van der Velden SK, Biemans AA, De Maeseneer M, et al. Five-year results of a randomized clinical trial of conventional surgery, endovenous laser ablation and ultrasound-guided foam sclerotherapy in patients with great saphenous varicose veins. Br J Surg. 2015;102(10):1184–94.
29. Shadid N, Nelemans P, Dirksen C. Randomized clinical trial of ultrasound-guided foam sclerotherapy versus surgery for the incompetent great saphenous vein. Br J Surg. 2012;99(8):1062–70.
30. Gloviczki P, Comerta AJ, Dalsing MC. The care of patients with varicose veins and associated chronic venous disease: clinical practice guidelines of the Society for Vascular Surgery and the American Venous Forum. J Vasc Surg. 2011;53(5 Suppl):2S–48S.
31. Bush RG, Derrick M, Manjoney D. Major Neurological events following foam sclerotherapy. Phlebology. 2008;23(4):189–92.
32. Forlee MV, Grouden M, Moore DJ, Shanik G. Stroke after varicose vein foam injection sclerotherapy. J Vasc Surg. 2006;43(1):162–4.
33. Hahn M, Schultz T, Jünger M. Vasa. 2010;39(1):108–10.
34. Leslie-Mazwi TM, Avery LL, Sims JR. Neurocrit Care. 2009;11(2):247–50.
35. Wong M. Should foam made with physiologic gases be the standard in sclerotherapy? Phlebology. 2015;30(9):580–6.
36. Morrison N, Neuhardt DL, Rogers CR. Comparisons of side effects using air and carbon dioxide foam for endovenous chemical ablation. J Vasc Surg. 2008;47(4):830–6.
37. Carugo D, Ankrett DN, Zhao X, et al. Benefits of polidocanol endovenous microfoam (Varithena®) compared with physician-compounded foam. Phlebology. 2016;31(4):283–95.
38. Regan JD, Gibson KD, Rush JE, et al. Clinical significance of cerebrovascular gas emboli during polidocanol endovenous ultra-low nitrogen microfoam ablation and correlation with magnetic resonance imaging in patients with right-to-left shunt. J Vasc Surg. 2011;53(1):131–7.
39. Gibson K, Kabnick L. A multicenter randomized, placebo-controlled study to evaluate the efficacy and safety of Varithena® (polidocnaol endovenous microfoam 1%) for symptomatic, varicose veins with saphenofemoral junction incompetence. Phlebology. 2016;32(3):185–93. (epub ahead of print)
40. U.S. Department of Health and Human Services, FDA, CDER, CBER, CDRH. Guidance for industry – patient-reported oucome measures: use in medical product development to support labeling claims. December 2009.
41. King JT, O'Byrne M, Vasquez M, Wright D, VANISH-1 Investigator Group. Treatment of truncal incompetence and varicose veins with single administration of a new polidocanol endovenous microfoam preparation improves symptoms and appearance. Eur J Vasc Endovasc Surg. 2015;50(6):784–93.
42. Todd KL III, Wright DI, VANISH-2 Investigator Group. The VANISH-2 study: a randomized, blinded, multicenter study to evaluate the efficacy and safety of polidocanol endovenous microfoam 0.5% and 1.0% compared with placebo for the treatment of saphenofemoral junction incompetence. Phlebology. 2014;29(9):608–18.
43. Todd KL, Wright D, Orfe E. The durability of polidocanol endovenous microfoam treatment effect on varicose vein symptoms and appearance in patients with saphenofemoral junction incompetence: one-year results from the VANISH-2 study. J Vasc Surg Venous Lymphat Disord. 2014;2(1):112.
44. FDA access data in: http://www.accessdata.fda.gov/drugsatfda_docs/nda/2013/205098Orig1s000SumR.pdf.

45. Anwar MA, Lane TR, Davies AH, Franklin IJ. Complications of radiofrequency ablation of varicose veins. Phlebology. 2012;27(Suppl 1):34–9.
46. Dexter D, Kabnick L, Berland T, et al. Complications of endovenous lasers. Phlebology. 2012;27(Suppl 1):40–5.
47. Green D. Persistent post-sclerotherapy pigmentation due to minocycline. Three cases and a review of post sclerotherapy pigmentation. J Cosmet Dermatol. 2002;1(4):173–82.
48. Sarvananthan T, Shepherd AC, Willenberg T, Davies AH. Neurolgoical complication of sclerotherapy for varicose veins. J Vasc Surg. 2012;55(1):243–51.
49. Kern P, Ramelet AA, Wutschert R, Hayoz D. Compression after sclerotherapy for telangiectasias and reticular leg veins: a randomized controlled study. J Vasc Surg. 2007;45(6):1212–6.
50. Kulkarni SR, Slim FJ, Emerson LG, et al. Effect of foam sclerotherapy on healing and long-term recurrence in chronic venous leg ulcers. Phlebology. 2013;28(3):140–6.
51. Gloviczki P, Comerta A, Dalsing M, et al. The care of patients with varicose veins and associated chronic venous diseases: guidelines of the Society for Vascular Surgery and the American Venous Forum. J Vasc Surg. 2011;53(5 Suppl):2S–48S.
52. Masuda EM, Kessler DM, Lurie F, et al. The effect of ultrasound-guided sclerotherapy of incompetent perforator veins on venous clinical severity and disability scores. J Vasc Surg. 2006;43(3):551–6.
53. Whiteley AM, Taylor DC, Dos Santos SJ, Whiteley MS. Pelvic venous reflux is a major contributory cause of recurrent varicose veins in more than a quarter of women. J Vasc Surg Venous Lymphat Disord. 2014;2(4):411–5.
54. Daniels JP, Champaneria R, Shah L, Gupta JK, et al. Effectiveness of embolization or sclerotherapy of pelvic veins for reducing chronic pelvic pain: a systematic review. J Vasc Intervent Radiol. 2016;27(10):1478–86.
55. Qui Y, Chen H, Lin X, et al. Outcomes and complications of sclerotherapy for venous malformations. Vasc Endovasc Surg. 2013;47(6):454–61.
56. Varithena® Instructions for use: http://varithena.com/Portals/VarithenaHCP/assets/Varithena_Instructions_for_Use.pdf.
57. Feied CF, Jackson JJ, Bren TS, et al. Allergic reactions to polidocanol for vein sclerosis. Two case reports. J Dermatol Surg Oncol. 1994;20(7):466–8.
58. Bzoza Z, Kasperska-Zajac A, Rogala E, Rogala B. Anaphylactoid reaction after the use of sodium tetradecyl sulfate: a case report. Angiology. 2007;58(5):644–6.
59. Goldman MP, Sadick NS, Weiss RA. Cutaneous necrosis, telangiectatic matting, and hyperpigmentation following sclerotherapy: etiology, prevention, and treatment. Dermatol Surg. 1995;21(1):19–29.
60. Davis LT, Duffy DM. Determination of incidience and risk factors for postsclerotherapy telangectatic matting of the lower extremity: a retrospective analsyis. J Dermatol Surg Oncol. 1990;16(4):327–30.
61. Goldman MP, Kaplan RP, Duffy DM. Postsclerotherapy hyperpigmentation: a histologic evaluation. J Dermatol Surg Oncol. 1987;13(5):547–50.
62. Tafazzoli A, Rostan EF, Goldman MP. Q-switched ruby laser treatment for postsclerotherapy hyperpigmention. Dermatol Surg. 2000;26(7):653–6.
63. Mlosek RK, Wozniak W, Malinowska S, et al. The removal of post-sclerotherapy pigmentation following sclerotherapy alone or in combination with crossectomy. Eur J Vasc Endovasc Surg. 2012;43(1):100–5.
64. O'Donnell TF, Eaddy M, Raju A, et al. Assessment of thrombotic adverse events and treatment patterns associated with varicose vein treatment. J Vasc Surg Venous Lymphat Disord. 2015;3(1):27–35.
65. Willenburg T, Smith PC, Shepherd A, Davies AH. Visual disturbance following sclerotherapy for varicose veins, reticular veins and telangiectasias: a systematic literature review. Phlebology. 2013;28(3):123–31.
66. Frullini A, Felice F, Burchielli S, Di Stefano R. High production of endothelin after foam sclerotherapy: a new pathogenetic hypothesis for neurological and visual disturbances after sclerotherapy. Phlebology. 2011;26(5):203–8.