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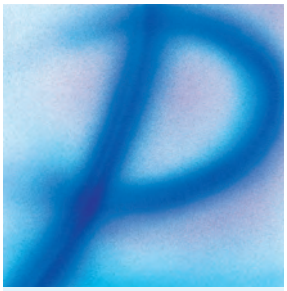

Phlebolymphology

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Aims and Scope

Phlebolymphology is an international scientific journal entirely devoted to venous and lymphatic diseases.

The aim of *Phlebolymphology* is to provide doctors with updated information on phlebology and lymphology written by well-known international specialists.

Phlebolymphology is scientifically supported by a prestigious editorial board.

Phlebolymphology has been published four times per year since 1994, and, thanks to its high scientific level, is included in several databases.

Phlebolymphology comprises an editorial, articles on phlebology and lymphology, reviews, and news.

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Contents

Editorial

Dear Readers,

In this new issue of Phlebolymphology, ***Jean-Luc Gerard*** *(France) reviews the interventional treatment methods for the small saphenous vein, which must be carried out very carefully because the vein ending is variable and it is in close proximity to the nerves. He also shares his personal experience with endovenous laser ablation, while providing clear recommendations for the optimal outcome.*

Sclerotherapy is an effective and safe treatment when used by trained and careful hands; however, complications can happen even to the most experienced practitioner. ***Lourdes Reina*** *(Spain) focuses on the possible minor and major complications after sclerotherapy and discusses how to manage these complications efficiently.*

Y. T. Tsukanov *and* ***Yurii Tsukanov*** *(Russia) analyze the potential tools and treatments to support the function of a weakened great saphenous vein. He presents his clinical experience, demonstrating the benefits of micronized purified flavonoid fraction in the treatment of situational great saphenous vein reflux in patients with early stages of varicose veins.*

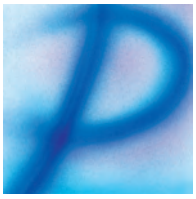
Lymphedema is a chronic, progressive, and debilitating disease. An early and accurate diagnosis and treatment is very important to alter the normal progression of the disease. ***Sarah Thomis*** *(Belgium) provides an overview of the available noninvasive and invasive diagnostic tools for lymphedema.*

Pregnancy is one of the major predisposing factors for developing venous insufficiency. ***Djordje Radak*** *and* ***Slobodan Tanaskovic*** *(Serbia) discuss the current guidelines for the diagnosis and treatment of chronic venous insufficiency during pregnancy and for the prevention of a venous thromboembolism. He also reviews the current role of low-molecular-weight heparin, warfarin, venotonic agents, and compression stockings in chronic venous disease treatment.*

Enjoy reading this issue!

Editorial Manager

Dr. H. Pelin Yaltirik



Small saphenous vein interventional treatment

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Keywords:

endovenous thermal ablation; foam sclerotherapy; interventional treatment; saphenous vein; varicose veins

Abstract

Evidence-based medicine can provide some clues about options for treating varicose veins, but there is no consensus on the best option. Even though the majority of practitioners have discarded several of the newer techniques available after having used them, they can nonetheless remain good options for others. However, the best procedure would be easily reproducible by the majority and for the majority. The adoption of these new and less invasive techniques, such as chemical ablation (foam sclerotherapy) and endovenous thermal ablation, could allow for treatment at a private doctor's surgery, thereby reducing the risk of recurrence and paresthesia that are often associated with traditional surgery under general or spinal anesthesia. Even though foam sclerotherapy is one of the best options for treating the small saphenous vein, thermal ablation, including endovenous laser ablation, can be more efficient for larger veins, regardless of the vein anatomy. The ideal treatment for varicose veins in all cases should be an ambulatory procedure without anesthesia or only local anesthesia because this will not require the patients to stop work or need nursing care. Due to the reduced convalescence, pain, and morbidity, thermal ablation has been graded 1B according to the 2011 American guidelines, 1B according to the 2014 European Venous Forum, and recommended by the 2013 NICE guidelines as a first-choice procedure.

Introduction

Great saphenous vein incompetence is the most frequent cause of varicose vein disease; however, small saphenous vein incompetence occurs in about 20% of patients presenting with varicose veins.[1,2] Treating the small saphenous vein must be carried out very carefully, even more so than for the great saphenous vein, because the ending is variable and it is in close proximity to the nerves.

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Conventional surgery, which has been the only treatment for small saphenous vein incompetence, is being challenged due to the high incidence of recurrence and the frequently associated postoperative complications. Due to hospitalization, general or spinal anesthesia, and too many days of sick leave, traditional surgery could be replaced with less invasive methods.

Chemical ablation is widely accepted as a safe and effective treatment for the small saphenous vein and especially for small and medium-sized veins. However, while ultrasound-guided foam sclerotherapy is safer than conventional surgery, it may result in rare, but major complications and litigation claims. During liquid or foam sclerotherapy, vascular physicians are afraid of mistakenly injecting the artery companion to the small saphenous vein. Therefore, to prevent this complication, the veins and arteries should be mapped carefully by using duplex ultrasound to locate the exact position of the arteries and avoid the high-risk zones.

Thermal ablation–endovenous laser ablation or radiofrequency ablation–is a minimally invasive technique that is mostly used for the great saphenous vein. However, for the small saphenous vein, ablation with the endovenous laser is preferentially used. We identified 15 specific studies on endovenous laser ablation of the small saphenous vein *(Table I)*.[3-17] The guidelines recommend mapping prior to any type of saphenous treatment, which is particularly true for the small saphenous vein. Now, due to improved duplex ultrasound technology, the small saphenous vein's nerves can be identified and mapped.

Treating the small saphenous vein using endovenous laser ablation

Procedure

The procedure is performed entirely under duplex ultrasound guidance. The varicose vein is punctured at the distal insufficiency point with a 19G (or 21G) needle. Then a guidewire is inserted through the needle, and, after removing it, a 6Fr (or a 4Fr) introducer sheath is placed over the guidewire into the vein. The guidewire is then replaced by a 600 µm or 400 µm laser fiber that is positioned accurately at the saphenopopliteal junction. Tumescent anesthesia is administered around and along the small saphenous vein. Laser energy is delivered using a diode laser generator and the small saphenous vein is ablated during withdrawal of the fiber.

Tricks and recommendations: personal experience

I began practicing endovenous laser ablation in June 2001 with a 980 nm and bare-tipped fiber, and, in June 2007, with a 1470 nm and bare-tipped fiber, and then, in June 2008, with a 1470 nm and radial fiber. This treatment is designed for symptomatic patients and a small saphenous vein trunk diameter >5 mm. The endovenous laser ablation procedure must be standardized in terms of the access site, positioning of the fiber tip, tumescent anesthesia (20 cc lidocaine [1% dilute in 250 or 500 cc of cooled saline] without bicarbonate or epinephrine), and energy according to the size of the vein needs to be very precise. Mapping both the vein and nerves prior to the procedure should become a routine practice.

Anesthesia

Before beginning thermal ablation, the entire length of the small saphenous vein to be treated is surrounded by a dilute local anesthetic that is injected at several points in the leg. Tumescent anesthesia is recommended for four reasons: (i) anesthesia reasons; (ii) to protect the surrounding tissues; (iii) to spasm the vein (for the treatment, it is better to have less blood in the vein); and (iv) to keep the patient conscious to stop the procedure when it is painful, thereby avoiding nerve damage. During tumescent anesthesia and under ultrasound guidance, the position of the nerves, previously identified, determines a safe puncture area, which is located a certain distance away from the nerves. The patient is only under local anesthesia, which may be associated with light sedation. General or spinal anesthesia should be avoided because they provoke vasoplegia (dilation of the vein), which reduces the treatment's efficacy. In addition, the patient is unable to feel anything, which increases the risk of nerve damage.

Access site

The access site is an important part of the procedure that must be considered. While the endovenous procedure is well documented in scientific literature regarding catheterization, tumescent anesthesia, positioning of the fiber tip, and the use of ultrasound guidance, there is little information available on the ideal puncture site. It is current practice to access the main trunk of the great saphenous vein or the small saphenous vein at the lowest incompetence area. In fact, the key point is where to begin the endovenous procedure. Catheterization should occur at the lowest part of the small saphenous vein incompetency, but the access should occur at an incompetent tributary.[18] The goal is to disconnect the competent part of the small saphenous vein from the incompetent part *(Figure 1)*. If we catheterize

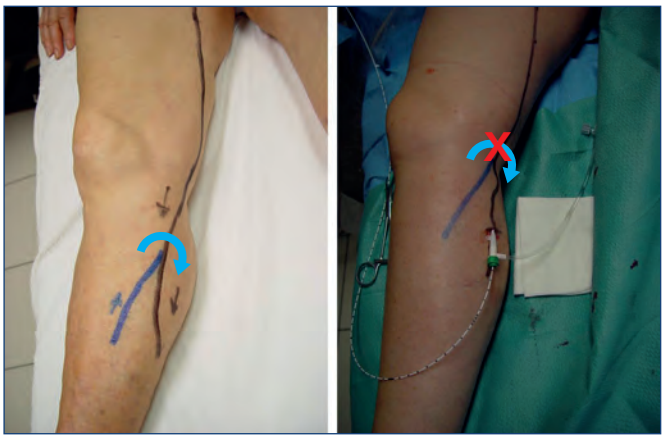

Figure 1. Introduction through the tributary to disconnect the competent part from the incompetent part.

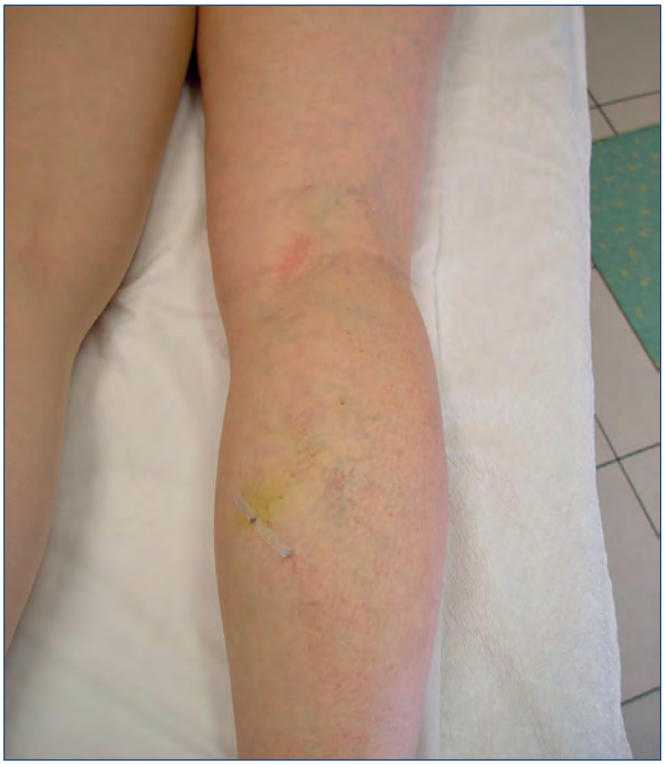

Figure 2. Introduction into the small saphenous vein through the tributary.

the small saphenous vein at the lowest incompetence area and above an incompetent tributary, then, after the treatment, the blood will flow from the competent small saphenous vein toward the tributary, which will necessitate a phlebectomy of this tributary. If we access the small saphenous vein at the lowest point of incompetence, but away from the incompetent tributary *(Figure 2)*, then we are treating both the small saphenous vein and tributary at the same time, which avoids a phlebectomy. In our practice, the access site is crucial.

How to avoid neurologic risks

Fifteen studies on endovenous laser ablation of the small saphenous vein *(Table I)*,[3-17] including two randomized clinical trials (endovenous laser ablation vs surgery)[16,17] and one meta-analysis *(Table II)*,[19] show that the rate of paresthesia is between 1.3% and 11% with only sensory damage (no motor nerve lesions). This rate was low, 4% on average, except for one study[18] in which the rate was up to 40%, but only for 2 weeks. Even if the paresthesia rate remains very low, irrespective of the nerves, it could be even lower if the small saphenous vein and the nerves are mapped prior to the procedure.

The sciatic nerve, which is located posterior to the thigh, is the largest nerve with a diameter >1 cm. It is divided at variable levels, but mostly at the summit of the popliteal fossa (a minimum of 3.5 cm above the popliteal skin crease). This division is slightly displaced (around 1.5 cm) from the longitudinal axis of the limb on the lateral aspect. It is divided into 2 nerves: the tibial nerve and the fibular nerve *(Figure 3)*.

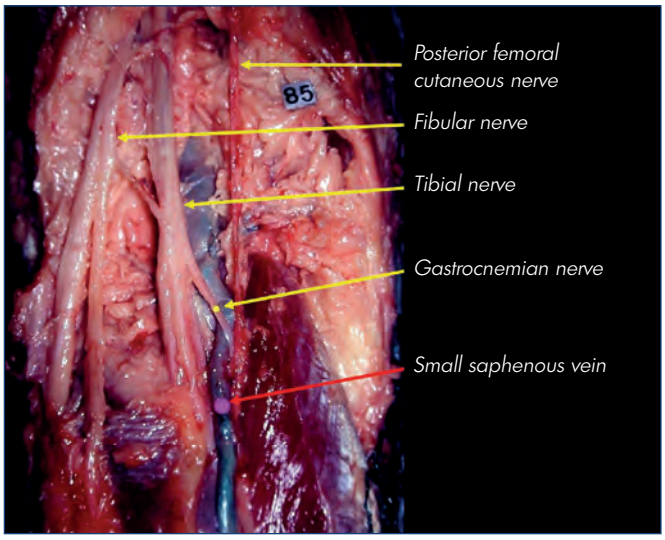

Figure 3. Division of the sciatic nerve slightly displaced from the longitudinal axis of the limb (the posterior femoral cutaneous nerve gives the midline of the limb).
Image courtesy of Prof Gillot.

The medial sural nerve, which arises from the tibial nerve, lies deep under the deep fascia on the middle of the popliteal fossa and then goes slightly toward the medial aspect of the middle third of the calf. At an indeterminate location, mostly below the groove of the two heads of the gastrocnemius muscle, the medial sural nerve pierces the deep fascia and joins the small saphenous vein in the superficial tissues. The lateral sural nerve, which arises

	Patients (please define)	Follow-up	Occlusion	Paresthesia	Deep venous thrombosis
Proebstle 2003[3]	35 (41)	3 months	100%	11% (4-8 weeks)	1
Ravi 2006[4]	37 (101)	3 years	84%		
Theivacumar 2006[5]	48 (68)	6 months	100%	4.4%	0
Gibson 2007[6]	120 (210)	4 months	96%	1.6%	12
Park 2008[7]	108 (390)	12 months	94%	2.6%	0
Nwaejike 2008[8]	66	14 months	100%	0%	0
Park 2008[9]	84 (96)	12 months	96%	4.2%	0
Kontothanassis 2008[10]	204 (229)	16 months	98.7%	2.25%	3
Trip-Hoving 2009[11]	52 (49)	6.5 months	100%	6%	1
Huismans 2008[12]	150	3 month	98%	1.3%	0
Desmyttère 2009[13]	128 (147)	3 years	97%	40% (2 weeks)	0
d'Othée 2009[14]	67 (63)		100%	2%	4 (4%)
Doganci 2011[15]	60 (68) 30 malleolus / 30 midcalf	6 months	100%	20% malleolus 3.5% midcalf (2 weeks)	0 0
Samuel 2012[16] (RCT)	53 EVLA /53 surgery	12 month	96.2% / 71.7%	7.5% / 26.4%	0/1
Roopram 2013[17] (RCT)	118 EVLA / 57 surgery	6 weeks	91% / 67%	6.7% / 31%	1

Table I. Specific studies on EVLA of the small saphenous vein: follow-up, occlusion rates, and paresthesia.
Abbreviations: EVLA, endovenous laser ablation; RCT, randomized control trial.

Type of intervention	Patients (n)	Occlusion rate (%; 95% CI)	Paresthesia (%)
Surgery	798	58.0%; 95% CI, 40%–75%	19.6%
Endovenous laser ablation	2950	98.5%; 95% CI, 97.7%–99.2%	4.8%
Radiofrequency ablation	386	97.1%; 95% CI, 94.3%–99.99%	9.7%
Ultrasound-guided foam sclerotherapy	494	63.6%; 95% CI, 47.1%–80.1%	
Mechanochemical endovenous ablation	50	94%	

Table II. Treatment modalities for the small saphenous vein: occlusion rates and paresthesia.
Data from reference 19: Boersma D et al. J Endovasc Ther. *2016;23(1):199-211.*

from the fibular nerve above the popliteal crease, lies on the superficial fascia on the lateral aspect of the leg, then goes medially to join the small saphenous vein at an indeterminate location, sometimes between two of the aponeurosis layers of the small saphenous vein. It joins the medial sural nerve mostly at the lower third of the calf to form one nerve, known as the sural nerve, which could be wrapped around the small saphenous vein.

Using a 10 MHz ultrasound probe, Ricci[20] showed that the sciatic nerve and its branches are easily identified in all cases into the popliteal fossa. Today, due to improvements in duplex ultrasound scanning and the high resolution of ultrasound probes (18 MHz), all the main nerves, including their branches up to 1 mm in thickness, are visible, and their entire path can be followed by ultrasonography. They are more easily visible in cross-section with their ultrasonic appearance being round and hyper-echogenic, in comparison with the surrounding tissues, and with their distinctive honeycomb pattern *(Figure 4)*.[18] Mapping the tibial nerve, fibular nerve, sural nerves, and the endings of the small saphenous vein prior to surgery or endothermal ablation can help the practitioner because there are numerous variations in the small saphenous vein endings (implantation level, aspect, and connection with the other veins that must be identified by ultrasound and reported) and divisions of the sciatic nerve *(Figures 5, 6, and 7)*.

Into the popliteal fossa. When the small saphenous vein ends in the longitudinal axis (midline) of the limb, at the popliteal crease or above, the risk of damaging the nerve

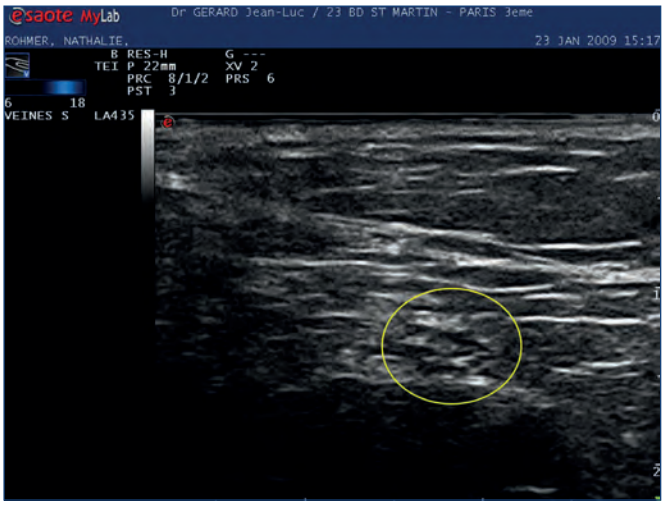

Figure 4. Cross-section of the tibial nerve using an 18 MHz ultrasound probe that shows the classic honeycomb shape (yellow circle).

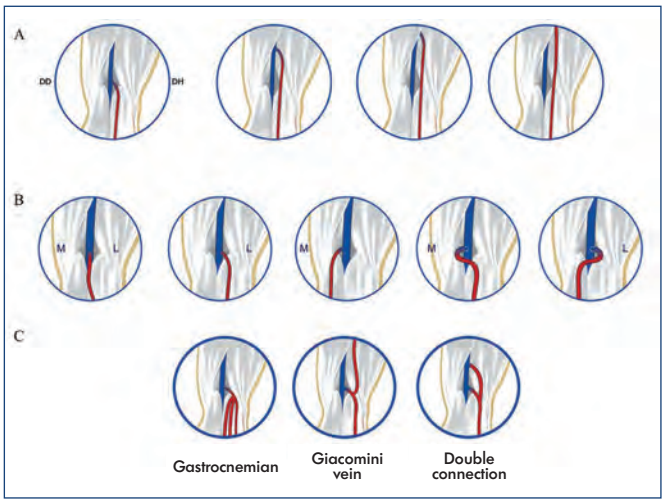

Figure 5. Variations in the small saphenous vein endings: implantation levels (Panel A), aspect (Panel B), and connection with other veins (Panel C).

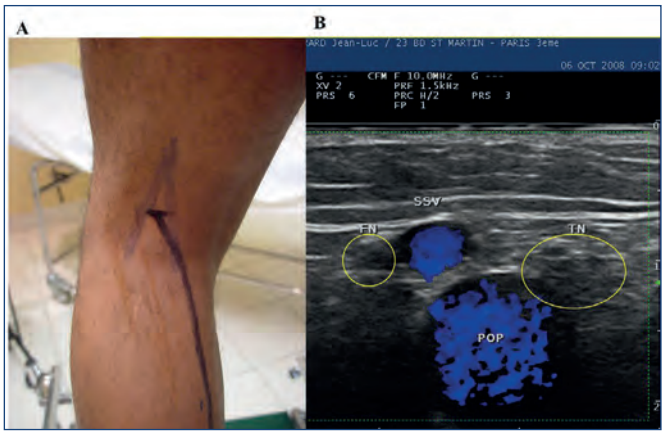

Figure 6. Panel A. mapping of the nerves (blue) and the small saphenous vein (dark). Panel B. duplex image.

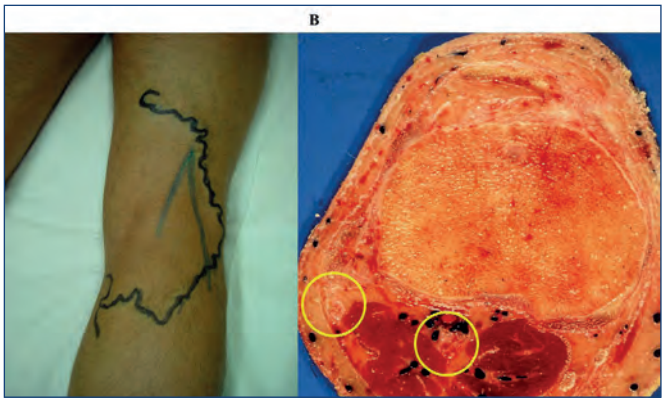

Figure 7. Panel A. mapping the nerves (blue) before phlebectomy (tributary in black). Panel B. Anatomical view with fibular nerve just under the skin.

is very small, while the risk of damaging the nerve increases when the small saphenous vein ends above the popliteal crease and is displaced on the lateral aspect. There is a branch of the nerve (from the fibular nerve), which hooks onto the vein *(Figure 8)*.

From below the popliteal crease to the end of the calf. The sural nerve (lateral sural nerve) can join the small saphenous vein and be close to or in contact with the vein, at variable levels between the two layers of the aponeurosis *(Figures 9 and 10)*. Fortunately, this situation is rare.

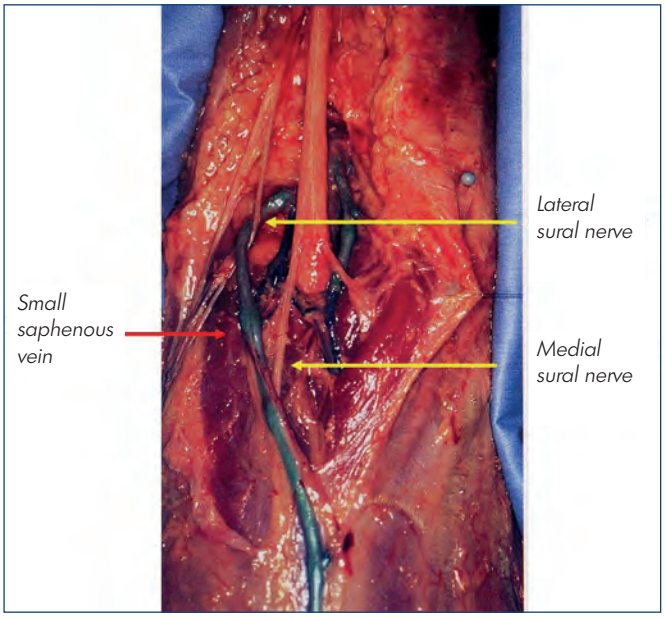

Figure 8. Ending of the small saphenous vein above the popliteal crease, which is displaced on the lateral aspect due to a branch of the nerve that hooks onto the vein.
Image courtesy of Prof Gillot.

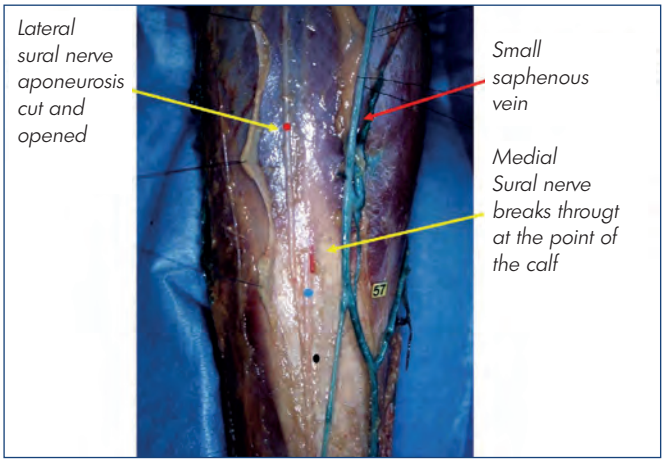

Figure 9. Medial sural companion of small saphenous vein between the 2 layers of the aponeurosis.
Image courtesy of Prof Gillot.

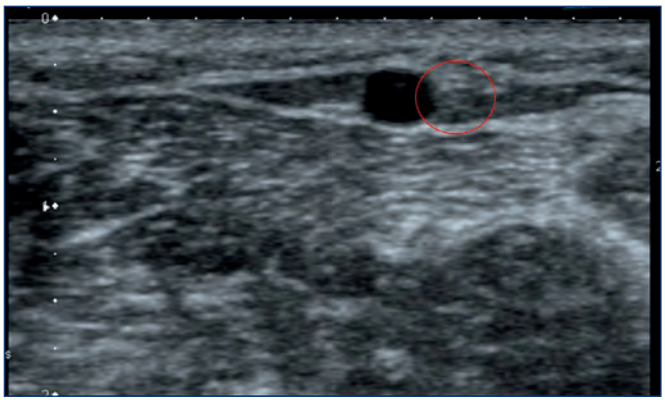

Figure 10. Duplex image of the sural nerve (red circle) close to the small saphenous vein (between the 2 layers aponeurosis).

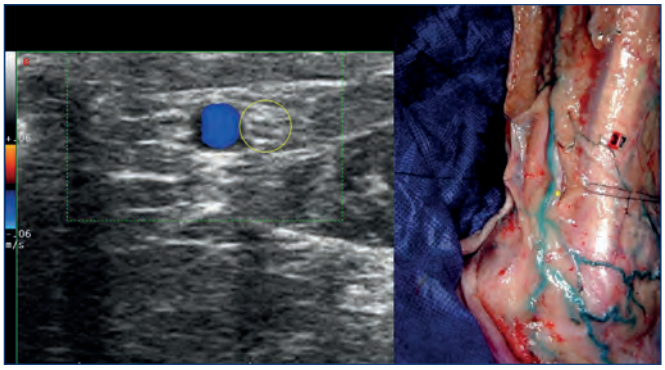

Figure 11. At the lateral malleolus: duplex image of the sural nerve (left), a nerve that is in contact with small saphenous vein (right - Image courtesy of Prof Gillot).

To the ankle. The nerve is always in contact with and possibly wrapped around the small saphenous vein *(Figure 11)*. Ablation of the lowest part of the small saphenous vein should be avoided.

Isolating the nerve from the vein during tumescent anesthesia would prevent postoperative numbness at the lateral malleolus *(Figures 12 and 13)*. In the event of an inability to separate the nerve from the vein (usually a segment <1 cm) due to a short endovenous laser ablation heating element (3 mm), it is possible to avoid treating these high-risk venous segments. When pain is felt, the generator pedal can be released, thereby immediately stopping the heat, like switching a light on or off. However, radiofrequency ablation of the small saphenous vein is more risky due to the length of the heating element (6.5 cm or 3.5 cm) and the impossibility of immediately stopping the heat (inertia), even after switching the device off when pain is felt, and it should be applied more cautiously. Therefore, the paresthesia rates are higher with radiofrequency ablation vs endovenous laser ablation, and the nerves may be damaged permanently. In some countries, treating the

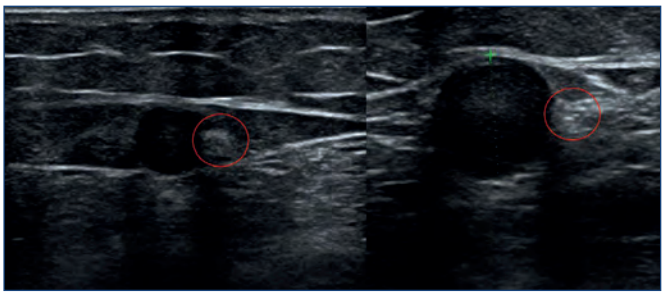

Figure 12. Sural nerve (red circle) close to the small saphenous vein before tumescent anesthesia.

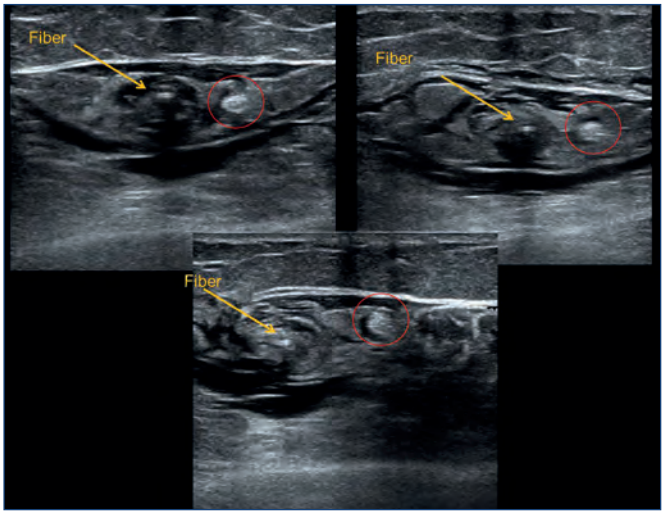

Figure 13. Sural nerve (red circle) pushed away from the small saphenous vein by the tumescent anesthesia.

small saphenous vein by radiofrequency ablation is not allowed due to a lack of specific studies.

Energy according to the size of the vein

With endovenous laser ablation, the energy can be adjusted continuously in accordance with the diameter of the vein to be treated, ie, the linear endovenous energy density (LEED).[21] We suggest a formula using 10 J/cm per diameter of the vein to be treated with a minimum of 60 J/cm. For example, if the vein diameter is 7 mm, then 70 J/cm should be applied. Laser energy is applied according to the information provided by duplex ultrasound mapping: increased for bulging veins or perforators and possibly decreased when proximal to the nerves. When treating larger veins, the energy needs to be increased, and, as the power should be invariable (10 watts maximum), the time must be increased.

Positioning the fiber at the ending of the small saphenous vein

During endovenous laser ablation, the positioning of the fiber tip needs to be very precise. The tip of the fiber has to be inserted into the small saphenous vein: (i) just below the saphenopopliteal junction if there are no tributaries; (ii) below the junction between the small saphenous vein and a competent vein: the Giacomini vein, the common trunk with a medial gastrocnemius vein or axial extension; and (iii) at any level in the thigh depending on the anatomy of the small saphenous vein thigh extension, just below the junction with a competent vein.

Postoperative ultrasound assessment, sick leave, and convalescence

After endovenous laser ablation, especially when there has been an adequate delivery of energy and a successful procedure, there should be a significant shrinkage of the vein at the early duplex ultrasound examination. Duplex ultrasound can determine the success of the procedure by verifying that there is a definite reduction in vein size; the cockade image (plane roundel) or bagel image reflects the thickening of the intima *(Figure 14)* due to the heating, which matches the histologic image *(Figure 15)*. Sick leave is not usually required and the patients can resume work in less than 2 days.

After ultrasound-guided foam sclerotherapy, duplex ultrasound images show a very slight reduction in vein size and very rarely a thickening of the intima. Consequently, there is a gradual reduction in the vein size; therefore, a long period of time is required for its disappearance (ie, 6 months [30% of cases], 1 year [63%], 18 months [80%], 2 years [85%]).[22] No sick leave is usually required and work can be resumed in less than 2 days according to the literature.

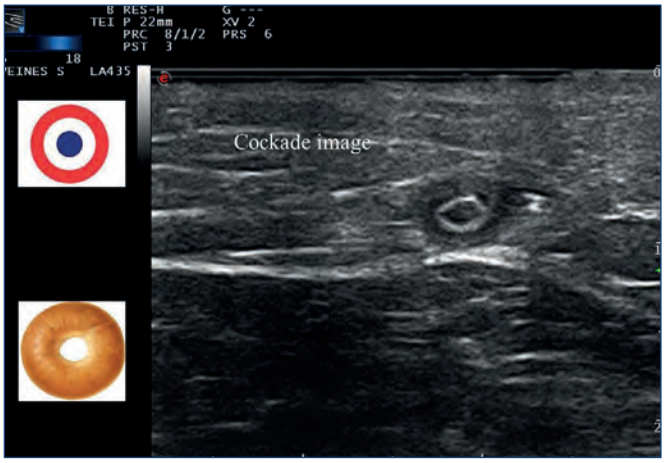

Figure 14. Cockade image: hypoechogenic image featuring the vein lumen, an hyperechogenic one for the intima and hypoechogenic one for the media-adventia or bagel image after treatment with a 1470 nm endovenous laser and radial fiber.

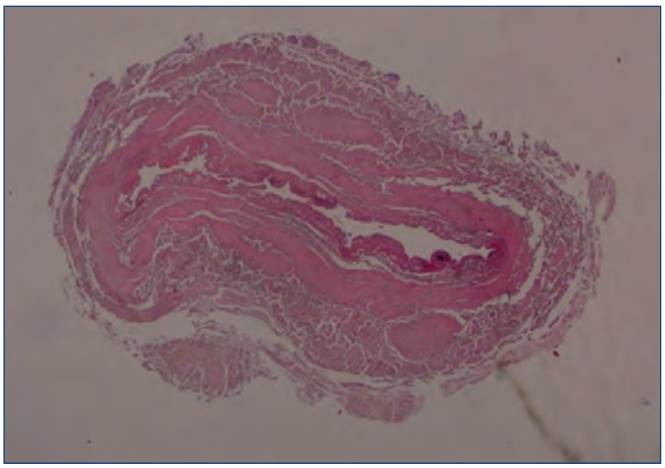

Figure 15. Histological examination of the great saphenous vein after endovenous laser ablation using a 1470 nm laser and a radial fiber.
Image courtesy of Dr Spreafico.

Outcome of endovenous laser ablation

Randomized clinical trials

The two randomized clinical trials comparing endovenous laser ablation with conventional surgery for the small saphenous vein[16,17] showed that abolishing the reflux of the small saphenous vein was significantly higher after endovenous laser ablation (96.2% and 91%) vs surgery (71.7% and 67%). Postoperative pain was significantly lower after endovenous laser ablation, allowing an earlier return to work. Minor sensory disturbances were significantly lower with endovenous laser ablation (7.5% and 6.5%) vs surgery (26.4% and 31%).

Case series

A meta-analysis on small saphenous vein treatment *(Table II)*[19] showed that the highest occlusion rate (mean, 98.5%; 95% CI, 97.7%-99.2%) occurred with endovenous laser ablation (number of small saphenous veins =2950). Neurologic complications were most frequently reported after surgery (mean, 19.6%) vs thermal ablation (endovenous laser ablation: mean, 4.8%; radiofrequency ablation: mean, 9.7%). Deep venous thrombosis was a rare complication (0% to 1.2%).

Treating the small saphenous vein using other procedures

Surgery

The incidence of recurrence from conventional surgery for small saphenous vein incompetence is high (up to 52% at 3 years),[23] and conventional surgery is frequently associated with postoperative complications.[24] Few studies give us the exact rate of paresthesia (26% to 28%)[16,17,25] after small saphenous vein surgery. Indirect information has shown that small saphenous vein surgery is probably responsible for around half of the litigation claims related to vascular surgery. A study carried out by Markides et al[26] from April 1995 to April 2007 identified 395 litigation claims that were related to vascular surgery. In terms of causes, 50% of the cases involved intraoperative problems, and, in ≈30% of these cases, varicose veins were involved. Nerve damage was the cause for complaint litigation claims in 36 cases. The fibular nerve was involved in 58%, the sural nerve in 6%, while, in 30% of cases, it was unclear which nerves were damaged. Thus, most of the litigation claims are due to small saphenous vein surgery, possibly because of the variable ending of the vein and its proximity to the nerves. Therefore, most of these claims could have been avoided if the position of the nerves (for the small saphenous vein and the tributaries) were marked preoperatively.

However, in a report by the CNAM (French public national health insurance)[27] showed that 122 000 patients were treated with surgery for varicose veins in France in 2010; the cost was 264 million euros, and, on average, 26 days of sick leave were taken by 36% of the patients, costing 34 million euros. Although this report did not detail which veins have been operated, meaning that it was not specific to the small saphenous vein, the number of days of sick leave is the same regardless of the varicose veins treated.

Traditional surgery has been graded 2B, according to the American guidelines[28] and 2A according to the European Venous Forum guidelines.[29] The NICE guidelines[30] propose surgery only if thermal ablation and ultrasound-guided foam sclerotherapy are unsuitable.

Therefore, treating the small saphenous vein with surgery should be the very last option due to the high incidence of recurrence and paresthesia and the excessive number of days of sick leave and fees for the nursing services required. Although open surgery provides good results in competent hands, it is no longer the gold-standard treatment for small saphenous vein incompetency. According to evidence-based medicine,[31] surgery is reserved for certain patients depending on the circumstances, the patients themselves, or their social (economic) problems.

Sclerotherapy

Sclerotherapy that is performed in a doctor's office is the easiest and cheapest procedure for varicose veins.

Vein size	Polidocanol foam	STS foam (Sodium tetradecyl sulfate)
Ø < 4 mm	0.5%	0.2 to 0.5 %
Ø ≥ 4 and < 6 mm	1%	0.5 to 1%
Ø ≥ 6 and < 8 mm	2%	1%
Ø ≥ 8 mm	3%	3%

Table III Algorithm for treating the small saphenous vein with sclerotherapy. The maximum volume of foam per session is 10 mL.
Ref. 36. Hamel-Desnos C. Echo-doppler per procédure: sclérothérapie à la mousse.
In Guex JJ, Hamel-Desnos C, eds. Ultrasons et Phlébologie. Editions Phlébologiques Françaises-Paris; 2016:109-121

Ultrasound-guided sclerotherapy was first described at the end of the 1980s,[32,33] and it provided better results with improvements in safety and precision. This procedure was improved with ultrasound-guided foam sclerotherapy,[34,35] which provided better efficacy (fewer injections and fewer sessions) compared with liquid sclerotherapy. Nevertheless, to provide optimal results, ultrasound-guided foam sclerotherapy must be performed with an adequate sclerosing agent and at the right concentration and volume *(Table III)*. Certainly, ultrasound-guided foam sclerotherapy is a standardized procedure, but, to do this, certain rules must be respected regarding efficacy and safety.[36] First, the mixture of the sclerosing agent and gas, which is done with a three-way tap or female-female biconnectors, must use 1 volume of sclerosing agent to 4 volumes of gas (room air-filtered or carbon dioxide or a mixture of carbon dioxide and oxygen). Second, a treatment algorithm should be adopted to adjust the doses according to the vein diameter. Third, for safety reasons, ultrasound-guided foam sclerotherapy must be carried out entirely under ultrasound control to monitor: (i) location of the vein to be injected and detect possible nearby arteries; (ii) vein puncture; (iii) needle position check; (iv) sclerosing injection; (v) postinjection check; and (vi) evaluation of vein spasm and vein filling.

The major complications of sclerotherapy occur by mistakenly injecting the artery companion to the small saphenous vein, which can cause large cutaneous necrosis, or even worse, muscular necrosis. There are no rules (no exact anatomical locations) that can determine the exact position of the arteries; therefore, it is mandatory to use duplex ultrasound to identify a safe zone without arteries before injection. The main advantage of the procedure is the rarity of paresthesia; however, when it occurs, it is probably due to excessive compression by bandages. The use of compression stockings after sclerotherapy, which is often recommended, has never been shown to offer any advantages; therefore, they are deemed useless and possibly deleterious.

If the diameter of the vein is <5 mm, sclerotherapy could be recommended. For veins between 5 and 6 mm, sclerotherapy could be balanced with thermal ablation. However, when the small saphenous vein is too large in diameter, the amount of sclerotherapy solution that needs to be injected into the patient could be beyond the safety recommendations (maximum of 10 mL of foam per session),[37] which could be less efficient during short- or long-term follow-up. In fact, the main disadvantage of ultrasound-guided foam sclerotherapy is high recanalization rates of veins >6 mm in diameter, which often necessitates at least a second treatment. Chemical ablation is, most of the time, not a one-go treatment, as it often requires several sessions. In addition, there are higher risks of phlebitis (inflammatory area) and brown staining of the skin when veins are superficial (tributaries).

Cyanoacrylate glue and mechanochemical endovenous ablation

There are no specific studies on treating the small saphenous vein with cyanoacrylate glue or mechanochemical endovenous ablation and very few patients have been treated with these methods; therefore, we cannot give recommendations.

Conclusion

All the wavelengths and optical fibers have shown a high rate of success, but a 1470 nm diode laser and protected fiber (radial fiber) offer a high rate of success with the lowest number of side effects. Endovenous laser ablation is adapted to the small saphenous vein, regardless of its size, ending, or anatomy, on the condition that the small saphenous vein and nerves are mapped

prior to the procedure. High-frequency ultrasound probes (18 MHz or at least 14 MHz) make the procedure easier, and these probes should be used widely to avoid nerve damage, which will consequently decrease the number of litigation claims. Adapted material and training in ultrasonography are indispensable for achieving this goal. Even if endovenous laser ablation seems to be a safe, less traumatizing, and efficient technique, the choice of a technique actually depends on the preferences of the patient (economic reasons, reimbursement, knowledge of the technique, age, etc) and the abilities of the practitioner to use one or more of the other techniques.

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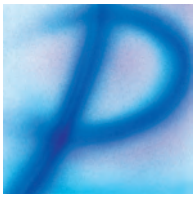

How to manage complications after sclerotherapy

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Keywords:

complications; foam; recommendation; sclerotherapy; side effect; treatment; varices; varicose vein

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Abstract

Sclerotherapy is an effective and safe treatment when used by trained and careful hands. Good technique, satisfactory imaging, general precautions, and compliance with posttreatment instructions may help avoid some of the adverse events. Even though complications can happen even to the most experienced practitioner, it is mandatory to know what they are and how to manage them. Fortunately, most of these adverse events are benign, but physicians must be aware of the potential serious events, and they should be trained to react adequately and immediately. All office settings using sclerotherapy should be equipped to administer oxygen therapy. Protocols for immediate action in case of anaphylaxis, intra-arterial injection, or neurologic deficits should be in place. A plan for transport to emergency services for further evaluation and treatment of vital emergencies, such as stroke or extended necrosis, are imperative. Access to hyperbaric oxygen therapy may be considered in this emergency planning. Minor complications require an adequate follow-up by the practitioner and adherence with post-sclerotherapy treatment by the patient. Very rare major complications could benefit from multicenter registers to provide evidence-based treatments.

Introduction

The European guidelines for sclerotherapy in chronic venous disorders recommend considering the following adverse events after sclerotherapy *(Table I)*.[1-5] Compared with liquid sclerotherapy, foam sclerosants do not result in many new or different complications, but appear to change their relative incidences.[1] Most adverse effects are minor and inconsequential, such as local injection site pain, urticaria, itching, erythema, and bruising. Other common, but usually self-limiting, side effects include visual disturbances and migraines (1.4% to 14%), cutaneous hyperpigmentation (10% to 30%), and telangiectatic matting (15% to 24%) or blisters or folliculitis caused by post-sclerotherapy compression. Significant and relatively rare complications include systemic life-threatening reactions and anaphylaxis (very rare), deep venous thrombosis (1% to 3%), stroke (0.01%), tissue necrosis (variable frequency), edema of the injected extremity (0.5%), and nerve damage (0.2%).[1-5]

Designation	Incidence
*****Very common	≥10%
****Common	≥1% – <10%
***Uncommon	≥0.1% – <1%
**Rare	≥0.01% – <0.1%
*Very rare and isolated cases	<0.01%

	Frequency	
Type of adverse event	With liquid	With foam
Severe complications†		
Anaphylaxis	*Isolated cases	*Isolated cases
Large tissue necrosis	*Isolated cases	*Isolated cases
Stroke and TIA	*Isolated cases	*Isolated cases
Distal DVT (mostly muscular)	**Rare	***Uncommon
Proximal DVT	*Very rare	*Very rare
Pulmonary Embolism	*Isolated cases	*Isolated cases
Motor nerve injury	*Isolated cases	*Isolated cases
Benign Complications		
Visual disturbances	*Very rare	***Uncommon
Headaches and migraines	*Very rare	***Uncommon
Sensory nerve injury	*Not reported	**Rare
Chest tightness	*Very rare	*Very rare
Dry cough	*Very rare	*Very rare
Superficial phlebitis	Unclear‡	Unclear‡
Skin reaction (local allergy)	*Very rare	*Very rare
Matting	****Common	****Common
Residual pigmentation	****Common	****Common
Skin necrosis (minimal)	**Rare	*Very rare
Embolia cutis medicamentosa	*Very rare	*Very rare

Table I. Complications observed in a prospective French Registry of 12 173 sclerotherapy sessions.

From reference 1: Guex JJ et al. Dermatol Surg. *2005;31(2):123-128.*

Major complications

Systemic allergic reaction and anaphylaxis

Systemic allergic reactions caused by sclerotherapy treatment occur very rarely. Local or generalized skin reactions, such as urticaria, are much more frequent (around 0.6%) than systemic involvement, and true anaphylaxis is an extremely rare complication constituting an emergency.[6-10] These reactions are unpredictable. Patients who have undergone multiple previous treatments with liquid sclerosants may be at a higher risk of developing post-sclerotherapy generalized urticaria, mastocytosis, or chronic urticaria.[3] Since the risk increases with repeated exposure to the antigen, it is important to always be prepared for this reaction.[6] Foam sclerosants are associated with a lower incidence of hypersensitivity reactions, and histamine release is responsible for the clinical manifestations of this reaction. Although urticaria and abdominal pain are common, the three principal manifestations of anaphylaxis are airway edema, bronchospasm, and vascular collapse.

Treatment

The treatment should be tailored to the clinical features of the allergic events; it is essential to have emergency protocols in place *(Figure 1).*[11-15] The injection should be stopped immediately and the standard emergency procedure should be followed, including the administration of oxygen and epinephrine when appropriate (grade 1A).[4,5] The treatment requires: (i) putting the patient in the Trendelenburg position; (ii) keeping airways secure; (iii) giving oxygen; (iv) gaining access for IV fluids; and (iv) administering drugs. Calling for emergency services should be done in parallel with initial patient support *(Figure 2).*[11-16]

The recommended treatment is a subcutaneous injection of epinephrine 0.2 to 0.5 mL (1:1000). This treatment can be repeated three or four times at 5- to 15-minute intervals to maintain a systolic blood pressure >90 to 100 mm Hg, and it should be followed by establishing an intravenous line with a 0.9% sodium chloride solution. Intravenous injections of dexclorfeniramine 5 to 10 mg every 8 hours or intravenous diphenhydramine hydrochloride 50 mg, is given next, along with cimetidine, 300 mg; both the intravenous solution and oxygen are given at 4 to 6 L/min. An endotracheal tube or tracheotomy is necessary for

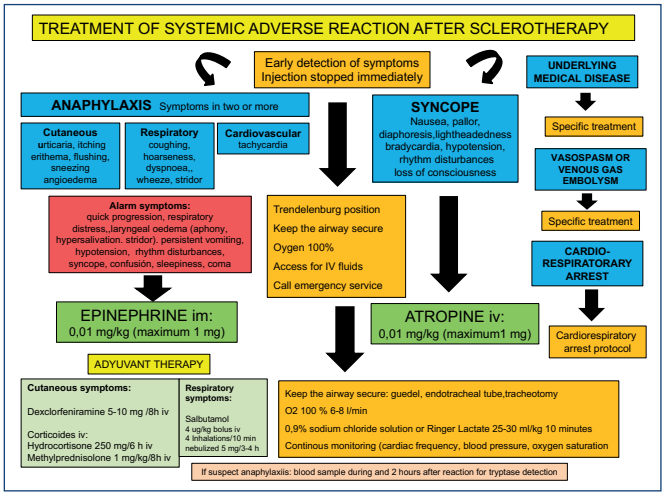

Figure 1. Local protocol for the management of systemic adverse reactions after sclerotherapy.

Office-setting, Vascular Department, Hospital Central de la Cruz Roja, Madrid, Spain.

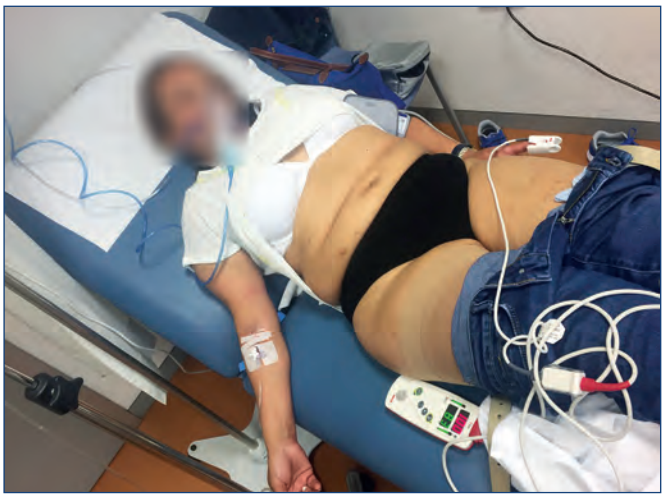

Figure 2. Transitory general effects.

The patient had painful chest tightness and an exacerbation of an underlying stress-related allergic disease after foam sclerotherapy of reticular veins and telangiectasia. The patient was managed with intramuscular epinephrine, intravenous antihistamines, bronchodilator therapy, intravenous line with sodium chloride solution, and 100% O_2, and the treatment occurred while the patient was in the Trendelenburg position with continuing evaluation of neurologic, cardiovascular, and respiratory systems. Intravenous corticosteroid was administered later. The patient was on observation until the clinical disturbances disappeared and she was discharged.

laryngeal obstruction. For asthma or wheezing, use salbutamol, 4 inhalations over 10 minutes, or nebulized salbutamol, 5 mg over 3 to 4 hours. For severe respiratory symptoms, use a 4 µg/kg intravenous bolus of salbutamol and, later, it is recommended to use 5 to 10 µg/minute as a continuing infusion. At this point, it is appropriate to transfer the patient to the hospital or emergency services. Methylprednisolone sodium succinate (1 mg/kg) or hydrocortisone (250 mg) is given intravenously and repeated every 6 hours for a total of 4 doses. Corticosteroids are not an emergency medication because their effects appear only after 1 to 3 hours, and they are given to prevent the recurrence of symptoms 3 to 8 hours after the initial event. The patient should be hospitalized overnight for observation.[11-15]

Minor degrees of angioedema can be treated with oral antihistamines. However, if stridor is present, an intravenous injection of dexclorfeniramine 5 to 10 mg or an intramuscular injection of diphenhydramine and intravenous corticosteroids should be administered; a laryngoscope and endotracheal tube should be available.[11-15] Bronchospasm has been estimated to occur after sclerotherapy in 0.001% of patients, but it usually responds to the addition of an inhaled or intravenous bronchodilator or to the already noted antihistamine-corticosteroid regimen.[11-15] Minor reactions, such as urticaria, are easily treated with oral antihistamines. The addition of corticosteroids is rarely needed, but they may be needed if the reaction does not subside readily.[11-15]

Tissue and cutaneous necrosis

Tissue necrosis most commonly presents as an ulceration, and it can result in extensive loss of tissue. Cutaneous necrosis may occur with the injection of any sclerosing agent, even under ideal circumstances, and it does not necessarily represent a physician error. Fortunately, its occurrence is rare and usually of limited sequelae.[6] Cutaneous necrosis can occur several weeks after the initial insult, and it can be associated with pain, localized inflammation, and edema.

Some classes of sclerosing agents, such as chemical irritants and osmotic agents, are more likely to cause tissue necrosis following extravasation.[16] The main mechanism leading to tissue necrosis following the use of detergents is arterial occlusion, which may be caused by an inadvertent intra-arterial injection or a venoarterial reflex vasospasm.[3,17-19] Passage of the sclerosants into the arterial circulation may be mediated by open cutaneous arteriovenous shunts.[17-19] Venoarterial reflex vasospasm may result from a high-speed or high-pressure injection in small caliber veins, which leads to rapid dilation of the target vein and vasospasm of the associated arteries. Venoarterial reflex vasospasm clinically presents with prolonged blanching of the skin a few centimeters away from the site of injection, followed by cyanosis and reactive erythema. Prolonged arterial vasospasm may result in tissue infarction and subsequent necrosis *(Figure 3)*.[17-19]

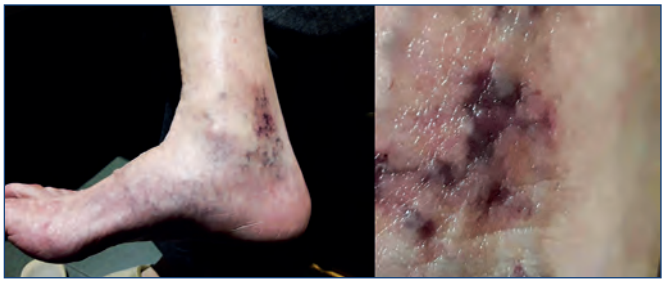

Figure 3. Cutaneous necrosis after extensive sclerotherapy with foam in an older woman with long-term reticular veins and telangiectasia in retromaleolar area.

The patient also suffered from severe edema and inflammation of the ankle, which improved with nonsteroidal anti-inflammatory drugs, medical compression stockings, and local corticosteroids.

Treatment of tissue necrosis

Extravasation

A vigorous massage where extravasation has occurred may decrease tissue damage. The solution must be diluted as soon as possible. Hypertonic solutions should be diluted with copious amounts of normal saline solution (at least 10 times the volume of extravasated solution). Dilution with hyaluronidase in normal saline solution limits the extent of the necrosis and prevents the development cutaneous necrosis when using a 3% solution with sodium tetradecyl sulfate.[20] Hyaluronidase should be reconstituted with a 0.9% sodium chloride solution immediately before use (75 U in a volume of 3 mL), and it is recommended to inject the diluted solution into multiple sites around the area where extravasation has occurred within 60 minutes of extravasation.[21]

Venoarterial reflex vasospasm

Treatments for venoarterial reflex vasospasm include topical vasodilators (2% nitroglycerine ointment), which are applied with a vigorous massage, oral antiplatelets, and oral non-steroidal anti-inflammatory drugs (NSAIDS). Systemic anticoagulant agents and systemic steroids may be used when extensive necrosis is anticipated.[6]

Treatment of cutaneous necrosis

For all causes of ulceration, it must be treated as soon as it occurs. Fortunately, ulcerations are usually small, averaging 4 mm in diameter. At this size, primary healing usually leaves an acceptable scar. As ulcers may take 4 to 6 weeks to heal completely, even under ideal conditions, excision and occlusive dressing of these lesions are recommended at the earliest possible time, which gives the patient the fastest healing time, with decreased pain and an acceptable scar.[6]

Large tissue necrosis: inadvertent intra-arterial injection

Direct arterial/arteriolar injections are exceptionally rare. In fact, less than 70 cases have been described to date,[22-26] most of which occurred after an injection in the ankle region and in the site of perforating veins above the medial ankle. Other risk areas include the cross-section of the small saphenous vein and the cross-section of the great saphenous vein. Several cases have involved arterioles of the medial thigh.[22-26] Ultrasound guidance has helped minimize the occurrence of this catastrophic event, which most frequently results in limb amputation (52.5%).[9,22] Intra-arterial injections commonly present with severe sudden pain at the injection site, which propagates along the artery distribution. Pain can happen quickly or progress over several hours. Rarely, patients have no complaints of pain and demonstrate only a mild, sharply demarcated erythema that becomes dusky and cyanotic after a few hours.[22]

Treatment

As endothelial damage occurs within the first minutes after injecting the sclerosant, prompt realization of the arterial complication and immediate therapy is essential to reduce the risk of subsequent amputation.[22] There are no evidence-based or consensus guidelines on the optimal management of this complication.[24] The European guidelines recommend that, if severe pain occurs, to stop the injection immediately, aspirate the sclerosant if possible, use local catheter-directed anticoagulation and thrombolysis if applicable, and possibly follow-up with systemic anticoagulation. Early administration of systemic steroids may help reduce the subsequent inflammation that causes tissue damage (grade 1C).[3-5] Aspiration of blood with any remaining sclerosant followed by local intra-arterial administration of heparin has not been identified in a single case report.[24]

Bergan et al[16] recommended 6 days of therapeutic heparin to treat arterial injury following sclerotherapy. The in-house protocol by Parsi and Hannaford includes a subcutaneous injection of enoxaparin at 1 mg/kg over 12 hours aiming for an anti-factor Xa level in the therapeutic range of 0.5 to 1.2 IU/mL for 1 to 4 weeks depending on the extent of the injury.[24] Anticoagulation may be complemented with an antiplatelet therapy of acetylsalicylic acid. Immediate intravenous application of acetylsalicylic acid, at a dosage similar to coronary events with an injection of 500 mg, might be beneficial, followed by 100 mg or 325 mg uncoated tablets of acetylsalicylic acid daily for the same period as the anticoagulation.[22,24]

Thrombolysis was used in four cases of inadvertent arterial injection. Complete recovery was only reported in one case, whereas amputation could not be prevented in two cases.[24] In cases where cellular lysis has already taken place and microcirculatory obstruction is caused by a sludge of cellular degradation, thrombolysis might be ineffective. Therefore, it should be especially considered in the very early phase and in proximal thrombosis.[24] Several authors recommend administering intravenous dextran (10%), 500 mL per dose for 3 days.[6]

Parsi and Hannaford published three cases that were treated with systemic steroids.[24] Vessel occlusion results in an inflammatory process that will ultimately lead to skin necrosis. Their current in-house protocol includes an intravenous administration of a systemic steroid for at least 48 hours before switching to oral prednisone at 0.75 to 1 mg/kg/day (maximum dose, 50 mg daily), with a gradual reduction over the course of 12 weeks. This protocol is based on anecdotal experience and should be tested in future cases.[24] In localized and less extensive cases, potent topical steroids, such as clobetasol, have been used with reported success.[22]

Another therapeutic goal is pain control. Given the proximity of nerves to arteries, arterial injury can result in perineural swelling and significant neuropathic pain. Pain contributes to significant morbidity, which must be managed carefully.[22] Parsi and Hannaford found that shorter-acting NSAIDS, such as ibuprofen, were more effective than longer-acting NSAIDS. Gabapentin was not particularly useful in any of their patients.[24] One patient found that electrostimulation therapy provided adequate pain relief.[24]

Hyperbaric oxygen may minimize reperfusion tissue injury by optimizing the oxygenation, inhibiting neutrophil migration, and minimizing proinflammatory cytokine production.[27] This treatment has been successfully used to prevent necrosis following a single case of an intra-arterial injection of sclerosants.[25] As its occurrence is extremely rare, it is recommended that an emergency flow sheet be readily accessible *(Table II)*.

Neurological complications

The overall frequency of neurological complications of sclerotherapy is around 0% to 2%,[28,29] and they include transient events, such as visual disturbances and migraine, and ischemic events, such as transient ischemic attacks and stroke, which is an event with a lower frequency that can result either from a paradoxical clot or a gas embolism. Patent foramen ovale and other cardiopulmonar right-to-left shunts are the most consistent risk factors.[9] The etiology of neurological symptoms following sclerotherapy is currently unknown.

Transient events: visual disturbances and migraines

A systematic review found that visual disturbances may occur in up to 14% of patients undergoing foam sclerotherapy,[30] but a recent systematic review found the overall incidence to be 1.4%.[29] The clinical presentation of these visual disturbances is similar to the aura of a migraine.[30] Transient neurologic events may be observed after any kind of sclerotherapy, although they occur more commonly after foam sclerotherapy and after treatment of reticular and spider veins.[1,2,4,5,30] All cases spontaneously regressed without after effects.

A patent foramen ovale or another right-to-left shunt, which is present in approximately 30% of the general population,[31] may be one etiologic factor. The pulmonary filter is short-circuited, which allows foam bubbles or endothelin-1 to be released from the vessel injected with sclerosants[32] and to pass into the arterial circulation.[28,30,32-36]

1. Leave the needle unchanged if possible; aspirate blood and remaining sclerosing solution if possible
2. Immediate intravenous heparin administration (5000 to 10 000 IU unfractionated heparin)
3. Consider immediate catheter-directed arterial thrombolysis
4. Intravenous injection of 500 mg of acetylsalicylic acid
5. Intravenous injection of dextran 10%, 500 mg/day for 3 days
6. Analgesia with non-steroidal anti-inflammatory drugs, anxiolytic therapy, and possibly electrostimulation therapy
7. Intravenous administration of a systemic steroid for at least 48 hours
8. Continue heparin therapy at a therapeutic dosage for 6 days or longer
9. Continue acetylsalicylic acid 100 mg or 325 mg uncoated tablets daily 6 days or longer
10. Oral prednisone at 0.75 to 1 mg/kg/day (max 50 mg daily), with a gradual reduction over the course of 12 weeks

Table II. Anaphylaxis treatment.

Gillet et al hypothesized that endothelin-1 reaches the cerebral cortex and induces a cortical spreading to trigger a migraine.[30] Frullini et al believes that endothelin-1 provokes a vasospasm, which is the key to understanding migraines, chest tightness, retinal transient ischemia, and neurologic ischemia.[32,33] There is no clear evidence for a relationship between bubbles and visual or neurological disturbances.[4,5,35-37] Bubbles are known to cause vasospasm, which may trigger migraine-type symptoms and other general transient effects, such as chest tightness.[28] Other factors, such as bubble load, treatment parameters, and patient factors, may be important.[28]

Ischemic events: transient ischemic attacks and stroke

The presence of a right-to-left shunt, particularly a patent foramen ovale, is the most consistent risk factor in patients with ischemic neurologic events (transient ischemic attacks and stroke). There are only a few published reports of transient ischemic attacks following sclerotherapy.[28] All reported cases were associated with a right-to-left shunt, had an immediate onset, and followed the use of air-based foam sclerosants. It has been suggested that right-to-left shunts might be a factor, allowing foam bubbles to pass into the arterial circulation.[28,35-37]

Stroke is a very rare, but significant, complication of sclerotherapy.[38-42] Ma et al reported two cases of stroke following 4059 foam procedures in a 6-year period, yielding an incidence of 0.01%.[41] Parsi reviewed 13 cases of stroke occurring after sclerotherapy that were published since 1994.[28] Four cases followed liquid sclerotherapy and nine followed foam sclerotherapy; 3 patients had a partial recovery, while the others had a complete recovery. Cases with an immediate onset following foam sclerotherapy were due to a paradoxical gas embolism,[28,38-41] while cases with a delayed onset of a few days were due to a paradoxical clot embolism.[28,41,42] A right-to-left shunt, particularly a patent foramen ovale, was the most consistent risk factor in all reported cases.[28]

The mechanism of infarction in a paradoxical gas embolism may be due to direct physical occlusion of intracranial arteries by the gas bubbles or the bubbles induce vasospasm and activation of the coagulation system, resulting in secondary thrombotic occlusion.[28,41] No gas or clot embolism could be demonstrated in 5 of the 13 patients with stroke reviewed.[28,41] The release of cell-derived sclerosant by-products may play a crucial role in the pathogenesis of neurological and other sclerotherapy complications.[28,32,33] Finally, a coincidental event due to general causes of stroke should be considered.[28]

A venous gas embolism presents with dyspnea, continuous cough, hypotension, dizziness, and substernal chest pain. A "mill wheel" murmur may be produced by movement of bubbles in the right ventricle.[28] A cerebral gas embolism can present with confusion, focal neurological symptoms, and stroke.[28,38-41]

Treatment

The neurological events may be self-limiting, which would necessitate a nonspecific treatment. A complete ophthalmologic and neurologic examination is recommended. In addition, patients should be evaluated carefully for deep venous thrombosis, a pulmonary embolism, and a right-to-left shunt. Migraine-like symptoms are mostly self-limiting and resolve with time, but also by applying 100% oxygen with the patient in the Trendelenburg position. Headaches generally resolve with analgesia, and triptans may be considered in selected cases.[43] Patients with a suspected venous gas embolism should be placed immediately in the left lateral decubitus position to reduce entry into the pulmonary arteries and a possible subsequent right ventricular outflow obstruction.[28]

If a neurological event occurs after foam sclerotherapy, then the possibility of a gas embolism increases[28] and the following steps should be taken immediately[40]: (i) administer 100% oxygen immediately; (ii) place the patient in a head-down position for up to 10 minutes to clear bubbles from the cerebral circulation; however, holding this position for >10 minutes can worsen cerebral edema, meaning that the patient should be returned to a supine position[28,39]; (iii) a paradoxical gas embolism stroke should be confirmed by imaging of bubbles in the intracranial arterial circulation as soon as possible[28]; (iv) transfer the patient to a hyperbaric chamber[40]; (v) start anticoagulation with heparin with a partial thromboplastin time >2 times the baseline to prevent progression of the thrombus beyond the occlusion[39,40,45]; and (vi) thrombolytic therapy with tissue plasminogen activator may be beneficial in selected cases, according to the standard stroke guidelines.[40,42,45]

Increasing the inspired oxygen decreases the partial pressure of dissolved nitrogen, which allows for a more rapid diffusion of nitrogen from the cerebral arterial air embolism. Hyperbaric oxygen has been recommended in the immediate treatment of a gas embolism to enhance the

diffusion of nitrogen into the blood, compression of existing bubbles, improving the oxygenation of ischemic tissues and lowering the intracranial pressure.[40] Some authors consider hyperbaric oxygen as the first-line treatment of choice for an arterial gas embolism.[38] Sixteen patients who underwent hyperbaric oxygen therapy for a cerebral air embolism resulting from invasive medical procedures obtained the best results when therapy was started within 6.5 hours.[44] Some studies, however, have found that hyperbaric treatment does not influence the clinical outcomes; therefore, its routine use has not been universally advocated.[28]

For an immediate stroke after liquid-based sclerotherapy and for a delayed-onset stroke, the management should follow the standard stroke guidelines; selected patients may benefit from thrombolytic therapy.[28,45] In patients with a patent foramen ovale and a paradoxical gas embolism, percutaneous closure of the patent foramen ovale is a second step in the management.[38,40] Patients with a cryptogenic stroke can benefit from this treatment; however, closure procedures are not risk free.[46]

Venous thromboembolism

Severe deep venous thrombosis, proximal or extensive, is rare. The vast majority of reported deep venous thrombosis cases are localized to the lower legs. The overall frequency of deep venous thrombosis is <1%.[29,47] The incidence is possibly higher as a significant number of procedural deep venous thromboses may be silent; most reports only include symptomatic cases. The incidence of symptomatic deep venous thrombosis is 0.02% to 0.6%[1,29,47] and the incidence with duplex ultrasound follow-up is 1.07% to 3.2%.[1,2,48-52] Most of the cases detected by duplex ultrasound during routine follow-up were asymptomatic.[1,2,48-52] Medial gastrocnemius vein thrombosis was a complication more commonly associated with foam sclerotherapy of the small saphenous vein than with the great saphenous vein, likely due to the anatomy of the small saphenous vein.[52] Pulmonary embolisms occur very rarely after sclerotherapy. In the study by Gillet et al,[2] 1 case of pulmonary embolism was reported in 1025 patients. In the French registry of 12 173 procedures, no cases of pulmonary embolism were reported.[1] There is no data regarding the incidence of postoperative silent pulmonary embolism.

Treatment

There are no evidence-based recommendations. The treatment depends on the presence of risk factors for venous thromboembolism and the extension and severity of deep venous thrombosis. A nonocclusive, postsclerotherapy, deep venous thrombosis located in the lower legs has a benign evolution and a rapid recanalization with ambulation, compression, NSAIDS, or short treatments with anticoagulation, usually with low-molecular-weight heparin.[2] Coleridge Smith managed distal and not completely occlusive deep venous thrombosis without anticoagulation.[53] Gillet et al showed that, in asymptomatic patients with nonocclusive distal thrombosis, a follow-up with duplex ultrasound and no anticoagulation is probably the best option, except for patients with risk factors for venous thromboembolism.[52] Oral anticoagulation for 3 weeks to 3 months has also been successfully used.[54] For extended deep venous thrombosis, Guex suggests looking for risk factors for venous thromboembolism.[55]

Superficial venous thrombosis

The definition of phlebitis after sclerotherapy in the literature is controversial. It is considered an adverse event if there is an extension beyond the treated area or an excessive inflammatory reaction.[4,5] Although venous sclerosis (collagen deposition resulting in scar formation), venous thrombosis (intravascular fibrin clot formation), and venous thrombophlebitis (clot formation accompanied by an inflammatory infiltrate) are histologically separate entities, these conditions cannot always be clinically or sonographically differentiated. Hence, the incidence depends on individual understandings and the real frequency is unknown[4,5]; the frequencies vary between 0% and 45.8%, with a mean of 4.7%.[1,3,5,29] Thrombophlebitis is a complication that should not be taken lightly. If untreated, the inflammation and clot may spread through perforating veins to the deep venous system. Patients with superficial venous thrombosis have a 5% to 40% chance of developing deep venous thrombosis.[56]

Treatment

Deep venous thrombosis can be ruled out in patients with superficial phlebitis using an ultrasound evaluation.[56] Most patients have minimal phlebitis and require no treatment or a simple drainage of an associated coagulum with a 22-gauge needle.[6] In symptomatic patients, drainage of the thrombi after liquefaction, approximately 2 weeks after sclerotherapy, hastens resolution of the otherwise slow and painful resorption process.[6] Adequate compression and frequent ambulation should be maintained until the pain and inflammation resolve. NSAIDS may be helpful in limiting both the inflammation and the pain.[6,54] Low-

molecular-weight heparin is rarely required; however, it may be used in cases with extensive involvement, particularly into the proximal part of the saphenofemoral junction. In those patients with concurrent deep venous thrombosis, anticoagulation for 3 to 6 months resolved the deep and superficial venous thrombosis, while preventing a pulmonary embolism. In addition, the use of low-molecular-weight heparin in patients with superficial venous thrombosis may decrease perivascular inflammation.[54]

Postablation superficial thrombus extension

A postablation superficial thrombus extension (PASTE) from the great saphenous vein into the common femoral vein occurs due to endovenous ablation of the great saphenous vein with thermal or sclerotherapy treatments. The PASTE entity was discovered after follow-up examinations with duplex ultrasound in the immediate posttreatment period. The thrombi are apparent by ultrasound within 3 to 7 days of treatment, are nonocclusive, asymptomatic, and rarely identifiable after 14 days. They do not cause venous obstruction or symptomatic pulmonary embolisms. Anticoagulation treatment was used at the beginning, but experience has shown that these thrombi are usually benign, harmless, and asymptomatic; therefore, it seems that no therapy, only observation, is needed in these cases *(Figure 4)*.[57]

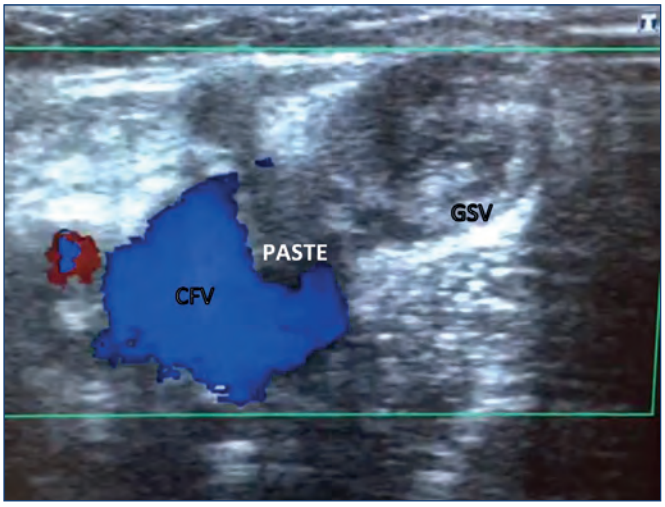

Figure 4. Postablation superficial thrombus extension into the common femoral vein after foam sclerotherapy of the great saphenous vein.

The thrombus was apparent on ultrasound after 3 days of treatment. The thrombus was nonocclusive and asymptomatic. The patient was treated with bemiparine 5000 UI for 7 days, and thereafter, bemiparine 3500 UI until the thrombus disappeared 20 days later, with a weekly duplex follow-up.

Nerve injury

Sclerotherapy using liquid or foam sclerosants is associated with both sensory and motor nerve damage that is usually transient in nature. The incidence is very rare (0.02%) with paresthesia and dysesthesia as the main presenting complaints.[58] Due to their close proximity to the veins, the saphenous and sural nerves may be inadvertently injected during sclerotherapy. Injection into a nerve is reportedly very painful and, if continued, may cause anesthesia and sometimes a permanent interruption of nerve function. Occasionally, a patient complains of an area of paresthesia that is probably caused by perivascular inflammation extending from the sclerosed vein to adjacent superficial sensory nerves.[6] Nerves are readily visualized on most modern ultrasound systems and inadvertent damage can be mostly avoided. While this is usually self-limiting, it may take 3 to 6 months to resolve.[6] Decreasing inflammation with NSAIDS, which speeds up the resolution in minor cases, and possible long-term therapy using neurotropic agents are the recommended treatments. Treatment may also include local infiltration of corticosteroids and local anesthetics.[6]

Temporary swelling: edema and lymphedema

the incidence of lower limb edema following sclerotherapy is rarely reported and probably underestimated, but the incidence is around 0.5%.[59] This complication is possibly more frequent following the obliteration of the small saphenous vein due to the contiguity of this vein with the superficial lymphatic vessels. Localized lymph stasis may occur due to sclerotherapy-induced chemical phlebitis. Extensive sclerotherapy may result in transient lymph stasis in predisposed patients, such as those with latent congenital lymphatic system abnormalities.[3]

Edema may also be due to deep vein occlusion (thrombosis or sclerosis). Extensive sclerotherapy of the superficial incompetent veins followed by occlusion of small segments of lower limb deep veins, such as the posterior tibial or peroneal veins, may contribute. In some patients, the etiology is multifactorial and involves a combination of obesity, lack of exercise, concomitant drugs, such as calcium channel blockers, and a lack of compliance with the use of medical compression systems.[3] This complication may be minimized by using careful techniques to avoid phlebitis and deep vein occlusion. Perivascular inflammation must be limited. Ankle edema occurs much less frequently if the

sclerosing solution is limited to 1 mL per ankle. A topical application of a strong-potency corticosteroid cream, lotion, or gel has been found useful.[6]

Systemic causes should be identified and excluded. Lymphedema may be investigated by lymphoscintigraphy and treated with a combined decongestive treatment. These patients should be encouraged to resume regular exercise and lose weight. Adequate compression is important in reducing edema and phlebitis in general.[3,6,60] Irrespective of the underlying cause, postsclerotherapy edema is mostly transient in nature.[3]

Minor complications

Telangiectatic matting

Telangiectatic matting is the proliferation of new small vessels (<0.2 mm) in the area of a sclerosed vein that typically appears 4 to 6 weeks after sclerotherapy.[61] The most common locations are on the inner and outer thighs and near the knees and calves. Unfortunately, even in the most expert hands, telangiectatic matting occurs in a significant percentage of patients. Telangiectatic matting may affect one-third of patients undergoing sclerotherapy, and usually resolves spontaneously in 3 to 12 months.[62] In many cases, inadequate or no treatment of the underlying reflux is the cause of telangiectatic matting *(Figure 5)*.[63,64] The precise cause of telangiectatic matting remains unknown, but its development is attributed to a reactive inflammatory or angiogenic mechanism, and it is more prevalent with high concentrations or volumes of sclerosant or high-infusion pressures that can result in inflammation or excessive vein obstruction *(Figure 6)*.[63,64] Patient risk factors include excessive body weight, female sex, hormone treatments with estrogens, a longer duration of spider veins, and a family history of telangiectasia.[61,63,64]

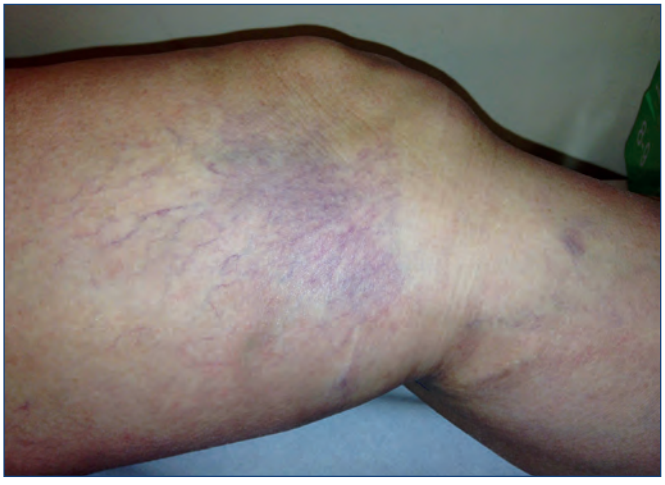

Figure 5. Matting after sclerotherapy of reticular veins in the medial lateral thigh that resolved after sclerotherapy of an unrecognized underlying reflux in a collateral of great saphenous vein.

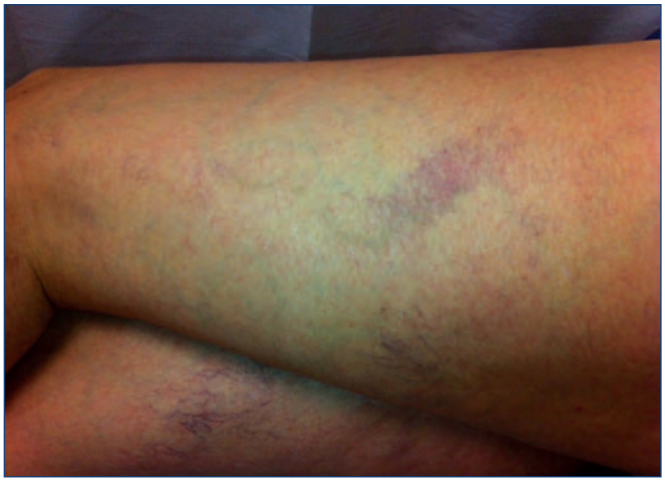

Figure 6. Matting after extensive foam sclerotherapy of telangiectasia in the lateral thigh with underlying reflux in the reticular veins.

The underlying reflux resolved with treatment of the reticular veins at a lower volume and concentration of sclerosant and the use of medical compression stockings, and finally resolved with sclerotherapy of telangiectasia using glycerin.

Treatment

Treatment of telangiectatic matting should concentrate on the underlying reflux and residual patent veins using noninflammatory concentrations of sclerosants or phlebectomy.[6] If there is no identifiable feeding vessel, instead of succumbing to the immediate urge for multiple treatments with stronger liquid sclerosants, often reassurance and passage of time is all that is required to resolve telangiectatic matting.[63] The patient can be given a mild anti-inflammatory cream; photographs are taken at 6- to 8-week intervals until resolution occurs. If it does not resolve within a reasonable time, inject any remaining telangiectatic matting with glycerin or low concentration of detergent sclerosant; 31- to 33-gauge needles can facilitate cannulation of these extremely small vessels. Treatment with a 595-nm or 1064-nm laser can also be useful if the vessels are too small to cannulate.[61]

Residual pigmentation

Postsclerotherapy hyperpigmentation refers to the appearance and persistence of pigmentation along the course of a treated vein *(Figure 7)*. Hyperpigmentation occurs in 10% to 30% of patients in the short term, and it

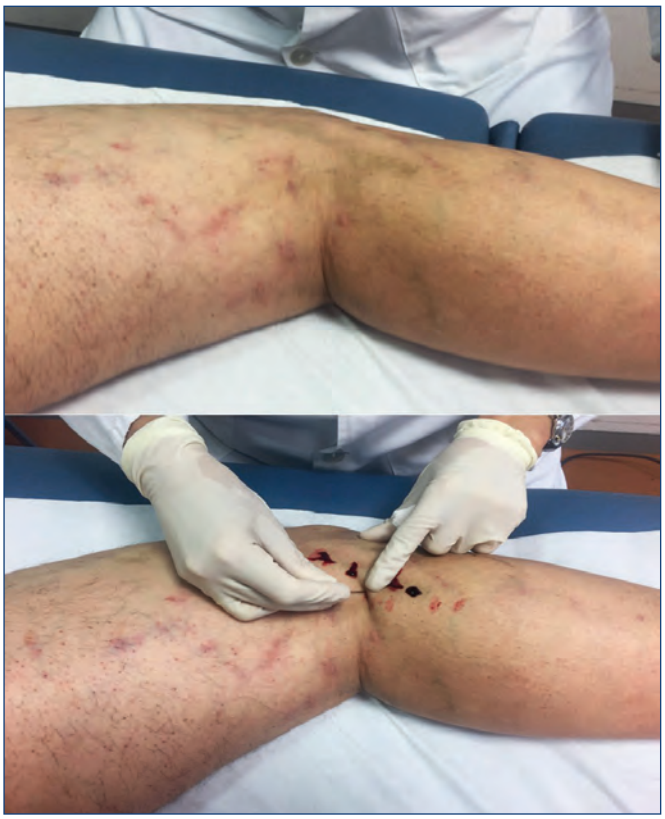

Figure 7. Hyperpigmentation after foam sclerotherapy of varicose veins in the lateral thigh that resolved with intravascular coagula drainage and medical compression stockings.

is usually noticed within 3 to 4 weeks after sclerotherapy. Although spontaneous resolution occurs in 70% of cases at 6 months, pigmentation may persist longer than 1 year in up to 10% of patients.[2,6,63] Hyperpigmentation is usually due to a combination of both melanin and hemosiderin pigment deposits secondary to either direct hemosiderin deposition, postinflammatory processes, or a combination of the two. The red blood cells extravasate after rupture of treated vessels or perivenulitis. The red blood cell dies and the hemoglobin is released into the dermis and degrades into hemosiderin.[5,6]

Treatment

Time is the first-line intervention. Most patients will have spontaneous resolution of hyperpigmentation within 1 year.[62,63] Untreated refluxing veins that connect to the affected area should be sought and treated.[5] Extracting the intravascular coagulum expedites the resolution of hyperpigmentation *(Figure 7)*.[64,65] Medical compression systems have anti-inflammatory effects, decrease chronic venous hypertension, and help resolve the intravascular coagula.[5] The evidence from two randomized clinical trials comparing the effects of compression vs no compression after sclerotherapy on the side effects (hyperpigmentation, bruising, migraine, and edema) is poor; there were no differences in the treatment of telangiectasia and reticular veins[66] or saphenous veins.[67] Nonrandomized studies have shown that compression decreases side effects from the sclerotherapy of telangiectasia and reticular veins.[60,68,69]

As this pigmentation is caused primarily by hemosiderin deposition and not melanin, bleaching agents that affect melanocytic function are usually ineffective. Treatments that may have some value include exfoliation with mild peeling agents and Q-switched laser therapy.[62,63] The exfoliants trichloroacetic acid and mercaptoacetic acid are of particular interest since hemosiderin is soluble in acids.[70] Izzo et al showed that the combination of 20% trichloroacetic acid, 0.05% retinoic acid, and 2% hydroxyquinoline successfully achieved a totally faded pigmentation in 76% of patients whose pigmentation persisted for 6 months to 5 years.[70] A treatment using 10% to 20% mercaptoacetic acid is the most effective and safe because of its affinity to ionize iron and bind it to the hemosiderin, ensuring good efficacy even at low concentrations.[70] Goldman has treated patients who have had pigmentation for >3 months with topical retinoic acid with good results and without any adverse sequelae.[6] Chelation of the subcutaneous iron deposition with intradermal injections of deferoxamine mesylate appears to be somewhat effective, but these are painful and expensive.[6] Weekly administration of 500 mg of deferoxamine mesylate reduced the time to depigmentation by 82%, although further studies are needed to determine the optimum dose.[71] The topical iron chelator 2-furildioxime may also be useful to treat cutaneous hemosiderin pigmentation.[72]

Hyperpigmentation is similar to tattooing with hemosiderin; thus, lasers may offer a reasonably effective therapy. It is believed that laser treatment causes physical fragmentation of pigment granules that are later removed by phagocytosis. In the past, a copper vapor laser[73] and a 510 nm flash-lamp–excited pulsed-dye laser[74] proved the most effective with 69% and 45% efficacy in patients with pigmentation lasting 12 or 6 months, respectively. The Q-switched ruby laser (694 nm) is also effective in removing recalcitrant pigmentation with a high rate of resolution (≈90%).[75,76] The Q-switched 532/1064-nm Nd:YAG laser, with its longer wavelengths, can safely treat darker skin and penetrate into the deeper dermis with a 75% resolution in persistent hyperpigmentation lasting 18 months with 2.8 treatments.[77] Most recently, Q-switched lasers that generate picosecond domain pulses have been introduced with an even

greater ability to target and destroy cutaneous pigment.[78] A Polish group has achieved a complete regression of hyperpigmentation in 90% of cases using an intense pulsed light that is equipped with radio waves.[79]

Intravascular coagulum

Sclerotherapy frequently results in the formation of a coagulum within the treated vessel. Intravascular coagulum/coagula/hematoma or microthrombi appear 1 to 6 weeks after sclerotherapy. Such coagulum, which is trapped between the two ends of a treated vein, tends to remain liquefied. In a systematic review of four randomized controlled trials on foam sclerotherapy, the frequency of retained coagulum ranged from 7.8% to 55.1%.[29] The larger the vessel size, the more frequently intravascular coagulum occurs.

The retention of coagulum is usually associated with tenderness and may predispose patients to posttreatment hyperpigmentation. Evacuation of the intravascular coagula reduces tenderness and inflammation and it may help prevent discoloration.[3,65,70] Microthrombi in veins ≤1 mm can be evacuated by puncture with a No. 65 beaver blade.[65] Larger veins can be punctured with a 16- or 18-gauge needle, and the intravascular coagulum manually expressed or aspirated. Intervention is recommended within 2 to 4 weeks after sclerotherapy, while the thrombus is gelatinous and not yet organized *(Figure. 7)*.[65] Continued use of compression is recommended, and evaluation for an underlying source of venous insufficiency is indicated for persistent intravascular coagulum.[65]

Transitory general effects

Transitory general effects are short-lasting disturbances and recovery occurs within minutes. Chest tightness and dry cough are reported the most *(Figure 1)*; nausea and a metallic taste can also occur. The physiopathology is not clear. In chest tightness, it is suggested that a coronary vasospasm is provoked by air bubbles[35] or endothelin-1 release[33]; however, it does not seem to be related to a myocardial infarction and no increase in troponin levels has been observed.[80] The management is similar to that of transient neurologic events *(Figures 1 and 2)*. Apply 100% oxygen, put the patient in the Trendelenburg position, and evaluate their neurological and cardiovascular state. If a venous gas embolism is suspected, apply the aforementioned maneuvers.

Stress-related symptoms

Vasovagal reflex

Vasovagal reflex is nonspecific and benign, but does increase the risk of falling. It is the most common cause of a simple loss of consciousness.[11] The vasovagal reflex is a common adverse sequelae of any surgical or invasive procedure. It has been estimated to occur in 1% of patients during sclerotherapy[6] and must be managed according to the protocol for the management of syncope *(Figure 1)*.[11] A characteristic of a vasovagal response is dysfunction of the autonomic nervous system, with parasympathetic activation, which results in an initial bradycardia and loss of sympathetic stimulation that results in initial hypotension. An environmental trigger, such as a needle stick, is a common cause.[11]

Treatment

The patient should be placed in the Trendelenburg position and observed. If the reaction persists or intensifies, consider a subcutaneous injection of 1 mL atropine 0.4 mg/mL *(Figure 1)*.[6,11] This safe and effective treatment rapidly reverses the vasovagal reaction and prevents its progression.

Underlying medical disease

Sclerotherapy can exacerbate certain underlying medical diseases. Patients with a history of asthma may start wheezing *(Figure 2),* or angina may develop in patients with cardiovascular disease. Polidocanol is a negative inotropic agent and slows cardiac contractility in a dose-dependent manner.

Urticaria

Urticaria and periorbital edema may be related to histamine release from irritated perivascular mast cells. Rarely, an urticarial reaction has been noted when using graduated compression stockings. Urticaria is easily treated with an oral antihistamine, but may be a sign of a systemic allergy.

Transitory local side effects

Transitory local side effects are common to all sclerosants; they tend to be mild, transient, and somewhat expected. Such complications are usually self-limiting and transient in nature, and they can be treated with topical agents.[3] The possible side effects include: (ii) injection site reactions (injection pain, pruritus, minor bruising, wheals, local swelling, indurations, and erythema) that are self-limited; (ii) skin irritation (itching and an irritant contact dermatitis may

follow the use of compression stockings) and excessive skin xerosis that can be treated effectively with emollient creams or oils; (iii) tape compression blister that can be prevented by using a tubular support bandage, and the resolution occurs within 1 to 2 weeks without any adverse sequelae. To aid healing, prevent infection, and alleviate any pain, the use of an occlusive hydroactive dressing is helpful; (iv) tape compression folliculitis that can be treated by removing the occlusive dressing and applying a topical treatment with an antibacterial soap or a topical antibiotic gel, such as a 2% erythromycin or 1% clindamycin phosphate topical solution. The folliculitis usually resolves within a few days, and systemic antibiotics are rarely necessary[6]; (v) localized urticaria, often in the form of wheal associated with itching, is usually relieved within 30 minutes, and it can be diminished by applying topical steroids and by limiting the injection quantity per injection site.[6]

Conclusion

Bad results are usually the consequences of an inappropriate use or indication. The best treatment is prevention. If performed properly, sclerotherapy is an efficient treatment method with a low incidence of complications, but some can be vital emergencies. Our improved knowledge of complications allows us to implement the treatment carefully. This article addressed the treatments that should be used for sclerotherapy complications. Early interventions may minimize possible sequelae. Physicians who perform sclerotherapy should have an emergency plan in the event of neurological deficits, intra-arterial injections, severe systemic adverse reactions, or anaphylaxis, including transport to emergencies services for further evaluation and treatment of vital emergencies. Access to hyperbaric oxygen therapy may also be considered in emergency planning. All office settings using sclerotherapy should be equipped with the ability to administer oxygen therapy.

Serious adverse events are very rare, meaning that there are no evidence-based recommendations to manage them, and most management options are based on anecdotal experience or data extrapolated from others pathologies. As other very rare entities, they would benefit from a multicenter register coordinated by an international phlebological association, to obtain enough numbers to provide management recommendations based on evidence or consensus. Minor complications, such as telangiectatic matting and hyperpigmentation, require time, a side-by-side follow-up by the practitioner, and a careful examination and treatment of residual inadvertent vein reflux that may cause these minor, but worrisome side effects. Compared with liquid sclerotherapy, foamed sclerosing agents do not cause many new or different complications, but it does appear to change their relative incidences *(Table I)*,[1] for example, neurological complications are more prevalent with foam vs liquid sclerotherapy.

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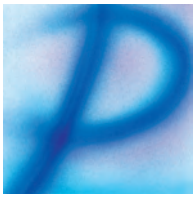

Diagnosis and treatment of situational great saphenous vein reflux in daily medical practice

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Keywords:

day orthostatic load; great saphenous vein; MPFF; reflux

Abstract

Aim: To analyze the treatments for situational great saphenous vein (GSV) reflux.

Methods: Patients with chronic venous disease who were classified as C_{0s}, $C_{0,1s}$, and C_2 (n=294) were analyzed using a day orthostatic load (DOL) test. Situational GSV reflux occurred in 78 patients. The patients classified as C_{0s} and $C_{0,1s}$ (group 1; n=46) and the patients with reflux still present after surgery on varicose tributaries (group 3; n=10) received micronized purified flavonoid fraction (MPFF) 1000 mg daily for 90 days. Patients classified as C_2 with situational reflux (group 2; n=32) underwent elimination of their varicose tributaries.

Results: MPFF eliminated the evening GSV reflux in 35 patients (76.1%) and decreased the GSV evening diameters from 5.49 mm to 5.09 mm for patients in group 1. Surgery eliminated the GSV reflux in 22 lower limbs (68.8%) and reduced the evening GSV diameter from 6.27 mm to 4.41 mm for patients in group 2. The combination of surgery and MPFF treatment eliminated the GSV reflux in 4 patients in group 3. The global index score (CIVIQ-20) decreased from 50.63±7.43 to 29.33±7.18.

Conclusion: A situational GSV reflux was detected in 33.3% of the patients classified as C_{0s}, C_{1s}, and C_2. A GSV reflux needs to be analyzed in detail using a DOL test. Out of the 78 patients with a situational reflux, 78.2% recovered the full function of the GSV due to MPFF treatment for C_{0s} and C_{1s} patients or a combination of MPFF therapy and surgery to eliminate the varicose tributaries for C_2 patients.

Introduction

Starting from Trendelenburg, great saphenous vein (GSV) reflux is considered the main hemodynamic phenomenon and surgical target of varicose veins.[1,2] GSV reflux surgery is supposed to be the leading technique to treat varicose veins.

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However, the problem of varicose veins after surgery has not been solved. In 3 to 5 years after stripping or ablating the GSV, the frequency of postoperative progression ranges from 15%–20% to 46.5%–54.7%.[3,4] Of note, the long-term results do not depend on the stripping or ablation techniques.[4] During GSV stripping or ablation, the main, non-doubled trunk that drains the blood from the subcutaneous tissue of the limb is eliminated, making this the main factor leading to postoperative varicose vein progression, not the technique itself.

While there is no alternative to GSV removal when the trunk is irreversibly changed, it is not clear whether the GSV needs to be eliminated in all cases of primary varicose veins. Pittaluga and Chastanet[5] showed that it might be possible to recover GSV function after eliminating its varicose tributaries. Other groups have shown the same results.[6-8] Research using the day orthostatic load (DOL) test as a preoperative criterion for GSV preservation is of great interest.[9] Modern data about the peculiarities of GSV reflux and the possible connection between mild and varicose forms of chronic venous disease were obtained by using the DOL test in patients with phlebopathy.[10] The GSV reflux that appeared in some patients after a prolonged working day and disappeared after sleeping/resting was called transient reflux. In addition, treatment with micronized purified flavonoid fraction (MPFF) eliminated the transient GSV reflux.[10] This data shows that the GSV reflux is predetermined by external (prolonged orthostasis) and internal (hypervolemia in varicose tributaries) factors that can be controlled.

Thus, some important questions arise:

- If one can save a weakened, but functioning, GSV, are there any tools to support its function?
- How effectively can drug therapy deal with this problem?

The answers received should not only correspond to the theory, but also find their place in daily practical implementation.

Aim

This single-center study aimed to analyze the treatment of situational GSV reflux in patients with primary varicose veins based on the functional assessment of the GSV during standard medical practice in one medical center.

Methods

All patients underwent repeated clinical and duplex ultrasonography. The key feature was the functional orientation, which was realized by assessing the GSV response to the day orthostatic load using the DOL test.[9] A previously proposed 4-grade division was used to characterize the evening leg heaviness, a basic chronic venous disease symptom. This 4-grade division takes into account the functionality of the venous system based on the patient's orthostatic load[11]: grade 0, no heaviness in the legs; grade 1, heaviness in the legs that occurs occasionally at the end of the day and with an increased load; grade 2, heaviness in the legs that occurs continuously with an increased load; and grade 3, heaviness in the legs that occurs continuously with a usual load.

All patients underwent a duplex ultrasonography examination using the SonoScape S6 system (SonoScape Co Ltd, Shenzhen, China). A special feature of the study was to conduct the ultrasonography in an upright position twice a day: in the evening at postloading status (after 6 PM) and in the morning after sleeping (before 10 AM). Alterations in the extent and duration of the GSV reflux and diameter were assessed. A reflux duration was considered pathologic if it was >0.5 seconds.[12] The extent of the GSV reflux was evaluated according to the general number of zones of reflux, which included three thigh and three calf zones.[9] The reflux localization was described using the differentiation published by Engelhorn et al.[13]

The GSV response to the day orthostatic load was evaluated using duplex ultrasonography and included determining both the evening diameter of the GSV at the saphenofemoral junction (mm) and the orthostatic gradient (mm), which is the difference between the evening and morning values for the GSV. As opposed to a constant GSV reflux, a situational reflux has significant differences between the morning and evening values and the values of the GSV itself.

Patients classified C_{0s}, $C_{0,1s}$, and C_2 according to the clinical, etiological, anatomical, and pathophysiological (CEAP) classification were examined. The C_{0s}, $C_{0,1s}$ patients underwent an examination 3 months after treatment with MPFF, and the C_2 patients were examined 1 month after a phlebectomy; patients who still had GSV reflux after surgery were also examined 3 months after MPFF treatment. At baseline and at the end of the treatment, the intensity of the symptoms, such as heavy legs, was measured on a

10-cm visual analog scale. The quality of life was assessed using a self-questionnaire CIVIQ-20, its global index score ranges from 0 to 100.

Patients

A total of 294 patients (male, n=46; female, n=248) with C_{0s}, $C_{0,1s}$, C_2 were examined from 2014 to 2016. The average age was 41.5 years (range, 20 to 63). Classification of the patients according to CEAP was done based on the results of ultrasonography that was performed after sleeping. The inclusion criteria included patients with C_{0s}, $C_{0,1s}$, C_2 and an informed consent to participate in the study. *Table I* shows the age and sex differentiation of the patients.

CEAP class	Male	Female	Total
C_{0s}	0	55	55
$C_{0,1s}$	0	51	51
C_2	46	142	188
Total	46	248	294

Table I. Age and sex differentiation of the patients who visited the clinic over a 3-year period (2014–2016) according to the CEAP classification.

Out of the total number of patients (n=294), 234 had an evening GSV reflux. The DOL test showed that 156 patients had morning GSV reflux parameters that only slightly differed from the evening parameters; this type of reflux is called a constant (unchanging) reflux. A total of 78 patients had a substantial difference between their morning and evening reflux parameters; this type of a reflux is called a situational (changing) reflux *(Table II)*. Of the 78 patients

	Total number of patients	Number of patients with a situational GSV re1ux (%)
C_{0s}	55	21 (38.2%)
$C_{0,1s}$	51	25 (49.0%)
C_2	188	32 (17.0%)
Total	294	78 (26.5%)

Table II. Number of patients with a situational GSV reflux in different chronic venous disease classes.

with a situational GSV reflux, 46 had the extreme form, ie, a transient evening reflux, which only appears in the evening; these patients were classified as C_{0s} and $C_{0,1s}$ and included in treatment group 1. The other 32 patients with situational reflux had a morning reflux, but with a smaller extent and duration than the reflux in the evening; these patients were classified as C_2 and were included in treatment group 2. In addition, the results of the treatment were also assessed in treatment group 3, which included patients after a surgery that preserved the GSV who still had reflux according to an ultrasonography after 1 month.

Treatment

The patients in groups 1 and 3 received monotreatment with MPFF.[14] The treatment guidelines included administering MPFF for 90 days (1000 mg per day). The patients in group 2, with situational GSV reflux, underwent a Muller phlebectomy[15] for all dilated GSV tributaries, while preserving the GSV (n=38 lower legs).[9] Multiple small phlebectomy incisions (maximum 2 mm) were made. In 19 cases, the procedures were performed under tumescent local anesthesia. In 13 patients with significant varicosities (including patients who had both limbs affected), the surgery was done under general anesthesia.

Statistical analysis

The statistical analysis was performed using the nonparametric Wilcoxon and Mann-Whitney tests. The mean values were determined along with the 95% CI.

Results

According to the morning ultrasonography results, all 106 women classified as C_{0s} and $C_{0,1s}$ had no GSV reflux in the lower limbs. Evening examination showed that, in treatment group 1, 46 people (43.4%) had GSV reflux in 59 lower limbs *(Table II)*. The evening GSV reflux was segmental (6 to 31 cm in length).

All 106 C_{0s} and $C_{0,1s}$ patients had complaints of leg heaviness at the end of the day. However, patients with transient GSV reflux had more severe symptoms than did the patients without reflux *(Figure 1)*. In the subgroup with a transient evening reflux, there was a significant difference *(Table III)* in the evening diameter (P=0.001344) and orthostatic gradient (P=0.000001). In the lower limbs with a transient evening reflux, the orthostatic gradient was 0.88 mm (95% CI, 0.83-0.94) and the evening GSV diameter was 5.49 mm (95% CI, 5.17-5.82). In the lower limbs without a transient evening reflux, the orthostatic

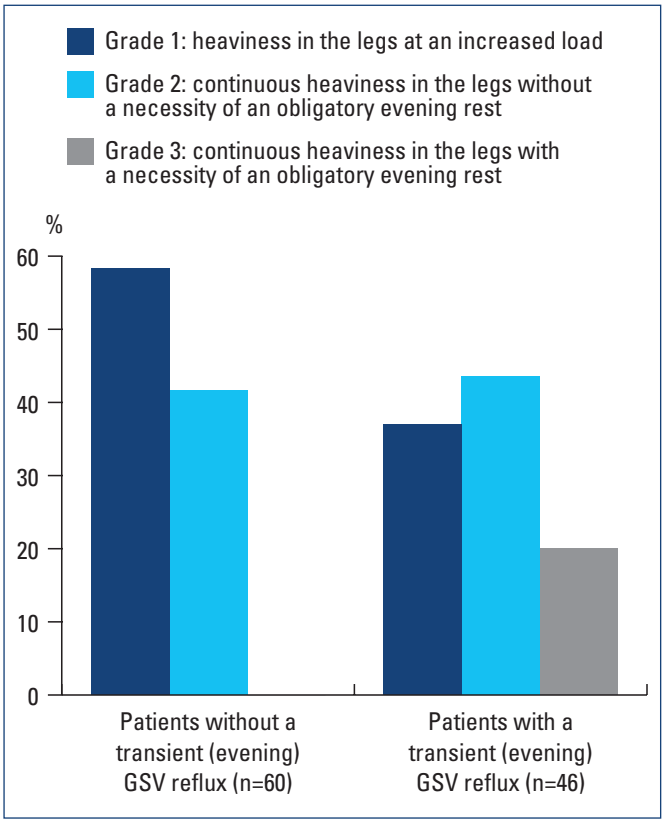

Figure 1. The severity of leg heaviness in patients with a transient evening GSV reflux (n=46) or without this symptom (n=60).

gradient was 0.61 mm (95% CI, 0.58-0.64) and the evening GSV diameter was 4.82 (95% CI, 4.51-5.14).

Of the 188 examined patients with varicose veins (C_2), 156 had the same GSV reflux parameters over 24 hours (extent [*P*=0.129083] and duration [*P*=0.357139]) *(Table IV)*. In the 32 people in treatment group 2, the evening reflux parameters (reflux extent, reflux duration) differed significantly (*P*=0.000001) from the morning parameters *(Table IV)*.

	Evening GSV diameter (mm)	Orthostatic gradient (mm)
With a transient GSV reflux (n=46)	mean, 5.49 95% CI, 5.17-5.82	mean, 0.88 95% CI, 0.83-0.94
Without a transient GSV reflux (n=60)	mean, 4.82 95% CI, 4.51-5.14	mean, 0.61 95% CI, 0.58-0.64
P value	0.001344	0.000001

Table III. The GSV parameters in patients classified as C_{0s} and $C_{0,1s}$ with a transient evening GSV reflux (n=46) or no transient evening GSV reflux (n=60) at duplex ultrasonography and a DOL test.

GSV reflux parameters	Examination time	Lower limbs with a situational reflux (n=32)	Lower limbs with a constant reflux (n=156)
Reflux extent	Evening	mean, 3.81 95% CI, 3.41-4.22	mean, 3.75 95% CI, 3.58-3.92
	Morning	mean, 1.53 95% CI, 1.31-1.76	mean, 3.60 95% CI, 3.45-3.75
	P value	0.000001	0.129083
Reflux duration	Evening	mean, 2.11 95% CI, 1.84-2.37	mean, 2.07 95% CI, 1.98-2.18
	Morning	mean, 0.93 95% CI, 0.82-1.03	mean, 2.01 95% CI, 1.90-2.11
	P value	0.000001	0.357139

Table IV. Comparison of the GSV reflux parameters in patients classified as C2 (n=188).

Results of the treatment

Treatment group 1

Dynamics of the GSV parameters in the classes C_{0s} and $C_{0,1s}$ with a transitory evening GSV reflux with MPFF treatment

The therapeutic effect in 46 women with a transient evening GSV reflux can be seen clearly when comparing the GSV parameters before and after a 3-month MPFF treatment *(Table V)*. The reflux was resolved in 76.1% of the women and all of them had the reflux previously located in one segment of the thigh or calf. There was a significant decrease (*P*=0.000001) in both the detected evening GSV diameters from 5.49 mm (95% CI, 5.17-5.82) to 5.09 mm (95% CI, 3.50-6.50) and the orthostatic gradient from 0.88 mm (95% CI, 0.83-0.94) to 0.64 mm (95% CI, 0.61-0.67).

	Evening GSV diameter (mm)	Orthostatic gradient (mm)
Initial value	mean, 5.49 95% CI, 5.17-5.82	mean, 0.88 95% CI,0.83-0.94
After a 3-month treatment with MPFF	mean, 5.09 95% CI, 3.50-6.50	mean, 0.64 95% CI, 0.61-0.67
P value	0.000001	0.000001

Table V. Comparison of the GSV parameters in patients with a transitory evening GSV reflux before and after a 3-month treatment with MPFF according to the duplex ultrasonography and DOL test (n=46).

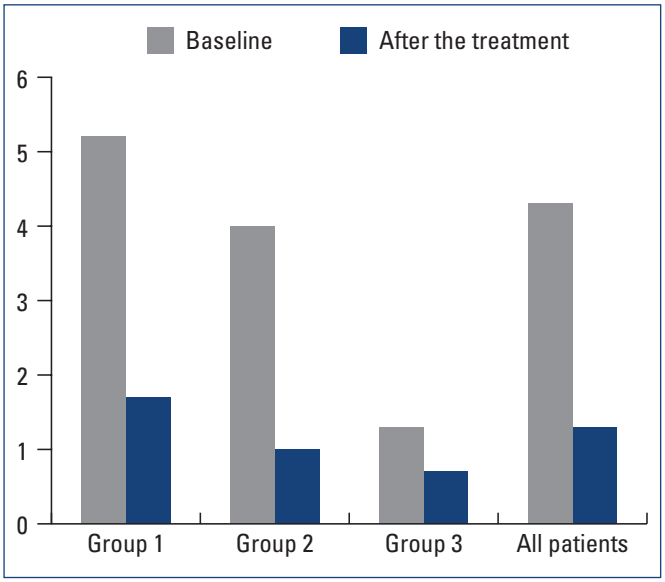

Figure 2. The severity of leg heaviness in different treatment groups with a situational reflux before (baseline) and after the treatment according to the 10-cm visual analog scale.

Dynamics of the clinical symptoms and the quality of life in patients with situational reflux

Initially, all 46 patients with transient reflux had complaints of evening leg heaviness, 14 had moderate pain at the end of the day, and 24 had nighttime leg cramps. After treatment with MPFF, leg heaviness disappeared in 89.3% of the patients and the symptoms decreased significantly in 10.7% of the patients. The intensity of the symptoms were reduced from 5.2 to 1.7 (*P*=0.000001) according to the 10-cm visual analog scale *(Figure 2)*, pain at the end of the day disappeared in all 14 patients, and nighttime cramps resolved in all 24 patients. The global index score (CIVIQ-20) decreased from 47.16±7.93 to 25.82±9.15 after treatment (*P*=0.000005).

Treatment group 2

Dynamics of the GSV parameters in C_2 patients with a situational GSV reflux after eliminating all varicose tributaries and preserving the GSV

The situational reflux was eliminated in 68.8% of the limbs 1 month after surgery.[22] *Table VI* represents a comparison of the reflux and GSV parameters. In the lower limbs with a resolved reflux, the initial orthostatic gradient decreased from 0.93 mm (95% CI, 0.89-0.98) to 0.59 mm (95% CI, 0.57-0.61) (*P*=0.000001) and the initial evening GSV diameter decreased from 6.27 mm (95% CI, 5.66-6.89) to 4.41 mm (95% CI, 4.11-4.70) after surgery (*P*=0.000001). In the lower limbs with persistent reflux, the orthostatic gradient (which was lower initially) decreased from 0.53 mm (95% CI, 0.46-0.60) to 0.50 mm (95% CI, 0.44-0.56) (*P*=0.108810) and the GSV evening diameter decreased from 7.50 mm (95% CI, 6.89-8.11) to 7.10 mm (95% CI, 6.39-7.81) after surgery (*P*=0.067890). Reducing the daily blood volume loading after a phlebectomy of the

	Resolved relux (n=22)			Persistent relux (n=10)		
	Preoperation	Postoperation	*P* value	Preoperation	Postoperation	*P* value
Evening diameter of GSV (mm)	mean, 6.27 95% CI, 5.66-6.89	mean, 4.41 95% CI, 4.11-4.70	0.000040	mean, 7.50 95% CI, 6.89-8.11	mean, 7.10 95% CI, 6.39-7.81	0.067890
orthostatic gradient of GSV (mm)	mean, 0.93 95% CI, 0.89-0.98	mean, 0.59 95% CI, 0.57-0.61	0.000001	mean, 0.53 95% CI, 0.46-0.60	mean, 0.50 95% CI, 0.44-0.56	0.108810

Table VI. Changes in the diameter of GSV near the saphenofemoral junction in lower limbs with (n=10) or without (n=22) persistent postoperative GSV reflux with a reflux duration >0.5 seconds before surgery and 1 month after surgery.

varicose tributaries preserved the muscular-tonic properties of the venous wall and provided recovery of the GSV valve function.[16]

Dynamics of the clinical symptoms and the quality of life in patients with situational reflux

Before surgery, 91% of C_2 patients with a situational GSV reflux had complaints of leg heaviness, 53.1% patients had moderate pain at the end of the day, and 71.8% had nighttime leg cramps. All 32 patients had complaints of esthetic defects associated with the varicose veins. In 1 month after the surgery, the feeling of heaviness in the legs disappeared in 89.3% of the patients and the symptoms decreased significantly in 10.7% of the patients. In general, the intensity of the leg heaviness was reduced from 4.0 to 1.0 (P=0.000005) according to the 10-cm visual analog scale *(Figure 2)*, pain at the end of the day disappeared in all 17 patients, and nighttime cramps resolved in all 23 patients. All patients emphasized an excellent esthetic result. The global index score (CIVIQ-20) decreased from 61.17±9.69 to 34.64±8.78 after the surgery (P=0.000005).

Treatment group 3

Dynamics of the GSV parameters in C_2 patients and a persistent postoperative situational GSV reflux after treatment with MPFF

All 10 patients who still had GSV reflux after surgery underwent a 3-month treatment with MPFF; the reflux was examined after MPFF treatment. After the treatment, the reflux was significantly reduced in 60% of the patients and the reflux was resolved in 40% of the patients.

Dynamics of the clinical symptoms and the quality of life in patients with situational reflux

In 1 month after surgery, all 10 patients were generally satisfied; only 2 still felt mild leg heaviness and increased tiredness. After MPFF treatment, leg heaviness decreased, but its intensity, being initially minimal, differed slightly from 1.3 to 0.7 (P=0.45632) according to the 10-cm visual analog scale *(Figure 2)*. Also, being generally satisfied with the operation results, patients noted small changes in their quality of life. The global index score (CIVIQ-20) decreased from 50.63±7.43 to 29.33±7.18 after the treatment.

Correlation of clinical and ultrasound results of MPFF treatment

Of the patients with a situational GSV reflux, patients complained of evening heaviness in their legs (n=77), moderate pain at the end of the day (n=31), and nighttime cramps (n=47). MPFF alone for C_{0s}, C_{1s} patients or the combination of MPFF and an elimination of the varicose tributaries and preservation of the GSV for C_2 patients, it is possible to recover an impaired GSV function in 78.2% of patients with a situational GSV reflux and to significantly improve the GSV function (ie, reflux extent and duration) in 21.8% of cases. MPFF led to the complete disappearance of leg heaviness in 87.2% of patients, and 12.8% of patients felt a significant decrease in the intensity of the heaviness. Moderate pain at the end of the day and nighttime cramps disappeared in all patients. These clinical changes occurred synchronously with the elimination of GSV reflux *(Figure 3)*. The global index score (CIVIQ-20) decreased from 50.63±7.43 to 29.33±7.18 after the treatment.

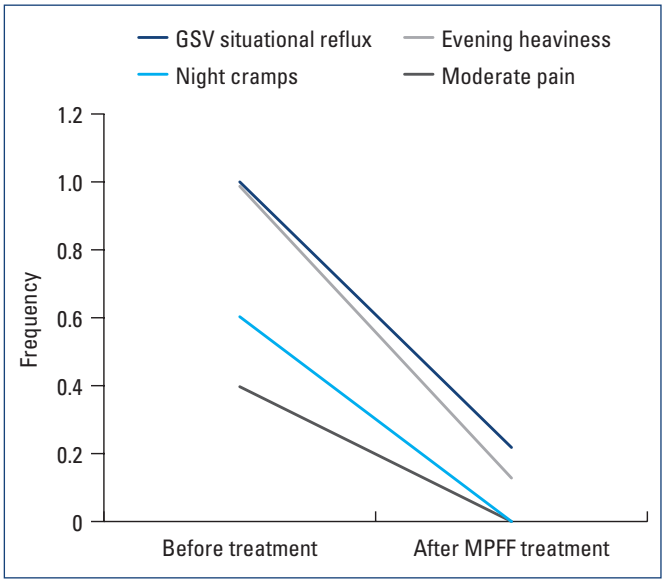

Figure 3. Correlation of clinical and ultrasound results of MPFF treatment.

Discussion

The research demonstrated that, in a real-world practice, there are two types of GSV reflux–constant and situational–and their reaction to the external and internal factors differs significantly. In the authors' opinion, the proposed term "situational GSV reflux" can adequately characterize the features of the latter as its parameters vastly differ after prolonged orthostatic load compared with the parameters after sleeping. An ultrasonography with a DOL test shows the situational nature of the reflux by assessing the competence level of the muscular-tonic function of the GSV wall. With the help of DOL test, a situational GSV reflux was detected in 33.3% of the C_{0s}, C_{1s}, and C_2 patients who

visited the clinic during their daily medical practice. The differentiation of an extreme form of situational reflux–a transient evening reflux–helps describe the development of primary varicose veins.

The modified viscoelastic properties of the venous wall are a feature of primary varicose veins.[17] Even the small veins have a muscular system.[18] Veins play a leading role in providing the constant blood flow to the heart.[19] The main pathological process of varicose veins is supposed to be myosclerosis, which arises as a result of leukocytes getting into the venous wall during the process of blood flow slowing.[20] However, the destruction of the venous wall does not occur in a single step. In the first stage, a muscular-tonic dysfunction of the GSV wall occurs according to the increased creep, a basic biophysical characteristic of the veins at phlebopathy.[11] Such functional insufficiency of a macroscopically unchanged venous wall due to a prolonged orthostatic load leads to transient hypervolemia in the lower limbs.[21] When the volume of the drained blood and the volemic load exceed the muscular-tonic potential of the GSV, it will expand; moreover, it will lead to a relative valvular insufficiency. The regional venous hypervolemia occurring in some C_2 patients occurs due to varicose tributaries that have already been formed due to the permanent deformation of the venous wall. At the end of the day, a bulk of the deposited blood in a limb with varicose veins is located mostly in varicose tributaries of the GSV, which form most of the superficial venous system.[22]

The comparison of the clinical severity of patients with or without a reflux at phlebopathy showed that, in the second case, the clinical manifestations of the disease are more pronounced. This fact points to a qualitatively new state of the venous system that arises from transient GSV reflux. This state may be a transitional stage and a binding link between simple phlebopathy (C_{0s}) and varicose forms (C_2) of chronic venous disease.

The detection of GSV reflux should not be the main indication for GSV ablation; on the contrary, the reasons for its occurrence should be understood to exclude its situational nature. For both variants of situational GSV reflux, there is a complex of therapeutic actions that may be effective without stripping or ablation of the GSV. Thus, by treating with MPFF alone for C_{0s} and C_{1s} patients or with the combination of MPFF and surgery to eliminate the varicose tributaries and preserve the GSV for C_2 patients, it is possible to recover an impaired GSV function in 78.2% of patients with a situational GSV reflux and to improve the GSV function significantly in 21.8% of cases. Moreover, a transient evening GSV reflux should be an absolute contraindication to ablation of this central subcutaneous trunk that has no other alternative.

MPFF is a treatment that attempts to enhance venous tone.[24] MPFF is an effective instrument for treating C_{0s} and $C_{0,1s}$ patients and transient reflux and after a surgery for C_2 patients who had an incomplete elimination of the GSV reflux. Moreover, in both cases, the main final trunk was saved. It is also vital to emphasize that 40% of patients who still had reflux after eliminating of the varicose tributaries felt improvements in their state after treatment with MPFF. The resulting normalization of the blood flow in the subcutaneous veins of the patients' lower limbs led to a significant regression in the clinical symptoms and a vast increase in the quality of life. The data confirm that MPFF treatment is a basic multipurpose instrument that stops orthostatic hypervolemia and reduces the volemic load on the GSV in the early stages of varicose veins.

In general, the present study demonstrated that, in a daily medical practice, greater attention should be given to the early stages of varicose veins and a wider use of drug therapy. These actions will allow for the preservation of the GSV in patients classified as C_{0s}, $C_{0,1s}$, and C_2. It can be hypothesized that such a treatment direction in phlebology may prospectively help decrease the number of patients with late (and severe) stages of varicose veins.

Conclusion

1. Situational GSV reflux, in which the duration and extent of the reflux differs over 24 hours due to external and internal factors, is detected in 33.3% of C_{0s}, C_{1s}, and C_2 patients who visited the clinic during their daily medical practice.

2. The detection of GSV reflux should not be the main indication for GSV ablation, a central final subcutaneous line that has no alternative; on the contrary, the reasons for its occurrence should be understood with the help of a duplex ultrasonography and a DOL test.

3. MPFF treatment is a basic multipurpose treatment that reduces transient ortho-dependent regional hypervolemia that results from a weakening of the muscular-tonic function of the venous wall. Treatment with MPFF alone for C_{0s}, C_{1s} patients or the combination of MPFF and the elimination of the varicose tributaries

and preservation of the GSV for C_2 patients, makes it possible to recover an impaired GSV function in 78.2% of patients with a situational GSV reflux and to improve the GSV function significantly in 21.8% of cases.

4. MPFF led to the complete disappearance of leg heaviness in 87.2% of patients, and 12.8% of patients felt a significant decrease in the intensity of the heaviness. Moderate pain at the end of the day and nighttime cramps disappeared in all patients. Moreover, there was a parallel improvement in all patients' quality of life, which was demonstrated using CIVIQ-20: the global index score decreased from 50.63±7.43 to 29.33±7.18 after treatment.

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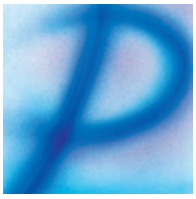

New diagnostic modalities in lymphedema

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Abstract

Introduction: Lymphedema is a chronic, progressive, and debilitating disease. An early and accurate diagnosis and treatment is very important to alter the normal progression of the disease. When lymphedema is diagnosed late, the options for treatment are diminished as fibrous tissue is formed. Until recently, lymphoscintigraphy was considered the gold-standard diagnostic technique; however, other new and renewed diagnostic tools have emerged. This article provides an overview of the available diagnostic tools based on the findings from a literature search.

Methods: A literature search for each of the diagnostic tools was performed.

Results: Diagnostic tools can be divided into noninvasive and invasive techniques. Ultrasonography is a noninvasive technique that can identify lymphedema by looking at the thickness of the skin and echogenicity. Magnetic resonance and computed tomography scans show similar alterations of the skin, but can detect other causes for lymphedema. Near-infrared fluorescence imaging gives a real-time image of the superficial lymphatic transport, evaluates the severity of the lymphedema, and determines the functionality of the lymphatics.

Conclusions: This literature search showed that there are many techniques available besides lymphoscintigraphy. A good clinical examination and history is a critical first step. Ultrasonography is a noninvasive and inexpensive technique that can be used to diagnose lymphedema based on tissue changes. Lymphoscintigraphy and near-infrared fluorescence imaging can diagnose lymphedema and visualize the lymphatic architecture. Near-infrared fluorescence imaging can guide treatment and evaluate the response to treatment.

Keywords:

diagnosis; lymphangioMRI; lymphedema; lymphoscintigraphy; near-infrared fluorescence imaging

Introduction

Lymphedema is a chronic, progressive, and debilitating disease. It decreases patients' quality of life due to an enlargement of the diseased limb, a decrease in mobility, and recurrent infections.[1,2] Edema is defined as the presence of an excess of interstitial fluid, which happens when the microvascular filtration rate is higher than the drainage. In the past, it was thought that venous reabsorption played the most important role in reducing interstitial fluid (the Starling principle)[3]; however,

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recent research has shown that there is no reabsorption by the venous end of the capillaries. Instead, there is filtration along the entire capillary bed and the fluid regulation depends on the lymphatic transport.[4] Fluid drains from the capillaries into the precollectors and the collectors. The collectors are lined with smooth muscle cells, and have lymphangions or vessel segments that are separated by valves, and are responsible for the unidirectional flow as they gradually contract and push the lymph forward.

Lymphedema can be divided into primary and secondary lymphedema. In primary lymphedema, there is an anomaly in the development of the lymphatic system, giving rise to structural and/or functional abnormalities in the lymphatic drainage. Until recently, a classification was used according to age of onset: congenital (from birth or shortly after), praecox (occurring before the age of 35), and tarda (occurring after the age of 35). Lymphangiographic findings, such as aplasia, hypoplasia, and hyperplasia, have been added to the age classification.[5] A better understanding of the genes involved in the development of lymphedema has shown that certain genetic forms of primary lymphedema can present later in life. As more causal genes are identified, a different classification arises according to the patient's phenotype. Primary lymphedema can also be part of a broader genetic syndrome, such as Turner syndrome or Noonan syndrome, or associated with overgrowth anomalies, such as Proteus syndrome.[3]

Most lymphedema cases are caused by secondary lymphedema,[6] which results from damage or malfunction of the lymphatic transport system, such as an obstruction of the lymphatic transport (previous surgery, infection, malignancies) or an overload of interstitial fluid (eg, advanced venous insufficiency). For example, the incidence of upper extremity lymphedema after breast cancer treatment (with axillary lymph node dissection) ranges from 9% to 41%,[7] and, when an inguinofemoral lymph node dissection is performed, approximately 20% of patients with melanoma, gynecological cancer, or prostate cancer will develop lymphedema.[7]

In most cases, the diagnosis of lymphedema can be made by obtaining the patient's history and conducting a good clinical examination, which consists of age of onset, medication, travel to tropical countries, all causes of secondary lymphedema, family history, etc. As part of the diagnostic workup, systemic causes of edema need to be excluded (eg, heart failure, nephrotic syndrome, pulmonary hypertension, hypothyroidism, deep vein thrombosis, and chronic venous insufficiency). Lymphoscintigraphy has replaced lymphangiography as the standard for the diagnosis of lymphedema; however, other promising techniques have recently been developed.

Clinical evaluation

Lymphedema can progress from a soft, pitting edema to a hard, fibrotic, nonpitting edema, which is because lymph stasis will cause extravasation of fluid in the interstitium and promote lipogenesis, fibrosis, inflammation, lymphangiogenesis, and immunosuppression.[8] However, if diagnosis occurs early, the progression to a fibrotic edema can be altered.

According to history and clinical examination, a clinical stage system can be used, based on the International Society of Lymphology.[1,9] Stage 0 refers to a subclinical state, where edema is not yet visible despite impaired lymphatic transport. Stage I refers to an early accumulation of fluid with a high protein content, whereby the edema subsides by elevating the limb. Stage IIa represents swelling that does not subside when the limb is elevated and pitting is manifest. In stage IIb, no pitting is visible and fibrosis together with fat emerges. Stage III, also known as "lymphostatic elephantiasis," is the most advanced form with skin abnormalities and further fibrosis of the tissue. This staging system is not complete because it does not take into account why some patients develop a soft, fatty lymphedema and others develop a hard fibrotic one. These differences are also seen when circumferential suction-assisted lipectomy is performed, where more fat is removed than fluid.[10] This fluid and fatty tissue can be measured with several clinical tools and a clinical examination.

Measuring the skin fold (Stemmer sign) can provide an estimation of the thickness of the cutis, which is a typical sign of lymphedema. The Stemmer sign is more often visible at the foot with primary lymphedema than with secondary lymphedema where the edema is more often seen proximal. The existence of pitting plays an important role in determining the clinical stage, and it can be determined with the "pitting sign" *(Figure 1)*. Puffiness of the forefoot can be noted. In more advanced cases, skin abnormalities, such as hyperkeratosis, papillomatosis, lymph vesicles, and eczema, can occur. The chronic accumulation of lymph can also promote infection.[8]

Volume can be assessed using different tools. Circumference tape measurements, with measurement intervals varying

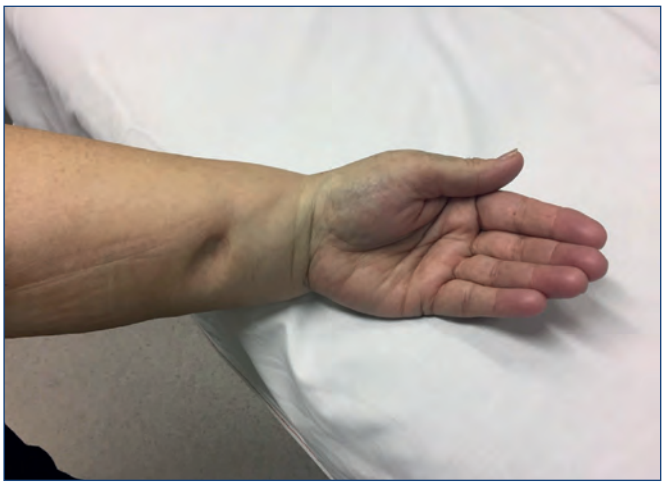

Figure 1. Pitting test.

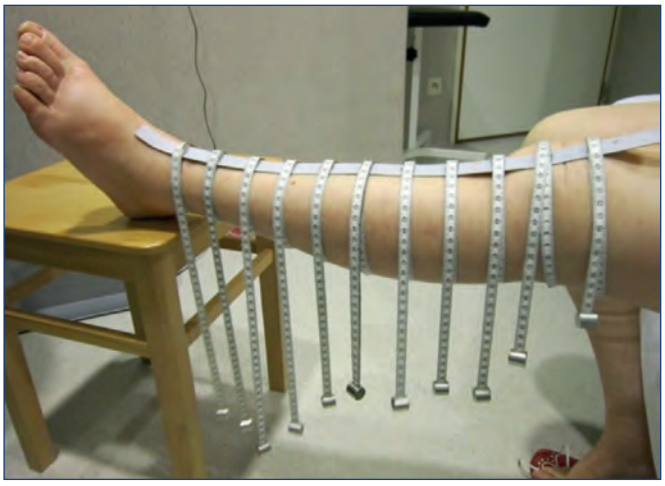

Figure 2. Tape measurements.

From reference 11: Devoogdt et al. Int Angiol. *2010;29(5):401-407. © 2010, N. Devoogdt*

from 3 to 12 cm, and different anatomical points can be used to calculate volume *(Figure 2)*.[11,12] Perometry, an optoelectric device, uses infrared light to image the external surface of the limb and calculate its volume. This measurement tool is not widely available and not easy to use accurately.[13] Volumetric measurements (volumetry) can be done with water displacement, where the extremity is immerged in a container of water, the amount of the displaced volume represents the volume of the limb.[14,15] Bioimpedancy spectroscopy (BIS), a noninvasive method to measure body composition, uses electric resistance to measure the amount of extracellular fluid.[16]

A recent review analyzed different measurement instruments used in clinical studies. They concluded that BIS, volumetry, perometry, and tape measurements can be recommended in clinical practice.[12] The usefulness of measurement tools depends on the stage of the edema, eg, BIS can detect edema earlier than volume measurements,[17] BIS and perometry are more expensive than water volumetry and tape measurements, volumetry and perometry are difficult to use for measuring midline lymphedema (head, trunk, genitalia). The suitability of the tool also depends on the feasibility and costs.[12]

Lymphography

Lymphangiography or lymphography is the oldest visualization technique that was invented by Kinmonth et al.[5] For this method, patent blue is injected intradermally to visualize the lymphatics, then a cannula is inserted through a microsurgical incision, and subsequently, an oil-soluble iodinated contrast medium is infused into the lymphatic vessel. Other methods involve an indirect uptake of an intradermally administered water-soluble iodinated contrast agent through the lymph capillaries and into the vessels.[18] These techniques are not easy to perform, meaning that they rarely used. In addition, an infusion of a contrast agent (as described by Kinmonth) or a puncture directly into a lymph node is still used in combination with a computed tomography (CT) or magnetic resonance imaging (MRI) to visualize leakages from the central lymphatics, identify lymphatic malformations, or diagnose and treat chylous reflux.[19] Therefore, lymphography has, in combination with CT or MRI, some diagnostic applications.

Ultrasonography

Ultrasonography can be used to visualize enlarged iliac, axillary, para-aortal, and paracaval lymph nodes and detect abdominal masses that are obstructing lymphatic flow. This technique is helpful to identify abnormal lymph nodes in the head and neck region. It is a simple, noninvasive technique; however, cannot visualize the lymphatic architecture. High-frequency ultrasonography is a noninvasive tool that can be used to evaluate the skin and subcutaneous thickness and echogenicity. Reticular patterns with little or no reflex can be seen, which corresponds to edema-filled gaps between fat lobules or to fat cells themselves. Using this technique, the postoperative evolution of the thickness of the cutis and subcutis was assessed in a healthy arm as well as in an arm with lymphedema. Ultrasound can be used as an adjunctive diagnostic tool, but not as a separate tool.[20] Suehiro et al showed that the thickness of the skin and subcutaneous tissue as well as the echogenicity correlated

well with the International Society of Lymphology staging system.[21]

Ultrasonography can also be used to differentiate lipedema from lymphedema.[22] The results of the study by Naouri et al[22] confirmed that lipedema is due to an increase in hypodermal tissue with no true dermal edema. Lipedema showed dermal echogenicity that was similar to normal skin. In lymphedema, the thickness of the skin and dermal hypoechogenicity is increased, especially in the distal part of the extremities for primary lymphedema. Duplex ultrasonography can be used to evaluate the function of venous valves (primary venous reflux) and exclude deep vein thrombosis or postthrombotic syndrome as a cause of the edema. In some cases of primary lymphedema, such as Milroy disease, venous reflux coexists.[23] In conclusion, ultrasonography is a good tool to diagnose lymphedema and assess the severity of the disease.[24]

CT and MRI scans

CT and MRI can be useful to visualize the lymph nodes, detect abnormalities, such as enlarged lymph nodes, visualize vascular malformations, or differentiate the causes of lymphatic obstruction in secondary lymphedema.[23] As with ultrasonography, the affected skin and the subcutaneous tissue layers can be imaged. Contrast-enhanced MRI provides anatomical and functional information on the lymphatic drainage of the limb. Pathological findings on MRI include vessel dilatation, collateral formation, delayed vessel filling, delayed lymph node enhancement, honeycombing (characteristic distribution of edema within the epifascial compartment), and dermal backflow.[25] MRI and CT are good tools to diagnose lymphedema and assess the severity of the disease. MRI lymphangiography has a good application when monitoring the treatment of chylous syndromes.[19]

Lymphoscintigraphy

The most commonly used diagnostic tool for examining extremity lymphedema is lymphoscintigraphy. This technique, first described by Sherman and Ter-Pogossian in 1953, directly images the lymphatic system.[26] A radionuclide (99mTc-labeled tracer) is intradermally injected in the patient's foot or hand and the uptake of the tracer into the lymphatic tissue is followed with sequential gamma imaging.[27,28] This technique is recommended by the International Society of Lymphedema and the American Venous Forum guidelines.[1] This technique not only provides dynamic imaging of the lymphatics and the lymph nodes, but also provides semiquantitative data on radionuclide transport. It also records the movement of the colloid from the injection site, the transition time to the knee, groins, or axilla, the absence or presence of major lymphatic collectors, the number and size of vessels and nodes, the presence of dermal backflow (reflux to the capillary network), the presence of collaterals, and symmetric activity with the opposite side.[1]

Signs of lymphedema include poorly visualized lymphatic collectors, delayed nodal enhancement, and dermal backflow. Lymphoscintigraphy can be used to diagnose lymphedema and estimate the severity of the lymphedema.[28] In addition, it can be used to assess the efficacy of the treatments for lymphedema, eg, after lymphovenous anastomosis or lymph node transfer.[29] Although lymphoscintigraphy is still the gold-standard technique, there is no standardization regarding the radiotracer, radioactivity doses, different injection volumes, intracutaneous vs subcutaneous injection, number of injections, different protocols of passive and active physical activity, varying imaging times, static and/or dynamic techniques.[23,30]

Near-infrared fluorescence imaging

Near-infrared fluorescence imaging is an alternative where a fluorescent agent is injected in place of the radionuclide; the main advantage is that this is a real-time image, as uptake is observed immediately. For humans, fluorescein sodium and indocyanine green (ICG) are used. Fluorescence is a phenomenon of light emission with a certain wavelength from a material when it is irradiated by light from another wavelength. The irradiated and emitted lights are called excitation light and fluorescence light, respectively.[31] Fluorescein sodium is excited by visible light and ICG by near-infrared light. ICG has already been used for hepatic clearance and ophthalmological indications. The fluorescence technique is also used for sentinel node mapping in cancer surgeries.[32,33] Fluorescein sodium is mainly used for microlymphangiography.[24]

After intradermally injecting ICG in the hand or foot, excitation light penetrates and fluorescence is observed with a photodynamic eye (PDE) camera to a maximum depth of 2 cm *(Figure 3)* with the frequency-domain photon migration technique (FDPM imager) to a maximum depth of 3 to 4 cm. Fluorescence from ICG is weak, but it becomes stronger when it is combined with plasma proteins and

Figure 3. Photodynamic eye camera.

From reference 11: Chi et al. Theranostics. *2014;4(11):1072-1084. © 2014, Ivyspring International Publisher.*

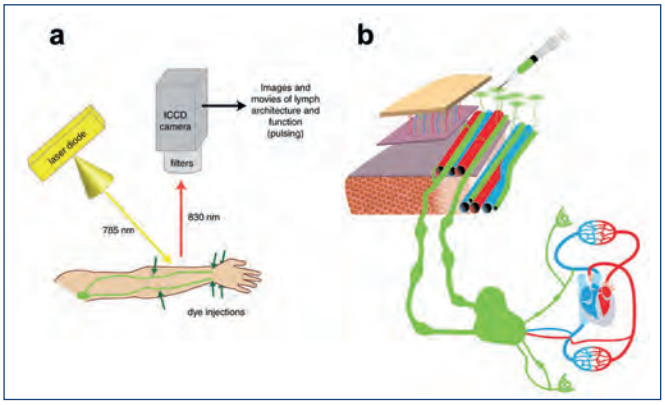

Figure 4. Fluorescence imaging.

A. The emitted excitation light. B. Indocyanine green (ICG) is injected intradermally, captured by the capillary network, and transported in precollector and collectors.

From reference 31: Aldrich et al. Biomed Opt Express. *2012;3(6):1256-1265. © 2012, Optical Society of America.*

illuminated with an appropriate wavelength *(Figure 4)*.[34] The near-infrared light penetrates the human tissue well, but it is still absorbed to a certain extent by hemoglobin. Therefore, veins can be observed even without ICG.[33]

Eva Sevick-Muraca's group performed a series of studies using this technique and a summary of the human studies is provided in the following paragraphs.[33] First, they optimized the technique in animals, moving to normal volunteers and finally to patients (upper and lower limb). Marshall et al[35] gave an update on near-infrared fluorescence imaging in humans with a 0.1 mL injection of ICG at numerous sites and a FDPM imager to capture the energy.

Rasmussen et al[36] described the use of two custom-built fluorescence imaging systems to try to measure the velocity, defined as the distance over the travel time of the fluorescent packet. A propulsion event was defined as the time when the lymphangion empties. The contractions (pumping actions) of the lymphangions create intermittent suction of lymph from one lymphangion to another. The mean propulsion rate is the total number of fluorescent packets over the total time spent imaging *(Figures 5 and 6)*.

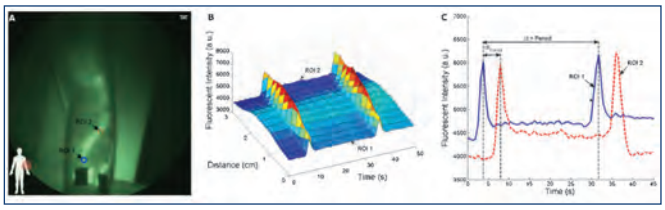

Figure 5. Quantification of the lymphatic flow.

Fluorescence intensity from one point to another.

From reference 36: Rasmussen et al. Transl Oncol. *2010;3(6):362-372. © 2010, Neoplasia Press, Inc.*

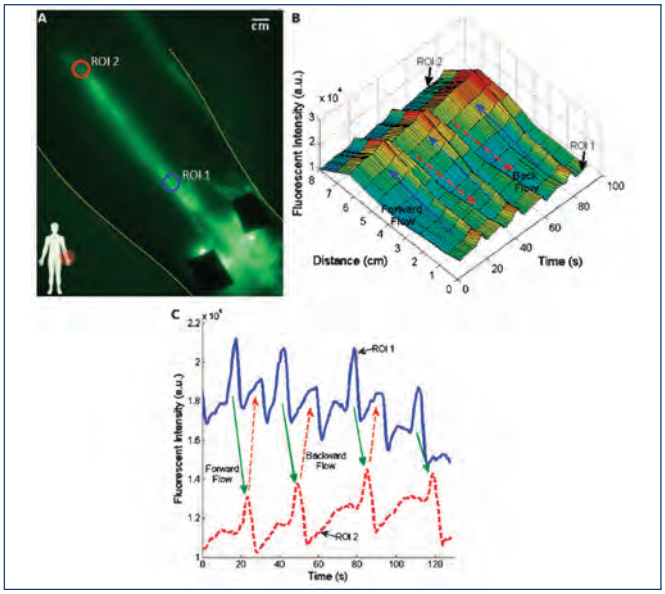

Figure 6. Lymphatic reflux.

Fluorescence intensity from one point to another and reflux.

From reference 36: Rasmussen et al. Transl Oncol. *2010;3(6):362-372. © 2010, Neoplasia Press, Inc.*

Tan et al[37] performed a feasibility study to assess the lymphatic system after manual lymphatic drainage. The study used two custom-built fluorescence-imaging systems to measure velocity, propulsion events, and period between peaks. Ten patients with stage I and II lymphedema and twelve healthy volunteers were recruited. ICG was injected, and, after 30 minutes of imaging, manual lymphatic

drainage was performed for 25 minutes, followed by a period of imaging during manual lymphatic drainage for 30 minutes. The results from the arm showed an increase in the velocity after manual lymphatic drainage (significant in the control and the asymptomatic group) and a decrease in the period between peaks (significant in the control group). The results from the legs showed an increase in the velocity after manual lymphatic drainage (significant in the control group) and a decrease in the period between peaks (nonsignificant in both the control group and the asymptomatic group). The stimulation of the lymphatic system was not as large in the symptomatic group as in the control group, probably because there are fewer lymph vessels to stimulate. With this technique, malfunction in the lymphangion contractions can result in slow uptake or passive filling of the ICG in the initial lymphangion, which can create an insufficient pressure gradient, reflux, or dermal backflow of the ICG.

Several schools in Japan have reported on their experience with near-infrared fluorescence. Unno et al[38] first published a preliminary experiment with fluorescence lymphography in patients with secondary lymphedema (16 extremities); 0.2 mL ICG was injected and a PDE camera system was used to capture whole limb panoramic images. Four abnormal patterns were described: dermal backflow, extended dermal backflow in the foot, dilated lymph channels with proximal obliteration, and diffuse glittering (twinkling like the Milky Way). In one case, different patterns were observed in the same extremity. The authors concluded that ICG fluorescence is a good qualitative examination. This "Milky Way" reflects the stage where the lymphatic capillaries are filled with ICG and leakage in the interstitial space exists. Several dots with high concentration of ICG can be seen.

Suzuki et al[39] investigated the effect of surgical treatment on lymph flow in the lower limbs of patients with varicose veins. A total of 39 patients were included and 15 healthy volunteers were used as controls, ICG lymphography was performed before and 6 months after great saphenous vein surgery. Transit time in a standing position was defined as the time until the ICG reached the knee (from dorsum foot to midpoint patella). They concluded that the transit time was longer in higher clinical, etiological, anatomical, and pathophysiological (CEAP) classes and the transit time was shorter after surgery.

Yamamoto et al[40-44] performed several studies and described a severity staging of the dermal backflow image in secondary lymphedema of the upper and lower limb. In normal individuals, a linear pattern was observed. When dermal backflow exists, three stages are identified: splash, stardust, and diffuse *(Figure 7)*. A splash pattern occurs when there is dermal backflow into the lymphatic capillaries, a stardust pattern represents the Milky Way, showing that some extravasation of ICG in the interstitial space has already occurred *(Figure 8)*,[45] and a diffuse pattern shows a fusion of all of the stars. In another study, a good correlation between the Campisi clinical classification and the dermal backflow patterns was observed.[42]

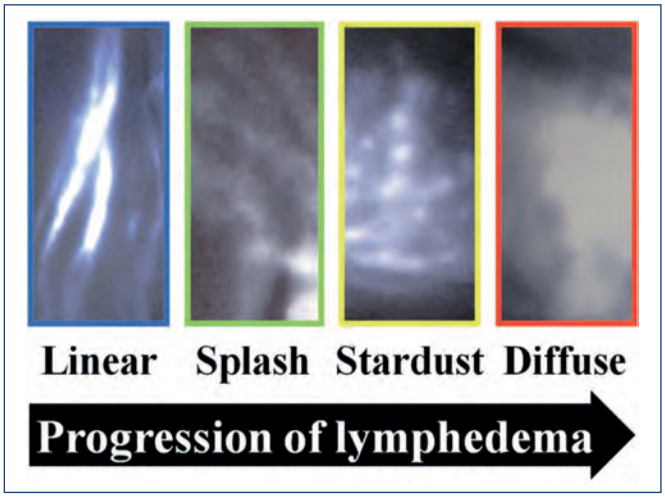

Figure 7. Classification of severity.

From reference 42: Yamamoto et al. Plast Reconstr Surg. *2011;128(4):941-947. © 2017, American Society of Plastic Surgeons.*

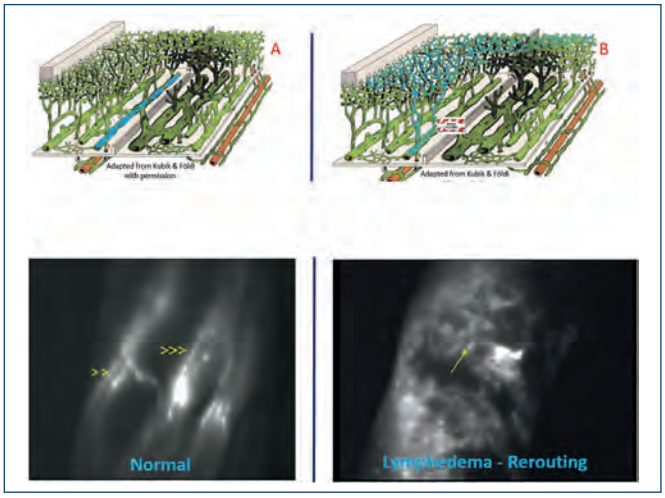

Figure 8. Superficial lymphatic network in the crook of the elbow.

A. Normal: linear pattern. B. Dermal backflow: stardust pattern.

From reference 45: Belgrado et al. Lymphat Res Biol. *2016;14(2):70-77. © 2016, Belgrado et al.*

In a prospective trial that included 29 patients with lymphedema after gynecological cancer, Mihara et al[46] compared the sensitivity and specificity of ICG lymphography with scintigraphy in secondary lower limb lymphedema. Another study, from a group in Chiba, Japan,[47] compared the same diagnostic tools in patients with secondary lymphedema of the upper and lower limbs and idiopathic edema (suspected primary lymphedema). Both studies concluded that ICG lymphography is more accurate and that it is useful for assessing the indications for surgery (abnormal pattern progresses or extension into the next stage). Compared with lymphoscintigraphy, this technique does not use a radionuclide, has a lower cost, and shows a benefit for an early detection of lymphedema.[47] However, standardization and further validation is needed before this technique can be used as a reproducible tool to characterize lymphedema patients. Furthermore, quantitative methods of the near-infrared fluorescence at all stages of lymphedema have not yet been developed. In this regard, it can be questioned whether it is possible to quantify the transport in a severe stage of lymphedema where there is not a linear structure to measure the velocity or propulsion rate.

Conclusion

Until recently, the gold-standard technique to confirm the presence of lymphedema has been lymphoscintigraphy; however, many newer diagnostic tools have become available. Clinical examination and history still play an important role, but noninvasive methods, such as ultrasonography are good additional diagnostic tools. A pitfall of ultrasonography is that it does not provide information on the functionality of the lymphatic transport or the architecture of the transport. Near-infrared fluorescence imaging seems a good tool to visualize the superficial lymphatic architecture, to assess the severity of lymphedema according to the different images, and to use it as a guide for manual lymphatic drainage. Compared with lymphoscintigraphy, this technique does not use a radionuclide, has a lower cost, and shows a benefit for an early detection of lymphedema.

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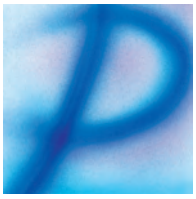

Prevention and treatment of venous disorders during pregnancy and the postpartum period

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Keywords:

breastfeeding; pregnancy; venous insufficiency; venous thromboembolism; treatment

Abstract

Chronic venous disease represents one of the most frequent medical conditions that could be observed in the general population. Pregnancy is one of the major predisposing factors for developing venous insufficiency due to an enlarged gravid uterus, which obstructs pelvic venous outflow, and an increase in hormone secretion, which weakens the vein wall. A clinical examination and Doppler ultrasound evaluation are used to diagnose venous insufficiency during pregnancy; these clinical findings can vary from insignificant telangiectases to severe varicose veins and skin damage. The relative risk of a venous thromboembolism (VTE) is increased by approximately 4 to 6 fold during pregnancy, and this risk is increased further during the postpartum period. In the first trimester, many fatal antenatal VTE events could occur; therefore, early prophylaxis for women with a previous VTE is necessary. In woman with a previous VTE, thromboprophylaxis should begin as early during pregnancy as practical, while women without a previous VTE, but with other risk factors, can start antenatal prophylaxis at 28 weeks of gestation. This article reviews and discusses the current guidelines for the diagnosis and treatment of chronic venous insufficiency during pregnancy and the prevention of a VTE. This article also discusses the current role of low-molecular-weight heparin, warfarin, venotonic agents, and compression stockings in preventing a VTE and treating venous insufficiency during pregnancy.

Chronic venous insufficiency

Chronic venous disease represents one of the most frequent medical conditions that could be observed in the general population.[1-3] The exact prevalence of chronic venous disease is difficult to determine due to differences in the selection criteria and the definition of the disease, but it is estimated to be present in >30% of adults in the Western population,[1] affecting 10% to 15% of men and 20% to 25% of women.[4] The American Venous Forum and Society for Vascular Surgery has classified chronic venous disease according to the clinical, etiological, anatomical, and pathological (CEAP) findings: C_1, no visible or palpable signs of chronic venous disease; C_2, telangiectasias or reticular veins; C_3, varicose veins (>3 mm); C_4, changes in skin or subcutaneous tissue; C_{4a}, pigmentation or eczema; C_{4b}, lipodermatosclerosis, white atrophy; C_5, healed venous ulcer; and C_6, active venous ulcer.[5,6]

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Chronic venous disease and pregnancy

Predisposing factors for chronic venous insufficiency include age, sex, obesity, lifestyle, heredity, and physical inactivity. Pregnancy is also a major predisposing factor for developing venous insufficiency, and it can be observed in 28% of all pregnancies.[7] Laurikka et al analyzed cohorts of 3284 men and 3590 women aged 40, 50, and 60 years, and they found that the prevalence of varicose veins in women with 0, 1, 2, 3, or ≥4 pregnancies was 32%, 38%, 43%, 48%, and 59%, respectively.[8] Venous insufficiency occurs during pregnancy for two main reasons: (i) an enlarged gravid uterus with consequent hypertension in the lower extremity veins, distension, and valve damage, which obstructs pelvic venous outflow; and (ii) an increase in hormone secretion, which weakens the vein wall.[9-12] Ciardullo et al[13] showed that higher serum estradiol levels during pregnancy were significantly associated with venous distensibility and clinical evidence of varicose veins in menopausal women.

Diagnosing venous insufficiency during pregnancy

A clinical examination and a Doppler ultrasound evaluation are used to diagnose venous insufficiency during pregnancy. Pain, swelling, itching, burning, or numbness are some of the clinical signs and symptoms that could be observed during the clinical examination and anamnestic questioning; it is also important to determine whether or not the varicose veins were present before pregnancy. If the patient has a family history of chronic venous disease, these symptoms might be more pronounced. The clinical findings vary from insignificant telangiectasias to severe varicose veins and skin damage. Varicose veins can be observed in the great and small saphenous veins, collaterals, or perforating veins *(Figure 1)*. These changes could involve one or both legs, while valvular and perineal varicose veins could be seen in 10% of the cases.[13] Skin changes are very rare given the young age of pregnant women and the relatively short period with symptoms of venous insufficiency. However, if such changes occur (C_5 or C_6 classification), it is recommended to initiate the use of compression stockings immediately. In all patients who have complaints about any type of venous insufficiency, a color Doppler ultrasound of the lower extremities should be performed as early as possible. Changes should be carefully noted and followed-up during regular check-ups.

Preventing a VTE during pregnancy

While the relative risk of a venous thromboembolism (VTE) is approximately 4- to 6-fold higher during pregnancy and increases more during the postpartum period, the absolute risk is low with an overall incidence of 1 to 2 per 1000 during pregnancy and the postpartum period.[14-19] The absolute incidence of a VTE during pregnancy and the postpartum period is 107 per 100 000 person-years in the UK, 175 per 100 000 person-years during the postpartum period in Denmark, and 175 per 100 000 pregnancies in Canada.[14,20,21] In the first trimester, many fatal antenatal VTE events could occur; therefore, prophylaxis for women with a previous VTE should begin early *(Figure 2, Figure 3)*.[22-24] The risk for a VTE increases with gestational age, with the maximum risk occurring right after delivery. While a cesarean section is a significant risk factor for a VTE, women having vaginal deliveries are also at risk.[25-28] In the postpartum period, the risk of VTE is 5-fold higher

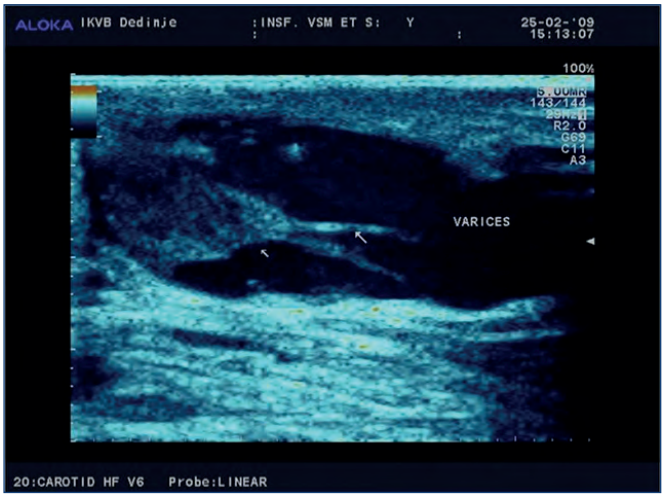

Figure 1. Varicose great saphenous vein in a pregnant patient.

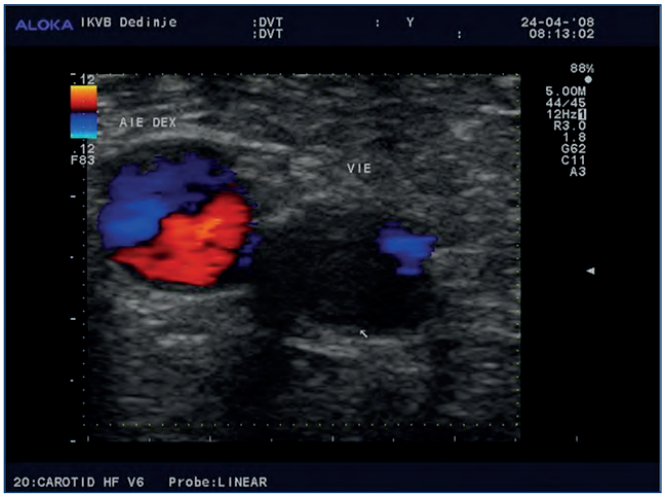

Figure 2. Postpartum external iliac vein thrombosis.

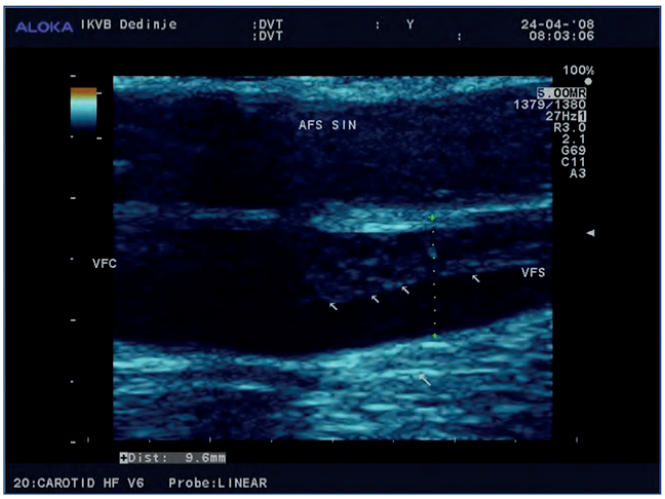

Figure 3. Superficial femoral vein thrombosis in a pregnant patient.

heparin throughout the antenatal period (grade C) *(Figure 4)*. For patients with heritable thrombophilia associated with antithrombin deficiency (these patients will often be on long-term oral anticoagulation) or antiphospholipid syndrome, thromboprophylaxis using a higher dose of low-molecular-weight heparin (50%, 75%, or full treatment dose) should be offered antenatally for 6 weeks postpartum or until returned to oral anticoagulant therapy after delivery (grade D). Antenatal prophylaxis should also be considered for all women with asymptomatic antithrombin, protein C or S deficiency, or >1 thrombophilic defect; these patients should be referred to a local expert. Even in the absence of additional risk factors, such patients are recommended to have 6 weeks of postnatal prophylaxis (grade D).

Preexisting condition	Obstetric risk factors	New-onset/transient risk factors
Heritable **Antithrombin deficiency** **Protein C deficiency** **Protein S deficiency** **Factor V Leiden** **Prothrombin gene mutation**	Multiple pregnancy Current pre-eclampsia	Any surgical procedure in pregnancy or puerperium except immediate repair of the perineum, eg, appendicectomy, postpartum sterilisation Bone fracture
Acquired **Antiphospholipid antibodies** **Persistent lupus anticoagulant and/ or persistent moderate/high titre anticardiolipin antibodies and/or β_2-glycoprotein 1 antibodies**	Cesarean section Prolonged labor (>24 hours) Mid-cavity or rotational operative delivery Stillbirth Preterm birth Postpartum hemorrhage (>1 L/requiring transfusion)	Hyperemesis, dehydration Ovarian hyperstimulation syndrome (first trimester only) Assisted reproductive technology (ART), in vitro fertilization (IVF)
Medical comorbidities eg, cancer, heart failure, inflammatory polyarthropathy, nephrotic syndrome, type I diabetes mellitus with nephropathy, current intravenous drug user		Admission or immobility (≥3 days' bed rest), eg, pelvic girdle pain restricting mobility
Age >35 years		Current systemic infection (requiring intravenous antibiotics or admission to hospital)
Obesity (BMI ≥30 kg/m^2) either prepregnancy or in early pregnancy		eg, pneumonia, pyelonephritis, postpartum wound infection
Parity ≥3 (a woman becomes para 3 after her third delivery)		Long-distance travel (>4 hours)
Smoking		

Table I. Risk factors for venous thromboembolism.

From reference 30: Royal College of Obstetricians and Gynaecologists. *https://www.rcog.org.uk/globalassets/documents/guidelines/gtg-37a.pdf.*

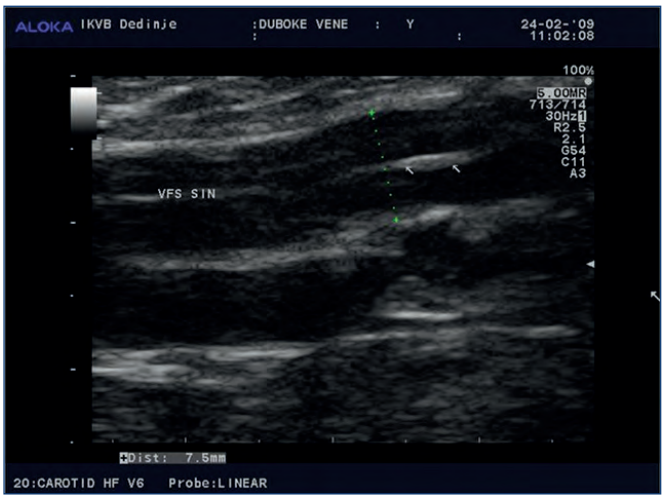

Figure 4. Postphlebitic syndrome in a superficial femoral vein in a breastfeeding patient.

Starting thromboprophylaxis

In women who have received VTE thromboprophylaxis previously, prophylaxis should be started as early as possible during pregnancy, while women without a previous VTE, but with 3 other risk factors, antenatal prophylaxis can begin at 28 weeks of gestation (grade B, grade C).

Interrupting thromboprophylaxis

When evaluating thromboprophylaxis interruption, women receiving antenatal low-molecular-weight heparin who are having an elective cesarean section should receive a thromboprophylactic dose of low-molecular-weight heparin 1 day before delivery, and, on the day of delivery, any morning dose should be omitted and the operation performed that morning. After delivery, if there is no postpartum hemorrhage and regional analgesia has not been used, the first thromboprophylactic dose of low-molecular-weight heparin should be administered as soon as possible. If spinal anesthesia was used, low-molecular-weight heparin should be given after 4 hours or after the epidural catheter has been removed; the catheter should not be removed within 12 hours of the most recent injection. If a hemorrhagic problem develops while taking low-molecular-weight heparin, the treatment should be stopped and a hematology specialist should be consulted. In women with a VTE after a cesarean section, others risk factors may also be identified, ie, severe pre-eclampsia, reoperation, twin pregnancy, obesity, immobilization, and placenta praevia.[34] The risk of a VTE after a cesarean section is at least 2 times higher than after a vaginal delivery .[25] In addition, the risk of a VTE is after an emergency cesarean section is 2 times higher than after an elective cesarean section, which is 4 times than the risk after a vaginal delivery.[35]

According to the official guidelines, all women who have had emergency cesarean sections should be considered for thromboprophylaxis with low-molecular-weight heparin for 10 days after delivery, apart from those having an elective cesarean section who should only be considered for thromboprophylaxis with low-molecular-weight heparin for 10 days after delivery if they have any additional risk factors (*Table I*, grade C). Low-molecular-weight heparin thromboprophylaxis should be continued for 6 weeks in high-risk women and for 10 days in intermediate-risk

Weight	Enoxaparin	Dalteparin	Tinzaparin (75 u/kg/day)
<50 kg	20 mg daily	2500 units daily	3500 units daily
50–90 kg	40 mg daily	5000 units daily	4500 units daily
91–130 kg	60 mg daily*	7500 units daily	7000 units daily*
131–170 kg	80 mg daily*	10 000 units daily	9000 units daily*
>170 kg	0.6 mg/kg/day*	75 u/kg/day	75 u/kg/day*
High prophylactic dose for women weighing 50–90 kg	40 mg 12 hourly	5000 units 12 hourly	4500 units 12 hourly

Table II. Low-molecular-weight heparin dosage.

From reference 30: Royal College of Obstetricians and Gynaecologists. *https://www.rcog.org.uk/globalassets/documents/guidelines/gtg-37a.pdf.*

women (grade C). The dose of low-molecular-weight heparin is determined based on the patient's weight *(Table II)*. The use of low-molecular-weight heparin should be reduced in women with renal impairment. Low-molecular-weight heparin is safe while breastfeeding. This treatment should be avoided, discontinued, or postponed in women at risk of bleeding after carefully considering the balance between the risks of bleeding and thrombosis (grade D), while women with allergic reactions to low-molecular-weight heparin should be offered an alternative preparation or an alternative form of prophylaxis (grade D). The contraindications for low-molecular-weight heparin are shown in the *Table III*.

Contraindications/cautions for using low molecular weight heparin
Known bleeding disorder (eg, haemophilia, von Willebrand's disease or acquired coagulopathy)
Active antenatal or postpartum bleeding
Women considered at increased risk of major hemorrhage (eg, placenta praevia)
Thrombocytopenia (platelet count <75x10^9/L)
Acute stroke in previous 4 weeks (hemorrhagic or ischemic)
Severe renal disease (glomerular filtration rate <30 mL/minute/1.73m^2)
Severe liver disease (prothrombin time above normal range or known varices)
Uncontrolled hypertension (blood pressure >200 mm Hg systolic or >120 mm Hg diastolic)

Table III. Contraindications/caution for using low-molecular-weight heparin.

From reference 30: Royal College of Obstetricians and Gynaecologists. *https://www.rcog.org.uk/globalassets/documents/guidelines/gtg-37a.pdf.*

Using warfarin during pregnancy

Warfarin has been described to cross the placenta, which increases the risk of congenital abnormalities in approximately 5% of fetuses exposed between 6 and 12 weeks of gestation.[36-40] According to the official guidelines, using warfarin during pregnancy is restricted to the few situations where heparin is considered unsuitable, eg, women with mechanical heart valves (grade B). Women receiving long-term anticoagulation with warfarin can be converted from low-molecular-weight heparin to warfarin postpartum when the risk of hemorrhage is reduced, usually 5 to 7 days after delivery. Warfarin is safe while breastfeeding.

Non–vitamin K antagonist oral anticoagulants and pregnancy

Although treatment with warfarin is effective, it has numerous limitations, such as a slow onset and offset of action, dosage variations based on differences in dietary vitamin K intake, and multiple drug interactions. To overcome these limitations, new non–vitamin K antagonist oral anticoagulants (NOACs) have been developed to replace warfarin in many indications,[41-44] including three inhibitors of factor Xa–rivaroxaban, apixaban, and edoxaban–and one inhibitor of thrombin–dabigatran. In contrast to warfarin, NOACs have a rapid onset and offset of action, a more predictable anticoagulant response with no impact from dietary vitamin K intake, and few drug interactions.

NOACs are indicated, among other indications, for preventing VTE and venous thrombosis. Several large trials compared conventional treatments for VTE with dabigatran, rivaroxaban, apixaban, and edoxaban.[45-50] In a recent meta-analysis that compared NOACs with warfarin, 24 455 patients with acute VTE were analyzed for recurrent VTE, fatal pulmonary embolism, and all-cause mortality.[51] While the final outcomes were not significantly different (ie, lower) in patients treated with NOACs, both the rate of major bleeding was significantly lower in patients receiving NOACs vs those receiving warfarin (risk reduction [RR], 0.60; 95% CI, 0.41-0.88), as was the rate of fatal bleeding (RR, 0.36; 95% CI, 0.15-0.87).[51] Overall, for VTE treatment, NOACs are noninferior to conventional therapies; however, they are associated with a lower rate of bleeding.

There is limited data published concerning the use of NOACs during pregnancy. According to the official guidelines,[52] oral direct thrombin inhibitors (dabigatran) and antifactor-Xa inhibitors (rivaroxaban, apixaban) are not recommended during pregnancy (Grade 1C). A recent Canadian study that examined the rate and extent of rivaroxaban transfer across the human placenta[53] found that rivaroxaban transfer across the term human placenta occurs rapidly from both the mother-to-fetus and fetus-to-

mother directions. Still, bearing in mind that rivaroxaban is highly bound to plasma proteins, the authors suggest that the amount of unbound drug that might reach the fetus is probably much lower.[53] In a study by Hoeltzenbein et al,[54] 63 exposed pregnancies where identified among 94 requests concerning rivaroxaban use during childbearing age. Indications for rivaroxaban were VTE, knee surgery, and atrial fibrillation. After surveillance of 37 pregnancies, there were 6 spontaneous abortions, 8 elective terminations of pregnancy, and 23 live births.[54] After recognition of pregnancy, most women discontinued the use of rivaroxaban, mostly in the first trimester, except for one woman that continued until gestational week 26. There was only one case of bleeding in the whole series. There is an obvious risk of taking dabigatran, rivaroxaban, or apixaban during pregnancy and breastfeeding; therefore, larger prospective studies concerning this issue are expected.

Compression stockings and venoactive agents

Therapy for venous insufficiency during pregnancy is mainly directed toward compression stockings and venoactive agents. Some studies showed that compression stockings improved venous blood flow of the lower extremities with a simultaneous decrease in the lumen diameter of the superficial femoral and common femoral veins in patients during late pregnancy and early postpartum.[55-57] In patients with known chronic venous insufficiency, compression stockings should be initiated at the start of pregnancy and after the appearance of the first venous disorder in patients with no previous venous abnormalities.[58] According to the official guidelines,[30] compression therapy of appropriate size and graduated compression pressure of 14 to 15 mm Hg at the calf is recommended during pregnancy and the postpartum period for women who are hospitalized and have a contraindication to low-molecular-weight heparin (grade D), which refers to women who are hospitalized after a cesarean section (combined with low-molecular-weight heparin), women considered to be at a particularly high risk of a VTE, and women travelling long distances, ie, >4 hours (grade D).

Conclusion

Venoactive agents are very useful for treating the symptoms of venous insufficiency.[59] So far, flavonoids have not shown teratogenic effects, and updated guidelines on the management of chronic venous disorders recommend the use of flavonoids because the benefits clearly outweigh the risks and there is moderate-quality evidence (grade 1B).[59] Flavonoids can be used to treat pregnant women with a gestational age greater than 12 weeks; however, the use of flavonoids is not recommended while breastfeeding.

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Instructions for authors

AIM AND SCOPE

Phlebolymphology is a quarterly peer-reviewed publication that aims to provide clinicians with updated information on every aspect of venous and lymphatic disorders, including epidemiology, pathophysiology, diagnosis, management, and basic science. Articles are usually review articles on current topics with a broad update on recent developments and their clinical applications.

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Articles

Articles should discuss a topic of current interest, outline recent knowledge on the subject, provide personal views and analyze the different opinions regarding the topic, and cite the latest data from the literature. The article should contain:

- **A title page** that includes a concise and informative **title,** the **full names of all the authors** (first name, middle initial, and last name), the **highest academic degrees of all authors** (in country of origin language) and **affiliations** (names of department[s] and institution[s] at the time the work was done), a **short running title** (no more than 50 characters and spaces), 5 to 10 **keywords**, the **corresponding author's complete mailing address,** telephone number, and e-mail address.
- **An abstract (200 to 230 words).**
- **A main text (2800 to 3200 words, not including the references**). All references should be cited in the text and numbered consecutively using superscript Arabic numerals. Please do not use the author-date system (see the section on references below).
- A current **color photograph** (head and shoulder) of the corresponding author (TIF or JPG files at 300 dpi).
- **Illustrations** are strongly encouraged (for file requirements, see the section on "Figures and Tables" below).
- **Videos** can be published in the online supplement, if they enhance the print articles. All videos must be approved by the editorial board. Poor-quality or lengthy videos will not be accepted. Videos should be cited in the manuscript (example of a video citation: "See video online for an example of this closure") and should be no longer than 2 minutes.

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The editorial should not exceed 450 words. No abstract, references, or illustrations should be included.

Text: Abbreviations should be used sparingly and expanded at first mention in the abstract, the main text, and legends of all figures and tables. The style of titles and subtitles should be consistent throughout the text. The editorial department reserves the right to add, modify, or delete headings when necessary. *Phlebolymphology* uses SI (Système International) units and generic names of drugs.

Submission: Manuscripts should be submitted by e-mail to the Editorial Manager (hurrem-pelin.yaltirik@servier.com), double-spaced, with 1-inch/2.5-cm margins. All pages should be numbered and submitted in the following order: title page, structural abstract, text, references, and figure, table, and video legends. All texts should be submitted in English.

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It is our policy to avoid self-citation; therefore, authors are strongly encouraged to cite references from journals other than *Phlebolymphology.*

Reference list: Presentation of the references should be based on the Uniform Requirements for Manuscripts Submitted to Biomedical Journals. *Ann Intern Med.* 1997;126:36-47 ("Vancouver style"). The author-date system of citation is not acceptable. "In press" references should be avoided. In the bibliography, titles of journals should be abbreviated according to *Index Medicus.* All authors should be listed for up to 6 authors; if there are more than 6 authors, only the first 3 should be listed, followed by "et al." Where necessary, references will be styled by the editorial department to *Phlebolymphology* copyediting requirements. Authors bear total responsibility for the accuracy and completeness of all references and for correct text citation.

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Journal article with more than 6 authors: Sessa C, Perrin M, Porcu P, et al. Popliteal venous aneurysms: a two-center experience with 21 cases and review of the literature. *Int J Angiol.* 2000;9:164-170.

Journal article that has been accepted and published online ahead of print: Gulcu A, Ozutemiz C, Ugurlu B, Kose T. Duplex ultrasonography findings are not related to menstrual cycle phases in women with early symptoms of lower extremity chronic venous disease. *J Clin Ultrasound.* 2015 July 16. Epub ahead of print.

Article in a supplement: Sansilvestri-Morel P, Rupin A, Badier-Commander C, et al. Chronic venous insufficiency: dysregulation of collagen synthesis. *Angiology.* 2003;(suppl 1):S13-S18.

Chapter in a book: Coleridge Smith PD. The drug treatment of chronic venous insufficiency and venous ulceration. In: Gloviczki P, Yao JST, eds. *Handbook of Venous Disorders: Guidelines of the American Venous Forum.* 2nd ed. London, UK: Arnold; 2001:309-321.

Web-based material: Nicolaides AN. Investigation of chronic venous insufficiency: a consensus statement. American Heart Association, 2000. http://www.circulationaha.org. Accessed October 17, 2005.

Presentation at a conference: Jantet G. Epidemiological results of the RELIEF study across different continents. Paper presented at: 15th World Congress of the Union Internationale de Phlébologie; October 2-7, 2005; Rio de Janeiro, Brazil.

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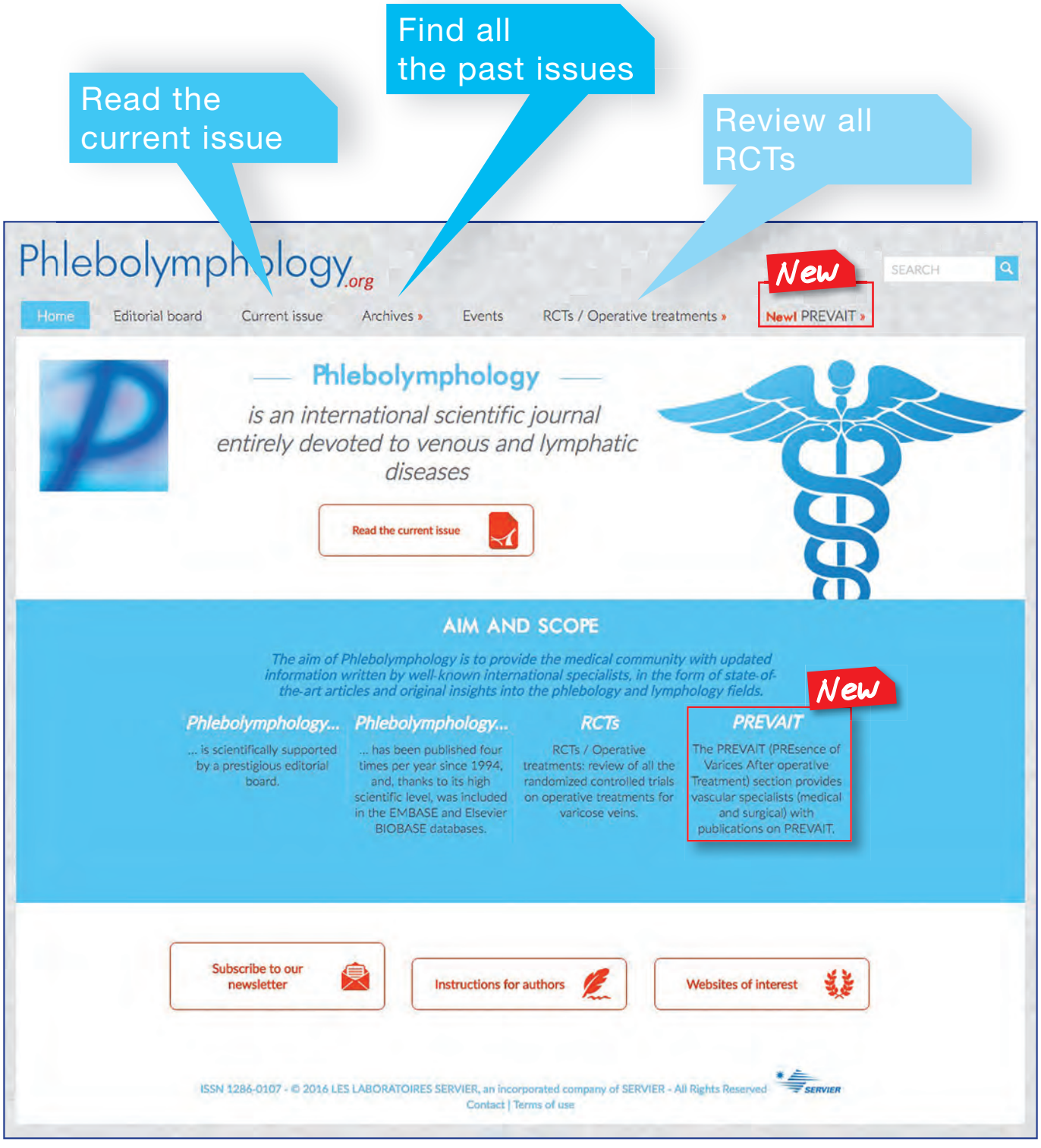

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