ARISTOTLE UNIVERSITY OF THESSALONIKI
FACULTY OF HEALTH SCIENCES
SCHOOL OF MEDICINE

TREATMENT OUTCOMES OF SAPHENOUS VEIN LIGATION PLUS FOAM SCLEROTHERAPY UNDER LOCAL ANAESTHESIA

A thesis submitted in fulfilment of the requirements for the degree of Master of Science in Medical Research Methodology

By

Skepastianos George

Thessaloniki, May, 2018

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Professor Papazoglou Konstantinos

Abstract 4
Abstract
This study aims to highlight and study intra-operative, short and midterm results with the application of the combined technique (saphenous vein ligation and foam sclerotherapy) for the treatment of saphenous vein insufficiency. Purpose of this study is to evaluate the saphenous vein occlusion rate, the invasiveness, the specific health related post-operative and the safety in patients with saphenous vein insufficiency after treatment with the use of catheter directed foam sclerotherapy combined with ligation of the saphenous vein and collaterals in the sapheno-femoral junction under local anaesthesia. 15 patients with symptomatic unilateral saphenous vein insufficiency underwent catheter directed foam sclerotherapy combined with saphenous vein ligation under local anaesthesia, and were followed up 6 weeks after the procedure and then further follow at 6 months. Results: except from one case who presented at the first follow up with clinical symptoms of DVT all other patients presented with decrease of complaints of chronic vein insufficiency and varicose vein symptoms was reported in 100% of the cases. Disappearance of varicose veins was also achieved in all patients.
GENERAL PART

Venous insufficiency (varicose veins) Definition

Venous insufficiency is defined as a condition, in which difficulty of the leg veins to return the blood back to the heart. The blood stays on the leg and finally leads to the end of a tiring day in swelling and feeling of weight. Over time, venous insufficiency will gradually develop into spider veins, varicose veins and skin discolouration, while ultraviolet ulcers may occur in very advanced stages, which are very difficult to heal. Varicose veins are the distended veins, visible through the skin of the foot like blue or purple knots perplexed as wires.

picture 1 Leg affected by varicose vein
**Anatomy**

The veins should not be confused with the arteries. The arterial system directs the flow of blood (rich in oxygen) from the heart to the whole body, while the venous system returns blood (poor in oxygen - consumed) to the heart. Have you seen any medical plans showing the vases in red or blue? The red vessels represent the arteries and the blue veins. It is a simulation of reality as high levels of oxygen in arterial blood give a bright red color, while low levels of oxygen in venous blood make it look dark blue.

Our legs have two distinct vein systems, a superficial (superficial) and a deeper (deep). The superficial system consists of veins that are close to the skin and the main ones are the "major saphenous vein" (on the inner side of the thigh and the tibia) and the "minor saphenous vein" (at the back of the calf). The deepest system consists of larger veins deep in the leg muscles.

The surface system communicates with the deeper with small veins ("patches"). Eventually all veins are connected to form the large central veins in the abdomen and chest. Venous return to the heart is mainly through the deep veins and this is especially important because when the superficial veins are diseased (spider veins and varicose veins) they can be removed without affecting the venous circulation which is now diverted to the deep vein network.

An important difference in the veins compared to the arteries is that the veins have unidirectional valves. Arteries do not need valves as blood flow is maintained by the pressure produced by heartbeat (blood pressure - the one measuring the blood pressure meter). Blood pressure in the veins (venous pressure) is lower than that of the arteries and thanks to the valves the blood flow is achieved (maintaining the venous return from the feet upwards against gravity).

When the leg muscles contract, they tighten the deep veins and the valves open, and when the muscles relax, the valves close to prevent the blood flow back. If the valves are "spoiled" or destroyed, the blood is backward and stays in the veins, stretching them as a result of increasing pressure. This stretch of veins weakens even more the vein walls and damages the valves more. This is called venous insufficiency or phlebitis and results in the appearance of spider veins and varicose veins.
**Histology**

The blood vessels are formed by the following skins:

**Intimal**

The intimal layer is formed by endothelial cells deposited on the basal membrane beneath which sits a layer of loose connective hypoendotheliak tissue containing few smooth muscle cells. The intima is separated from the tunica media with a rubber inner petal, which forms the outermost boundary of the intima.

**Medial**

The tunica media is mainly composed of concentric layers of smooth muscle cells, arranged in helical fashion. Between the muscle cells inserted elastic fibres, reticular fibres (collagen type III) proteoglycans and glycoproteins in varying amounts.

**Adventitia**

The adventitia consists mainly of collagen and elastic fibbers. The collagen in the adventitia is type I [7]

Furthermore veins contain valves in their lumen. This accessory prevent the back flow of blood in the low pressure venous system.

**Physiopathology**

75% go the body’s total blood volume is contained in the peripheral venous system. The amount of blood in the legs is a body position function. The venous system, especially in the legs, is an important component of the cardiovascular system’s circulatory reservoir. Venous blood pressure is controlled by various factors among which is the pressure that the heart generates, hydrostatic- gravitational forces, blood volume, efficiency of the vein valves, contraction of veins smooth muscle layer influenced by
temperature - sympathetic - parasympathetic system and anatomical composition.

Indeed according to the law of Laplace \((T = pxr)\) The voltage applied to the walls of the vessel is directly proportional to the internal pressure and radius of the vessel.

The blood is generally fusiform dilatation, and has rarely saccate morphology [8].

Because of the one-way valves, blood flow is directed from the superficial venous system to the deep venous system through perforating vessels.

In a normal vein, during the “heel-up” position of the walking cycle, the increased pressure exerted by the calf muscle on the veins will open the valve’s two leaflets and blood is pushed uphill. With cessation of the calf muscle pressure in the “foot-down” position of the walking cycle, the pressure drops, the leaflets immediately close and the blood that was pushed uphill remains up. This means that the blood that reached the thigh is unable to return to the ankle, the knee, not even if one strains with all his force. This is what a normal and physiological blood vessel valve is doing.

![FIGURE 2](image)

up-flow of blood allowed

down-flow of blood not allowed

Major cause of blood vessel insufficiency - varicose veins are changes in the vein wall, smooth muscle proliferation, increased MMP, collagen deposition, decreased elastin content. Changes in the vein wall lead to overstitching of the veins and an increase in their size but without an increase in the size of the leaflets that comprise the valve, thus there is a secondary valvular incompetence resulting in back flow and further dilatation of the veins leading to a condition called varicosity which means dilated tortuous veins.
We can distinguish three different reasons why venous insufficiency can occur in the lower limbs of a patient. Sometimes there are two or more rarely all three reasons in the same patient.

Firstly: When there are deficiencies of superficial vein valves (veins immediately below the skin), skin lesions with or without varicose veins may progressively develop.

Secondly: When there is a valve defect in the deep veins, edema of the leg may occur and skin lesions gradually become visible. In the case where the damage of the deep vein valves is due to venous thrombosis, the condition is called post-thrombotic syndrome.

Thirdly: When there are agents that disrupt the normal function of the calf myoflavous pump (such as, for example, muscular atrophy of the calf, ankylosis of the ankle, walking weakness), the sequence of dermal lesions of chronic venous insufficiency can also be gradually triggered without necessarily having a problem with their veins or valves.

Studies suggest that in patients with aneurysms, there is abnormal increased activity of proteolytic enzymes such as elastase. From clinical observations it is known that aneurysms of the abdominal aortic aneurysms often coexist with peripheral vascular (femoral-popliteal artery) and with inguinal hernia. 40% of patients with carotid tortuosity have an aneurysm, the diameter of peripheral
Risk factors for creating varicose veins

Factors associated with increased risk for varicose veins include:

- Wide age
- Sex
- Tribe
- Family history
- Smoking
- Pregnancy
- Lifestyle
- Body habitus

Research shows that gender, age and family history are the most important factors that increase the likelihood of developing varicose veins by 2.3, 3.4 - 6.5 and 5.2 times respectively. A positive family history (a degree relatives) varicose veins by the mother were more frequent in contrast to varicose veins by the father or from both parents.

In addition, the following factors have been associated with varicose vein formation: homocysteine metabolism, lack of physical activity, previous injury in legs, prolonged standing although the evidence for some of these factors are not consistent, and studies may not have been the subject of many variables and have reported false results. More recently, studies have shown correlation with variants on Vascular endothelial growth factor A (VEGF-A) and its receptors (VEGF R1, VEGF R2). The contents of VEGF-A, VEGF R1, and VEGF R2, in the wall of varicose veins may be accepted as one of the reasons for the clinical symptoms of the disease and can predispose to its progression.
**Epidemiology**

Most common location of varicose veins is the lower limb. 1 in 8 Greeks suffer from symptoms of the disease. Of these, 72% said they did not go to events, 19% canceled activities (theatre, cinema) and stayed at home, over 9% avoided wearing shorts or shorts in the summer, while 7% avoid hot places in the summer.

Symptoms mainly affect workers who are standing up for more than 4 hours a day, obese, over 45 years of age, most of whom are women.

The most common discomfort is leg pain (58%) and swollen, "heavy" feet (37%). Also 26% of the patients show spider veins and 19% varicose veins.

Screening studies provide better data

on the prevalence of AAA. Several of these have been conducted as randomised studies to evaluate the benefits

screening (MASS, Western Australia, Viborg and Chichester, the latter is the only one that includes women). Other evidence comes from Rotterdam, the Troms and other large epidemiological studies. The prevalence rates vary with age, sex and location.

**Classification of varicose veins**

The varicose veins disease may be classified as follows:

A comprehensive classification system has been develop in order to compare, diagnose and treat patients with chronic venous disorders. The classification system was created by the American venal committee in 1994 and is an accepted standard for classifying venal disorders (CEAP)

**COMPREHENSIVE CLASSIFICATION SYSTEM FOR CHRONIC VENOUS DISORDERS.**

It includes a description of the clinical case (C) based on objective signs, the aetiology (E), the anatomical distribution (A) of reflux / obstruction / deep / superficial veins, an the underlying pathophysiology (P), if its due to reflux or obstruction
### CLASSIFICATION OF VALVE INSUFFICIENCY OF THE GREATER SAPHENOUS VEIN BY HACH

1) **SAPHINOPOPLITEAL INSUFFICIENCY**

2) **VALVE INSUFFICIENCY FROM THE SAPHENOFEMORAL JUNCTION UNTIL THE KNEE**

3) **INSUFFICIENCY THAT EXTENDS TO THE CENTRAL 1/3 OF THE LOWER LIMB**

4) **TOTAL INSUFFICIENCY UNTIL THE UNCLE**

<table>
<thead>
<tr>
<th>CEAP classification of chronic venous disease</th>
<th>Clinical classification</th>
</tr>
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<tbody>
<tr>
<td>C0</td>
<td>No visible or palpable signs of venous disease</td>
</tr>
<tr>
<td>C1</td>
<td>Telangiectasies or reticular veins</td>
</tr>
<tr>
<td>C2</td>
<td>Varicose veins</td>
</tr>
<tr>
<td>C3</td>
<td>Edema</td>
</tr>
<tr>
<td>C4a</td>
<td>Pigmentation or eczema</td>
</tr>
<tr>
<td>C4b</td>
<td>Lipodermatosclerosis or athrophie blanche</td>
</tr>
<tr>
<td>C5</td>
<td>Healed venous ulcer</td>
</tr>
<tr>
<td>C6</td>
<td>Active venous ulcer</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Etiological classification</th>
<th>Anatomical classification</th>
<th>Pathophysiology</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ec: congenital</td>
<td>As: superficial veins</td>
<td>Pr: reflux</td>
</tr>
<tr>
<td>Ep: primary</td>
<td>Ap: perforating veins</td>
<td>Po: obstruction</td>
</tr>
</tbody>
</table>
The S = Symptomatic, including ache, pain, tightness, skin irritation, heaviness, and muscle cramps, and other complaints attributable to venous dysfunction

A = Asymptomatic

Telangiectasis or reticular veins are: intradermal vein dilatations of 1mm or less, that may be localised or diffuse red purple or blue. They are found mostly in the thighs but also in other areas of the lower extremities.

Primary Varicose veins are: dilated veins that function abnormally. Anatomically they may be superficial or deep. They may also be secondary to insufficiency of the superficial or deep venous system or of insufficiency of the large perforators. It is known that the deep venous system may be subject of primary valvular incompetence but the superficial is mostly often affected.

Pigmentation / eczema: darkening of the skin (brown colour) resulting from extravasated blood most often found in the ankle region. Erythematous dermatitis that may progress to blistering and scaling, mostly found near areas with varicose veins.

Lipodermatosclerosis is: chronic inflammation and fibrosis of skin and subcutaneous tissue.

Atrophy blanche is: circular white atrophic skin areas surrounded by dilated capillaries.

THE aforementioned classification in 4 categories by HACH is formed in auction with the imaging methods of the saphenous vein

**Imaging methods -diagnosis of varicose veins**
clinical examination

Organised and meticulous inspection progressing from distal to proximal and from the front to the back. Physician must look for pigmentations, visible varicose veins, reticular veins, telangiectasis, eczema, white atrophy, corona phlebectasia and ulcers of the medial ankle. The surface of the limb should be palpated lightly in order to detect dilated palpable veins that are not visible. The sapheno-phemoral junction must be palpated as well as the posterior surface of the calf where the great and small saphenous veins are situated respectively. Finally by percussion it is determined whether two vein segments are interconnected or not. During this technique the patient must be standing and the physician with one hand perpetuates and with the other feels for a pulse wave at another position.

ultrasound

Doppler Continuous wave ultrasound can diagnose venous translucency and reflux in cases of valve failure.

Duplex (colour) ultrasound (Triplex) is responsible for finding the majority of cases with chronic venous disease of the lower limbs and used to confirm the clinical diagnosis. Also used to monitor the expansion of disease (varicosity) diagnosed cases. The imaging of the lower limb demonstrates also anatomical patterns of the veins but also venous blood flow abnormalities in the limb.
Computed Venography (CTV)

Computed tomography is another examination for the accurate imaging of varicose veins on the lower limb. The procedure enables excellent visualisation of varicose veins. The entire length of the great saphenous vein (GSV) was visualised and the 3D volume images are better when a thick subcutaneous layer, no skin changes and no subcutaneous oedema are present.

Magnetic resonance venography (MRV)

The magnetic resonance imaging for varicose veins offers similar results with CTV in assessing the size, extent, expansion of the veins and grounds, and has the additional advantage of being non-invasive. In the pelvic region this technique has shown to be more accurate than conventional venography. However the process is not tolerated by claustrophobic patients and the
limited availability and high cost is a consideration or second choice applies to patients whose CT scan is inappropriate (eg allergy obscuration).

Screening of finding varicose veins

There is talk of the advantages of implementing a national screening program to detect venous diseases. As the population ages the incidence of venous diseases increases dramatically. Because the prevalence of the disease is relatively high early detection could help people learn about the risks of these diseases and also lead to prevention. Recent studies in England have shown that a screening program could actually lead to a decrease in vein diseases by 50%. Other research groups suggest a screening program would have greater diagnostic performance would be even less expensive through the localisation of specific groups of high risk patients such as elderly female smokers. Regardless of the proposed an early ultrasound monitoring and a physical examination would help in early treatment of vein diseases, but requiring a wide application in many medical centres with sufficient numbers of patients to establish whether it is cost-effective approach to this disease. [9]

complications

The major complications of varicose veins are:

• bleeding
• thrombophlebitis
• deep vein thrombosis
• pulmonary embolism
• chronic venous insufficiency
• varicose eczema
• venous leg ulcers.
The most dangerous complication that occurs in a patient who leaves varicose veins untreated is deep vein thrombosis and pulmonary embolism.
SPECIAL SECTION

Treatment of varicose veins

1) Conservative treatment methods

Loss of weight
Exercise
Avoid standing or sitting for an extended period of time
Use of elastic compression
Administration of phlebotonic medication

2) Interventional treatment methods

a) Minimally invasive methods
Foam sclerotherapy
Endo-venous laser ablation

b) Surgical methods
Lateral ligation of sapheno-femoral junction or sapheno-inguinal junction and saphinectomy
Muller’s Hook phlebotomies (removing damaged venous branches through multiple small incisions and capturing varicose veins with special hooks)

SCLEROTHERAPY

Injection sclerotherapy is being used for more than 150 years for the treatment of varicose veins. The first attempt of sclerotherapy was done by Dr Zollikofer at Switzerland at 1682 at a patient to whom he injected an acid in his vein in order to create blood clot. Furthermore both Debout and Cassaignaic reported successful treatment of varicose veins with injection of
υπερχλωρίδιο υδραργύρου με ενδοσκληρυντική τεχνική. Unfortunately due to the vast number of side effects by the use of the drugs at that time sclerotherapy was abandoned. Foam sclerotherapy was invented in 1939 by MC Ausland for the treatment of telangiectasia, and in 1944 Egmont James Orbach proposed the use of foam just by mixing the liquid sclerant with air. Sodium tetradecyl sulphate (STS) is being used from 1946 for the treatment of varicose veins. Schneider and Fischer, in 1964, showed that endothelial damage is dependent on the concentration of hardening substances and occurs immediately after the injection, resulting in the rapid formation of a thrombus leading to vascular sclerosis. The regeneration of foam sclerotherapy is largely credited with the work of Cabrera et al in the 1990s after proposing the use of STS and polidocanol as a hardening agent for foam production. In 2000 a new technique for the manufacture of foam was proposed by Tessari, the "three-way tap technique" method, which was also named (Tessari method). The method of sclerotherapy is used to treat venous varicose veins and the popularity and acceptance of this therapeutic method has been greatly increased in the international vascular community. It is based on the injection of a hardening agent into the vein of the superficial venous mesh that is inadequate and the damage to its endothelium resulting in coincidence of the walls, the formation of fibrous tissue and eventually the subsequent vaginal obstruction. The most commonly used hardening agents are: polidocanol, sodium tetradecyl sulphate (STS) chrome-plated glycerin, hypertonic sodium chloride solutions. Sclerotherapy is done under ultrasound guidance, using vein-light or by direct inspection by injection of liquid or foam. Still new material is the special adhesives, which are introduced by means of a catheter in the vein that is inadequate. The liquid hardeners are diluted with blood as it diffuses away from the injection site, thus reducing the release concentration in the vein wall. The foam, on the other hand, shifts the blood and allows direct contact with the endothelium. Therefore, the efficacy of a given concentration of a hardening liquid can be enhanced with a foamed preparation. The air contained in the foam is homogeneous and makes it visible when injected under ultrasonic control. Variables such as the type and concentration of the hardener, the gas, gas-liquid ratio, bubble size and the time between preparation and use determine the efficacy of the agent. Small bubbles make the foam highly interactive, while large bubbles produce ineffective foam. Foam is usually produced using the Tessari method, with two disposable syringes and a 1:4 fluid-to-air (air) tripod valve.

EFFECTIVENESS: Cabrera et al published a clinical series of 500 patients with chronic venous insufficiency - varicose veins treated with sputum sclerotherapy and reported that after 3 years 81% of the major saphenous strains remained blocked and 97% of the surface varicose veins had disappeared. This required a sclerosis session in 86% of patients, two
sessions in 11% and three sessions in 3% of patients. There was no deep vein thrombosis or pulmonary embolism in this order.

**HARDENING SUBSTANCES**

The hardening agents cause chemical damage to the venous wall, mainly to the endothelium of the vessel and less to the middle tunic. This reaction depends on the type of drug, its concentration and the duration of its contact with the vessel wall.

**PHARMACEUTICAL SUBSTANCES USED IN SCLEROTHERAPY**

1) POLIDOCANOL (POL)

The most widely used FDA-approved use in sclerotherapy
POL consists of two components: a non-polar hydrophobdodecyclic alcohol chain and a polar hydrophilic polyethylene oxide chain
The average value of the ethylene oxide units is 9 (n = 1-24) (the average degree of polymerisation is n = 9)The average molecular weight is about 600
The average molecular weight of the ethylene oxide units is 400.
Advantages: safe and painless during infusion, low probability of tissue damage in low doses, very low rates of allergic / anaphylactic reactions
Disadvantages: it can cause hyper pigmentation. POL has many names such as: Polyethylene glycolmonododecylether, Polyethylene glycol laurylether, Polyoxyethylene lauryl alcohol ether, Laurylpolyethylene glycolether, Macrogol laurylether, Lauromacrogol-9, Laureth 9, Thesit®, Pistocain
ACTION: is membrane-active and interacts with protein / lipids of the cell membrane and destroys it by dissolving the proteins / lipids.

2) SODIUM TETRADECIL SULFATE (STS)
Commonly used synonym of the sodium salt of 7-ethyl-2-methyl-4-undecane sulphate authorised use in sclerotherapy. It is used in concentrations ranging from 0.1% to 3%
Advantages: FDA-approved, low allergic reactions, strong hardener
Disadvantages: possible necrosis and extravasation, broad-wound matting
ACTION: acts on the lipid molecules in the venous wall cells, causing inflammatory damage to the vein's inner lining and clot formation that eventually leads to cervical vein formation.
REACTION TO THE HYDRAULIC SUBSTANCE
2 minutes → total detachment of the endothelium

15 minutes → endothelial damage - endothelial necrosis

2 hours → microtubule formation
2 days → creation of a hard thrombus
18 days → capillary growth
8 weeks → capillary network organisation
9 months → shrinkage of the vein submitted to sclerotherapy
Study on Variglobin (Mancini 1980)

3) CHROMED GLYCERINE 72%
Category: alcoholic
FDA-non-approved use in sclerotherapy
Advantages: low overgrowth - pigmentation, necrosis and allergic reactions
Disadvantages: unapproved substance, is a weak hardening agent, severely painful in the infusion, causes hematouria at high doses

4) SODIUM CHLORIDE SOLUTIONS
Category: osmotic
FDA-approved use in the sclerotherapy method
Advantages: low chance of allergic reactions, widely available, rapid response
Disadvantages: unauthorised use, painful infusion, rapid dissolution, not recommended for facial veins

Indications - contraindications of sclerotherapy
As mentioned, sclerotherapy is a minimally invasive, transdermal method that involves the infusion of irritants - hardens into pathological subcutaneous veins, with the aim of damaging their endothelium, fibrosis, transforming them into fibrous strings and eventually eliminating them.
In particular, indications for the application of sclerotherapy include the treatment of:
larvae
mesh veins or small varices (1-3 mm) when there is no significant regurgitation
varices <3 mm that remain symptomatic after surgery
deficient or inverse infiltrative veins
bleeding varicose veins
large varicose veins with venous ulcers

Absolute contraindications:
signs of acute thrombosis / phlebitis due to increased risk of deep vein thrombosis
pregnancy (treatment should be postpartum)
allergy to polidocanol
permanently sedentary patients
severe and acute systemic conditions.

Related contraindications:
Diabetes
peripheral arterial obstructive disease (hamstrung index <0.9)
history of migraines
open oval forage because of the risk of micro-emulsions
known hyper-coagulability
fever
inflammation in the treated area
micro-angiopathy
neuropathy
asthma or strong suspicion of allergies
leg oedema.

TECNİQUES-PREPARATION OF LIQUID AND FOAM-USE OF SPECIAL GLUE

Liquid: Fluid-induced sclerotherapy is the method of choice to deal with most of the leg-teleangiectasis of the legs and phlebiectasis. Because of the risk of discolouration from phototherapy and laser therapy, fluid sclerotherapy is the most appropriate choice for Fitzpatrick IV, V and VI skin type patients.

Foam: The hardening foam contains the hardening agents, it aims to increase the exposure area and is mainly used for the treatment of larger veins. The foam is prepared before infusion by the Tessari method. According to this method, two plastic syringes are connected with a three-way stopcock. The foam is prepared by mixing the liquid hardener with 4 or 5 parts of air, after 20 injections from one syringe to the other, with a 30° gradient. This gradient narrows the passageway to the three-way stop cock, generates air gap and this leads to the creation of high quality foam.

The foam prepared according to the Tessari technique has a half-life of about 90 seconds. Therefore, the process must be completed within one minute before the foam dissolves. The hardening foam is sonic due to the small air bubbles it contains, which are easy to see with ultrasound duplex. The larger volume of the foam in relation to the fluid provides a greater contact surface, a more uniform coverage of the endothelial surface and the use of smaller volumes of hardener. Generally, veins of all diameters are suitable for applying sclerotherapy. However, it is mainly used for large diameter varicose veins. For the treatment of teleangiectasis or phlebiectasis, fluid sclerotherapy can be used, since no superiority of the foam in small diameter vessels has been established.

The concentration of the hardening agent used in each application depends on the size of the vessel and on the type of agent used.
The sclerosing fluid or foam (with or without lidocaine) is mixed in a syringe at the correct concentration for the vein to be used. The syringe is attached to a 27G or 30G (or butterfly) needle, which is angled to be inserted more easily into the vessel. The patient is in the Trendelenburg position during the infusion to avoid regurgitation in the veins injected. Once the area is cleaned, the needle is inserted into the vein and blood is drawn to verify that the needle is in the correct position and then the hardener is injected.

Below are more details about the use of foam in various cases.

Teleangiomas, phlebecuasis, varicose veins: A specific amount of curing agent is injected, which depends on the size of the vein. When larger and deeper phlebetacts are identified, they must be eliminated before the most superficial telesales. Veinlight is used to identify the phlebiectasis. The needle is removed and topical compression and kneading applied to keep the blood away from the lumen of the vessel and thereby aiding the dispersion of the hardening agent. Local compression pads (e.g., molefoam, sorbopads, dental bumpers) are mounted and tapered to maintain compression over the rest of the session.

Saphenous ablation: Sclerotherapy with foam to treat regurgitation in the major saphenous vein is done with ultrasound guidance. The saphenous vein is gated approximately from the middle to the circumference of the thigh with the needle pointing towards the foot end. The tip is lifted and hardened foam injected and when it reaches the saphonium junction, the infusion is interrupted. Aspirate with syringe and if blood returns, repeat the procedure until the soaked liquid is white, indicating that the sapphire is full of foam. Squeeze in the groin may be applied. A study evaluating a small number of this practice reduced but did not completely prevent the dispersion of foam. It is also probable that removal of the compression could lead to minor bleeds.

Perforator ablation: the sclerosing solution at the level of a dislocation that can be used to excise it or to treat surface veins associated with it (Fegan technique). This technique has been used with good long-term results and without significant complications, but requires user experience. After the UGS of the diatribes, duplex ultrasound (three to six weeks after sclerotherapy) should be performed to monitor and find recurrent recurrences that may lead to recurrent nerve ulcers.

<table>
<thead>
<tr>
<th>Indication</th>
<th>STS</th>
<th>POLIDOCANOL</th>
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<tbody>
<tr>
<td>varicose veins &lt;8mm</td>
<td>0.5% - 3%</td>
<td>1% - 3%</td>
</tr>
<tr>
<td>net veins 2-4mm</td>
<td>0.25% - 0.5%</td>
<td>0.6% - 1%</td>
</tr>
<tr>
<td>telangectasia 0.1-2mm</td>
<td>0.125% - 0.25%</td>
<td>0.25%- 0.6%</td>
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</table>
In larger areas, multiple infusions can be made in one session and this depends on the patient's tolerance. However, over 10 mL of glycerol / lidocaine / adrenaline solution should not be used in one session because patients may develop transient hematuria. There is no generally recognised maximum dose for NaCl or STS, but is recommended for the last dose of 120 to 300 mg. The process is completed either when the maximum amount of hardener has been introduced, or when all affected veins have been treated. Then a lightweight cap and compression socks or bandages (CobanTM, ElastocrepeTM, AceTM) are then applied for 48 hours. Immediately after the treatment, the patient has to walk for 20 minutes and on the day of treatment it is recommended to walk 2-3 times, from 20 minutes each time. Compression is maintained for about 2-3 weeks. Repeat infusions in the same area, which are often needed, should not be done for at least six weeks after the first treatment.

**Intraluminal block with cyanoacrylate adhesive**

Injection of cyanoacrylate adhesive for depletion of veins that are inadequate is a recently used method. Cyanoacrylate is a liquid adhesive used to treat varices in humans for over 20 years and was first used for endoscopic intravenous infusion in varicose veins. It is also used for the treatment of arteriovenous malformations. The mechanism is simple: blood and plasma activate the polymerisation of cyanoacrylate and as a result the target vein closes. When the glue is used endoscopically as a haemostat agent or embolisation is generally safe but some cases of bleeding and pulmonary embolism have been reported when using glue for the endoscopic treatment of digestive varices.

Wang et al. have shown that when the cyanoacrylate is mixed with lipidol and injected into rabbit veins, their vessels shrink immediately. Subacute vasculitis and a chronic granulomatous reaction occurred in a foreign body and within 2-3 months the fibrous tissue developed in the region. Min et al. report that 30 days after injection into pig veins, these were blocked and there was no evidence of re-transcription. Histologically it was found that dilated intercellular spindle cells replaced the intima and displaced the medium. At 60 days, the histological lesions included mainly partial fattening of the wall and fibrosis.

With regard to lower limb varicels, the use of medical glue without thermal energy is recent. VenaSeal Sapheonclosure system is commercially available in Europe since September 2012. The procedure is performed under local anaesthesia at the site of injection into the major saphenous, mid-tibia or thigh, with ultrasound guidance. The catheter is placed with an intravenous guide, with its edge 5 cm from the sphincter junction. No intravascular
tumescence anaesthesia is required when the cyanoacrylate is injected intravenously, as well as compression after the end of treatment.

**Adverse effects-complications**

Sclerotherapy, like any invasive method, is not free of complications. To date, skin hyper-pigmentation, local hirsutism, folliculitis, teleangiectatic matting, injection pain, dizziness, headache, skin fusion burns, swelling, urticaria, blisters, skin necrosis, superficial thrombophlebitis, nerve injury, transient visual disturbances, haematuria, systemic anaphylactic reaction, deep vein thrombosis and pulmonary embolism, as well as bronchospasm, cerebrovascular accident and myocardial infarction. However, its complications can be classified into three major categories:

1) Frequent and transient

2) Rare and self-limited

3) Rare and serious
### Categorization of Sclerotherapy Complications

<table>
<thead>
<tr>
<th>Type</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Frequent, transient</strong></td>
<td>Telangiectatic matting (10–30%), Postsclerotherapy pigmentation (10–30%), Pain with injection (HS), Urtication post-injection (worse with polidocanol)</td>
</tr>
<tr>
<td><strong>Rare, self-limited</strong></td>
<td>Cutaneous necrosis, Superficial thrombophlebitis, Nerve damage (saphenous, sural), Transient visual disturbances, especially in migraine patients, hematuria (using foam sclerotherapy, and using chromated glycerin)</td>
</tr>
<tr>
<td><strong>Rare, major</strong></td>
<td>Anaphylaxis, Deep vein thrombosis, pulmonary embolism</td>
</tr>
</tbody>
</table>

**1) Frequent and transient**

Skin hyper-pigmentation

The hyper-pigmentation of the skin following sclerotherapy involves the appearance and the presence of a caffeine-like skin on the skin following the course of vein treatment. Overdose occurs in 10-30% of patients, and usually occurs within the first 3-4 weeks and may last up to 6-12 months after surgery despite attempting to eliminate it. Although auto remission occurs in 70% of patients within the first six months, pigmentation remains even after the first year in 10% of patients. The appearance of pigmentation depends primarily on the size and location of the vessel, the type of hardening agent and its concentration, as well as the general condition of the patient, the type of skin, and other medications. Generally it is more common in larger than 1mm veins, as opposed to smaller veins and veins. There is also a positive correlation with the amount of curing.
agent injected, but it varies depending on the species (10-30% serum overdose, 11-30% polidocanol, STS 11-80%). "Patient" plays an important role in predicting the appearance of pigmentation. Total iron stores in the body, increased histamine susceptibility, elevated ferritin levels, and iron transport disorders have all been associated with an increased incidence of hyper-pigmentation. In addition, an increased incidence of complication has been observed in patients with dark skin, as well as in black and yellow patients, where it appears even with mild manipulations and requires at least 4-6 months until remission is observed. Pigmentation can occur at any point in the limb, with a greater frequency in the swelling area and the hammer area. This distribution is probably the result of increased vascularity sensitivity and intravascular pressure, and the difficulty of exercising continuous pressure after intervention in these increased mobility areas. It should be noted that it is possible to have pigmentation at the lower limbs already before treatment, especially if there was chronic disease or was followed by stopping dermatitis. Therefore, a thorough pre-operative check is necessary to avoid confusion during followup. Aetiology often involves a combination of inflammatory pigmentation and direct haemosidirin deposition. Initial histological testing demonstrates the presence of hemosiderin, regardless of the type of hardening solution. Hemosiderin enters the epidermis by extravasation after rupture of the veins under treatment. Auto pigmentation is also common in patients with chronic renal failure. Although no fully effective method for treating hyperpigmentation of the skin following sclerotherapy has been reported, laser treatment appears to be most effective.

**TELANGIECTATIC MATTING**

Teleangitic matting involves the appearance of a complex of intact red veins around the vein where sclerotherapy was performed. It is probably due to neovascularization in the area and is observed in 15-24% of patients. It is often associated with a faster infusion or higher amount of hardener. It is more frequent in female patients, but this does not rule out the appearance in males. It is a factor of confusion for both the patient and the doctor, however, as well as pigmentation, usually self-limiting, within 3-12 months of surgery, but it may remain. It may be associated with a persistent burning sensation and oedema of the limb in which sclerotherapy was performed. It is usually seen in the middle and on the back of the thigh, as well as in the gastrocnemius. The area of the inner side of the thigh just above the knee is the most
common occurrence. This distribution may be due to knee motility, which causes rapid changes in venous flow, or relative hypoxia of the area during sleep, for example: due to pressure from the other end. In case of a stay, the matting can be controlled either by further sclerotherapy in feeding veins or by transdermal laser, as well as by a combination of methods.

of the most decisive factors for the survival of patients with ruptured abdominal aortic aneurysm undergoing restoration and open for patients

B. Rare - self-limited

URTICARIA

Local urticaria is a common complication of sclerotherapy and is most likely to represent a localised histamine response to vascular injury. Indeed, swelling and erythema develops within a few minutes of infusion, in a perivascular pattern. Itching and redness recede within 4-24 hours. Patients with known history of dermographism and urticaria should have received mild antihistamine treatment in advance to mitigate the reaction. Preferred are 3rd generation antihistamines, which are free of the undesirable effect of drowsiness.

PAIN

A patient complains of limb pain following the injection of the hardening agent, especially when using a hypertonic serum solution that is osmotically effective. Typically, it is described as burning or cracking. It has not been observed with the use of other hardening agents, and therefore its use has been limited.

OEDEMA

It is a rare occurrence of sclerotherapy and can be prevented with good attachment afterwards.

SKIN NECROSIS

Fortunately, skin necrosis is a rare complication of sclerotherapy. It concerns local tissue damage that may occur around the infusion site as a direct result of the action of the hardening agent. The most common cause is the exudate of the substance in perivascular tissues. It is more common when a hypertonic serum solution is used, but it also appears with other hardening agents, except for polidocanol, in which the use of necrosis is a rare complication. It is mainly related to the misapplication of the method. Prognoses of imminent necrosis are immediate localised pain after injection, and prolonged paleness of the area. Another cause of necrosis is reported to be the regurgitation of the hardener through an unknown arteriovenous dysplasia causing necrosis of the tissue that is bleeding from the corresponding arteritis. Such necrosis can occur by injecting any hardening agent even under ideal conditions and regardless of the practitioner's experience. Other causes include excessive strain on the area and direct intra-infusion - which can of course be avoided if the technique is properly applied. The infusion should be discontinued immediately if the patient complains of sudden pain as the arterial paracentesis is far more painful than venous. Some cases have
been reported where the incorrect injection of hardener into an artery or larger artery caused extensive ischemia and limb necrosis. However, we know that in the majority of cases the meticulous application of sclerotherapy is the key to preventing necrosis. Skin necrosis is the main cause of malpractice after sclerotherapy. Topical massage, 2% nitroglycerin ointment, or a combination of these, may be included in the treatment. Immediate treatment with hyaluronidase (75 units in 3 ml) is recommended in the case of large volume extravasation or high concentration of hardening agent. Injections of saline, lidocaine or both have also been proposed. Strong attachment has been shown to reduce wound healing time. Once ulcerations are created, conservative treatment is recommended. No surgical exception is proposed. Indwelling purification with benzoyl peroxide or foaming water, enzymatic cleansing with local agents as well as vascular "socks" with Duo-derm can contribute to the faster apnea. More importantly, socks also reduce the pain associated with the ulcer. Small ulcers usually become self-infected within 4-6 weeks of the operation.

![Image of skin ulceration after sclerotherapy](image)

**OPTICAL DISORDERS**

Transient visual disturbances are observed in 2% of patients after sclerotherapy and are most likely dose-dependent. There is a correlation with both fluid and foam sclerotherapy, but more frequent is observed after using foam. Although as an adverse event they may manifest in any patient after surgery, they appear more often in patients with a previous history of migraine. Check-ups are likely to occur due to fragments of foam entering the optic nipple. It is recommended that these patients stay in supine position for a while not more than 30 minutes after foam injection to alleviate this complication.
Symptoms of visual disturbances and angina pain have been reported to be mitigated by the use of CO2 foams instead of simple air, ligation of the saphe-nofemoral interference, limb lifting.

Rare - major

ANAPHYLACTIC REACTIONS

Allergic reactions from the injection of hardener appear rarely (frequency ~ 0.3%). However, it is possible, and it is vital that an emergency protocol, resuscitation equipment, oxygen and appropriate medication (diphenhydramine, epinephrine, cimetidine, corticoids) are available to prevent such a major complication.

DEEP VEIN THROMBOSIS

Deep vein thrombosis is also an extremely rare complication of sclerotherapy, but it is worrying for patients. It occurs at a frequency of <2% in sclerotic sclerotherapy, and is usually associated with an infusion of a larger amount of hardener sufficient to damage the endothelium of the deep veins. Particular attention is needed to prevent this complication when the treatment is for veins of the femur and knee, as the function of the vessels in these areas cannot be substituted by flanking circulatory networks. Patients should be screened for any disorder of the gastrointestinal tract, and placed immediately under anticoagulation.

ARTERIAL EMBOLISM

A limit of 10ml has been proposed for the injection of total foam volume to prevent paradoxical arterial embolism. Between 1994 and 2012, only 13 incidents of paradoxical stroke after sclerotherapy were described. Four (4) of them concerned with fluid sclerotherapy while the remaining nine (9) were associated with sclerotherapy. Ten (10) of the cases described showed complete healing without long-term complications. The most common predisposing factor was right-left communication and, most importantly, the open owl (PFO). The prevalence of open oval foray is estimated at 25% in the general population. Paradoxical air embolism was observed in cerebrospinal fluid or even intracranial arteries of five (5) patients with direct ischemic stroke after sclerotherapy. There was hypothesis of paradoxical thrombus embolism in three (3) patients with delayed onset of ischemic stroke and current venous thrombosis. In the remaining five (5) cases, which included two sclerotherapies with fluid accelerating from the onset of cerebral ischemia symptomatology, no specific cause was identified. Patients with a history of cryptic stroke or a history of migraine with aura are more likely to develop neurological complications after sclerotherapy and preoperative screening and subcutaneous occlusion of the open oval foramen are recommended. Major neurological complications and post-injection strokes are rare, but have been reported. As a first-line remedy, direct ventilation of the patient with 100% oxygen supply and possibly hyperbaric oxygen chamber should be
considered. Factors that increase the risk of thromboembolic stroke include: large bubble size, oval foramen, impossibility to lift the tip as well as prolonged immobility after surgery, and use of more foam in one session. Fixed bubble size can be ensured by the use of commercially available ready-made micro-foam. Finally, replacing simple air with CO2 can reduce the risk of neurological complications.

COMPARISON OF THERAPEUTICAL EFFECTS AND COMPLICATIONS: FOAM-LIQUID

Differences in fluid-foam complications

Foam sclerotherapy has common all the unwanted effects of the method with fluid, however, foam-specific adverse effects have also been observed. These include pulmonary symptoms, visual disturbances and neurological signs (especially in cases of ovoid toad) and a higher likelihood of developing local venous inflammatory reaction and post-treatment pigmentation.

Comparison of sclerotherapy results Foam vs Liquid

In general, it has been observed that the foam is less harmful than the fluid in the event of extravasation (more air than a hardening agent), and extremely effective in hardening non-palpable venous varicose veins, as opposed to fluid. At the same time, it has proven its suitability for the major strains of the major and minor saphenous and for large primary varicose veins and relapses.

Short-term and mid-term effects of fluid sclerotherapy show a good response to varices of 1mm in diameter and greater, but the long-term success of the surgery depends heavily on the presence or absence of regression. Patients with deficient saphenous vein insufficiency have the highest recurrence rate. Kern et al reported sclerotherapy with fluid in spider veins and small varices in 96 patients. Those who had elastic socks for 3 weeks after surgery experienced successful results earlier than the rest 76%. Liquid sclerotherapy has poor results in major saphenous deficiency, however, sclerotherapy with foam has more encouraging results.

Rabe et al conducted a randomised, study to demonstrate the efficacy and safety of conventional sclerotherapy with foam in a deficient major saphenous vein. The 3% concentration foam was more effective than and equally safe with the 3% liquid to deal with the major saphenous deficiency.

Yamaki et al compared the effects of ultrasound-guided sclerotherapy with foam and that with fluid in 77 patients. After a one-year ultrasound examination, a full-blown 25-edge (67.6%) major saphenous outbreak, meaning a statistically significant difference from ultrasound-guided sclerotherapy with 7-point fluid (17.5%)

Recurrence of varicose veins was found in 3 patients (8.1%) in the foam method, and 10 (25%) in the fluid group at 1 year.

Cabrera et al report a 80% blockage rate at 4-6 years after using a micro-foam to treat a major saphenous deficiency at 415 lower extremities.
Coleridge Smith used 1% polidocanol, 1% STS, and 3% STS to make the foam used in saphenous stem deficiency, and 459 lower limbs were available for 6-month follow-up duplex retrospective. The major saphenous vein remained abolished in 88% of cases and the sapwood was 82%.

A review of the Cochrane library on sclerotherapy was published by Tisietal in 2006 supporting the current position of sclerotherapy in clinical practice, usually confined to the treatment of recurrences following surgical treatment. The efficacy of foam sclerotherapy in quality of life was recently published in a cohort study by Darvall et al. They pointed out that ultrasonographically guided sclerotherapy with major and minor saphenous veins leads to a significant improvement in the quality of life in both the general condition of the patient and his/her venous insufficiency for at least 12 months after surgery.

Our experience

From November 2017 to January 2018 patients referred because of unilateral symptomatic varicose veins were examined in the vascular outpatient clinic. History was taken physical examination was performed, allowing assessment of the varicose vein distribution.

All patients underwent Doppler ultrasound scanning to establish the extent of the saphenous vein incompetence. Patients were examined according to the UIP consensus document with the GSV diameter measured 3 cm below the sapheno-femoral junction and venous reflux defined as retrograde flow lasting for more than 0.5 s.

Inclusion criteria were: patients of either sex, age group of 16-70 years, presenting with saphenous vein insufficiency of state two and stage three.

Exclusion criteria were: deep vein thrombosis history, thrombophilia, acute thrombophlebitis, allergy to polidocanol, severe systemic disease, immobility, pregnancy, breast feeding, known patent foramen oval.

A total of 15 patients with symptomatic unilateral saphenous vein insufficiency underwent catheter directed foam sclerotherapy combined with saphenous vein ligation under local anaesthesia.

The procedure was performed outpatient theatre list, in a surgical theatre under total aseptic conditions. Before the treatment the patient undergoes Doppler ultrasound sonography and the incompetent (affected) vein is marked (mapped) with a blue medical skin marker pen on the skin. Under local anaesthesia, a transverse 3cm long incision was performed on the groin of the affected side. Dissection of the saphenous - femoral junction. Ligation of the major saphenous vein and its branches. Ligation of the sapheno-femoral junction. Palindrome supply of foam 4ml with a 6F-11cm sheath that was inserted centrally to the ligated saphenous vein. 1% foam insertion to several cutaneous branches of the saphenous vein. The foam sclerosis ant was generated using the Tessari method by mixing 2ml of 3% polidocanol solution with 8ml room air using two silicon silicon free syringes attached by a three way stopcock to obtain 10ml of foam. Closure and suturing of the groin incision wound. Compression of the lower limb with rolled gauze pads placed placed along the saphenous vein and secured in place with elastic bandage and a tight length compression garment type stocking. All patients were encouraged to mobilise fifteen to thirty minutes after the procedure (treatment) and were discharged approximately 3 hours after. The primary outcome was
decrease of complaints of chronic vein insufficiency and varicose vein symptoms was reported in 100% of the cases. Disappearance of varicose veins was also achieved in all patients. During the first follow up visit six weeks after the procedure, patients were examined to exclude deep vein thrombosis and to assess the desired rate of occlusion. Doppler ultrasound examination and clinical examination revealed signs of deep vein thrombosis in 1 patient. All other patients were asymptomatic, and had correctly occluded GSV.

CONCLUSION

If we accept that the clot collection in the treated vein and the transient hyper-pigmentation of the skin are not true complications but more likely consequences of sclerotherapy, we can say that its complications are rare and usually minor. However, adequate information of the patient about their likelihood is vital, and could be considered a success factor in the method.

Despite the abundance of publications on methods of venous varicose veins, there has not been a whole or the most optimal method. In fact, analyses mainly help in selecting the right treatment for each patient. For example, sclerotic sclerotherapy can be chosen as the most ideal method for a patient with relapsing varicose veins, while the surgical exception for someone with large elongated deficiency veins, bilaterally.

All widespread studies converge to the conclusion that complications are rare irrespective of the method to be followed, however, intraleural cauterisation, either lasers or radio frequencies (EVLA and RFA respectively) is likely to bring even lower rates of complicated complications and longer-term effects.

In terms of cost-effectiveness curve, foam sclerotherapy seems to be the most cost-effective alternative, as although multiple sessions may be needed, its materials are most economical.

References


19. Venous Insufficiency Guest Editor R. Torrance Andrews M.D.


21. Δασκαλόπουλος Μ.Ε. Υπερηχογραφικά καθοδηγούμενη σκληροθεραπεία με αφρό. Διάλεξη στο Διακρατικό Μεταπτυχιακό Πρόγραμμα «Master of Science στην Αγγειοχειρουργική», 1 Νοεμβρίου 2014, Αμφιθέατρο ΠΓΝ Αττικόν “ΑΡΕΤΑΙΟΣ”.

22. Λιάκου Αικατερίνη Η. Ανατομία, φυσιολογία φλεβικού συστήματος κάτω άκρων. Διάλεξη στο 11ο Πανελλήνιο Συνέδριο Δερματολογίας-Αφροδισιολογίας.