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ORIGINAL ARTICLE

Effect of polidocanol foam sclerotherapy for the treatment of venous ulcers: a randomized clinical trial protocol

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ABSTRACT

Objective: To evaluate the effect of polidocanol foam sclerotherapy in patients with venous ulcers (VU) undergoing clinical treatment with elastocompression.
Method: This will be a randomized, prospective, single-center, exploratory clinical trial with two parallel groups and 1:1 allocation. Participants aged 18-80 years with active VU and vascular Doppler ultrasound findings indicating chronic superficial venous insufficiency in both sexes will be included. Participants will be randomized into two groups: the Clinical group (undergoing conservative treatment with elastocompression) and Foam group (undergoing treatment of varicose veins with polidocanol foam associated with elastocompression). Thirty-four patients will be selected for each group. Participants in the Foam group will undergo superficial vein sclerotherapy using the Tessari technique, with the aid of ultrasound. Patients will be reassessed 30, 90, and 180 days after the intervention. The primary outcome will be lesion healing within 180 days. The secondary outcomes will be the VU healing time, rate of lesion area reduction, side effects, pain, quality of life (QOL) using the EQ-5D, and the Venous Clinical Severity Score. The data will be subjected to inferential tests and Kaplan-Meier survival analysis, assuming a significance level of 5%.

INTRODUCTION

Chronic venous insufficiency (CVI) comprises a set of clinical manifestations caused by an abnormality of the peripheral venous system, which may affect the deep and/or superficial systems due to reflux, obstruction, or both, usually affecting the lower limbs. It is a common cause of edema and pain, constantly associated with varicose veins, itching, a feeling of heaviness, and fatigue in the lower limbs, and may progress to more severe forms of the disease, with the formation of ulcers and skin lesions, which reduce the quality of life and functional status of patients[1].

Venous ulcers (VUs) are characterized by recurrent and long-standing loss of skin integrity[2]. They present with irregular borders surrounded by brown hyperpigmentation and are classically located on the lateral or medial malleolus of a routinely edematous limb[3]. VUs have an adverse effect on quality of life, causing morbidity and distress, and placing a considerable socioeconomic burden on the public and private healthcare system[4,5]. This condition restricts individual function, work, and social life and affects up to 1% of adults in developed countries. This proportion increases to 4% among people over 65 years of age[6,7].

Many treatment options are available, including compression stockings, surgical ligation of the saphenofemoral junction with removal of the great saphenous vein, and minimally invasive procedures, such as radiofrequency ablation, endovenous laser ablation, and sclerotherapy.

Compression has been recommended as the initial therapy for CVI. However, low-quality evidence suggests that

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compression stockings are effective for treating varicose veins in the absence of active or healed venous ulcers[8,9].

The discovery by Tessari et al.[10] of a simple method of forming sclerosing foam using two syringes connected with a three-way stopcock has improved the results of sclerotherapy and allowed its use in everyday practice, and it is increasingly used as a first-line treatment for this disease. The foam is visible on ultrasound, which allows controlled obliteration of large veins under imaging control.

Foam sclerotherapy has been considered particularly attractive because it avoids the need for anesthesia, hospital admission, and long recovery times, is a low-cost procedure with faster recovery and minimal discomfort, and evidence in the literature shows its efficacy and safety. The procedure is performed under ultrasound guidance and involves the injection of a chemical agent (sodium tetradecyl sulfate or polidocanol) that acts more intensely on the intima because of its homogeneous distribution over the surface of the endothelium[11]. This action leads to the occlusion of the treated vein, removing its contribution to chronic venous hypertension, with subsequent healing of the ulcer and prevention of its recurrence[12].

Although well documented for treating venous disease, published studies have primarily focused on the rates of occlusion of treated veins and the remission of CVI symptoms. Furthermore, most studies published in developed countries with greater public funding for health focus on the use of ablative therapies (laser and radiofrequency), to the detriment of the accessible and inexpensive method of foam sclerotherapy. Finally, no previous randomized study has compared foam sclerotherapy with or without elastocompression for VU healing. It is extremely plausible that combined sclerotherapy and elastocompression allows for higher rates of VU healing compared with elastocompression alone.

Objectives

To evaluate the effect of sclerotherapy with polidocanol foam on UV healing in patients with CVI undergoing clinical treatment with elastocompression.

METHODS

Design

Single-center exploratory clinical trial with two parallel groups, 1:1 allocation, and blinding of the researchers responsible for measuring the main outcome. One group (Clinical group) will use only elastocompression (elastic bands), and the other (Foam group) will undergo treatment of CVI with polidocanol foam in the superficial venous system, associated with elastocompression. Elastocompression will be performed daily for 6 months in both groups.

Study location

Vascular Surgery Outpatient Clinic of the Hospital de Clínicas de Itajubá (HCI), located in the city of Itajubá, Minas Gerais, Brazil. HCI is a quaternary hospital that is a reference in the macroregion of Southern Minas Gerais for high-complex cardiovascular surgery and is directly responsible for serving the Microregion of Alto Sapucaí, which has approximately 300,000 inhabitants.

Eligibility criteria

Inclusion criteria

CVI classified as CEAP C6 (active venous ulcer) by vascular surgeon;

Vascular mapping ultrasound with Doppler indicating chronic superficial venous insufficiency (varicose veins, reflux of saphenous and/or perforating veins);

Not having undergone previous surgical treatment of varicose veins;

Age between 18 and 80 years, of both sexes.

Exclusion criteria

Polidocanol allergy;

Bronchial asthma;

Lack of agreement and signature of the free and informed consent form (TCLE);

Contraindication to the use of anticoagulants;

Coagulation disorder (INR > 1.5; platelets < 100,000)

Peripheral arterial occlusive disease (ankle brachial index < 0.8);

End-stage renal disease (CrCl < 15 mL /min);

Pregnancy;

Liver disease with cirrhosis;

History of recent deep vein thrombosis;

Immobility or confinement to bed;

Inability to receive outpatient care;

Heart failure - New York Heart Association classification II or III;

Infected ulcers or locoregional infectious cellulitis.

Lack of understanding of the therapeutic proposal;

Active neoplasia;

Diabetic foot (peripheral neuropathy or plantar ulceration).

Expected non-use of elastic band;

Documented or presumed thrombophilia ;

Nonrecanalised subacute or chronic deep vein thrombosis.

Hypotheses

The null hypothesis (H_0) is that there will be no differences in the healing rate between the Clinical and Foam groups at 6-month follow-up.

The alternative hypothesis (H_1) is that the Foam group will have a higher healing rate at 6 months than the Clinical group (one-tailed).

Sample size

We estimated that 93% of patients treated with foam sclerotherapy will have their VU healed, whereas only 68% of patients submitted to elastocompression alone[13]. The sample size for each group (Clinical and Foam) considering statistical proportions for the outcome "healing in 6 months", with a test power of 80%, assuming a significance level of 5%, is 30 patients for each group. Assuming a loss of 10% of participants during follow-up, a minimum

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Chart 1 – Chronogram.

Stage	2nd semester 2023	1st half 2024	2nd semester 2024	1st semester 2025	2nd semester 2025	1st semester 2026
Preparation of the protocol	X					
Ethical approval	X					
Randomization and allocation		X	X	X		
Follow-up		X	X	X	X	
Data analysis						X
Disclosure of results						X

recruitment sample of 34 is estimated for each group. The sample size was calculated using G*Power software v. 3.1.9.4 (Universität Düsseldorf).

Recruitment

Patients treated at the HCI vascular surgery outpatient clinic will be covered by the Unified Health System and will be referred from primary healthcare units. All patients who meet the inclusion criteria will be approached, and the reasons for the study will be explained during their routine or initial consultation. After agreeing to participate in the study, signing the informed consent form, and applying the exclusion criteria, the selected patients will undergo randomization.

Randomization

Participants will be randomly selected for each of the two treatment groups through Randomizer (randomizer.org) to generate random numbers (1 or 2). Participants drawn in number 1 will be allocated to the Clinical group. Participants drawn in number 2 will be allocated to the Foam group. This process will be carried out until the 68th participant is reached.

Allocation and blinding

Each patient will be allocated at a 1:1 ratio to their respective intervention groups and entered into a data acquisition spreadsheet.

There will be no blinding of the participants. The trained researchers performing the vascular Doppler ultrasound of the participants will be blinded. The data from the examination (performed following a specific study protocol) will be included in the CRF RedCap.

The researchers responsible for the statistical analysis will not contact the participants and will only have access to the data at the end of the intervention and monitoring stages.

Elastocompression

Compression therapy is a fundamental part of CVI treatment, particularly in more severe cases involving edema, inflammation, or ulcers. Patients will be prescribed elastic compression bandages measuring 13 cm wide × 2 m or 3 m long, depending on the size of the treated leg. Patients will be instructed to apply the bandage daily over the dressing. The bandage will be used in the morning and will last until the end of the day. Patients will be taught how to bandage the affected limb from the toe to the proximal third of the leg.

Foam sclerotherapy

All sclerotherapy will be performed on an outpatient basis on a previously scheduled date. The patient will remain in the supine position with the limb elevated during the foam infusion. The puncture will be performed in the saphenous vein (great or small, according to the reflux mapping performed prior to the treatment) with a Jelco ® needle (number 18 G) or butterfly needle (number 21 G or 23 G), chosen according to the depth of the vein selected for puncture, guided by ultrasound. Local anesthesia using a "button" of 2% lidocaine without a vasoconstrictor will be used only to avoid pain during the puncture. The preferred puncture site will be where the vein is closest to the skin, in the distal third of the thigh or the proximal third of the leg. A mixture of 2 mL of 3% polidocanol and 8 mL of room air will be used, with foam produced using a three-way stopcock connected to two 10 mL screw-type syringes (Tessari technique) injected into the punctured vein, always with ultrasound monitoring. The volume of the mixture per session will be limited to 10 mL[14].

Vascular ultrasound

A vascular ultrasound examination with Doppler mapping of the veins of the affected limb will be performed, where the diameters of the superficial and deep veins, as well as their patency, compressibility, and flow direction will be recorded. The examinations will be performed by a vascular surgeon with at least 2 years of experience in vascular ultrasound.

Criteria for discontinuing the study

The criteria for study participant discontinuation include severe bleeding, patient refusal, serious disease discovered (e.g. cancer), loss of follow-up, ulcer evolving to malignancy, and death.

Criteria for discontinuing the study

The study will be interrupted if at least 70% of the estimated sample is not recruited after 2 years of study.

Outcomes

Primary outcome

The primary outcome will be the occurrence of VU healing after 6 months of follow-up.

Secondary outcomes

Ulcer healing time: period in days after treatment in which VU healing occurs.

Ulcer area reduction rate. The ulcer area will be calculated using a smartphone application before and during follow-up at 30 days, 3 months, and 6 months after treatment. The obtained result will be measured in cm^2/month.

Adverse effects. The presence of hyperpigmentation, allergy, deep or superficial vein thrombosis, bleeding, or any other signs/symptoms reported by the participant will be assessed.

Pain. Assessed using a score of 0 to 10 on a visual analogue scale, after 30 days, 3 months and 6 months of intervention.

Assessment of quality of life. The results will be assessed using the EQ-5D© scale (EuroQol, The Netherlands, euroqol.org) before and during follow-up at 30 days, 3 months, and 6 months posttreatment.

Severity score assessment. It will be assessed using the Venous Clinical Severity Score (VCSS)[15] before and during follow-up, at 30 days, 3 months, and 6 months after treatment. The VCSS is scored from 0 to 24, where 0 indicates the least possible severity, and 24 indicates the worst possible.

Data collection

Participants will answer a protocol with structured questions and will be examined by HCI vascular surgeons. Clinical history and physical examination will be performed to assess the distribution of varicose veins and classification as well as attribution based on clinical signs, etiology, anatomy, and pathophysiology (CEAP)[16] of the disease and the Venous Disease Severity Score (VCSS). Data will be entered into a cloud-based spreadsheet (Google Sheet®) shared exclusively with the study researchers (Chart 1).

All selected patients will receive detailed information related to the use of elastic bands and ultrasound-guided polidocanol sclerotherapy.

Monitoring

There will be no data monitoring committee since the intervention will occur at a single point in the study, and the post-intervention follow-up will only be observational.

Statistics

Prism v.10 software (San Diego, CA, USA) will be used. The intention-to-treat principle will be considered. Pearson's chi- square test will be used to compare categorical variables. Student's t-test. The one-tailed and Mann–Whitney tests will be used to compare continuous quantitative variables, with normal or non-normal distribution, respectively. To establish actuarial curves for wound healing, patency, survival and limb salvage, we will use the Kaplan-Meier survival curve. The Log Rank test will be used to compare the curves. The significance level will be set at 5%.

Ethical approval

Ethical approval for this study was obtained from the Research Ethics Committee of the Itajubá School of Medicine (CAAE: 79577917.6.0000.5559, opinion number: 2,384,578). The universal trial registration number is U1111-1297-1789.

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