PILOT STUDY OF CYANOACRYLATE OCCLUSION OF THE LOWER LIMB VEINS IN PATIENTS WITH VENOUS ULCERS– FINAL PROTOCOL

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BACKGROUND / RATIONALE

Minimally invasive techniques are now routine for the treatment of lower limb varicose veins. Endovenous laser therapy and radiofrequency ablation enable lower limb venous occlusion to be performed under local anaesthesia, minimising operative risk and reducing healthcare costs. However, both techniques generate heat which may injure adjacent nerves, risking long term disability. Non-thermal venous occlusion technology avoids the need for tumescent local anaesthesia and further reduces both risk and healthcare costs.

The Medtronic VenaSeal™ system uses an n-2-butyl-cyanoacrylate adhesive to occlude incompetent veins. It does not require local anaesthetic tumescence and there is very low risk of peripheral nerve injury. The delivery catheter is introduced into the target vein under ultrasound guidance, and slowly withdrawn as the adhesive is injected. Manual compression is applied to each treated segment of vein for 30 seconds to ensure adhesion.

The current literature suggests that cyanoacrylate embolization is a safe, effective treatment for lower limb venous incompetence. One randomized control trial in patients with varicose veins has been completed and demonstrated that cyanoacrylate embolization was as effective as radiofrequency ablation in maintaining great saphenous vein occlusion 3 months post-procedure.[1] Non-comparative studies with longer follow-up periods have shown recanalization rates of less than 8% during the first year after treatment.[2,3] In addition, Venous Clinical Severity and Aberdeen Varicose Vein Questionnaire scores were significantly improved following cyanoacrylate treatment and were similar to scores in patients treated by radiofrequency ablation.[1] Patients in the other clinical studies also showed an improvement in symptom scores.[2,3] Importantly, adverse effects were minimal, with mild phlebitis reported in 6-16% of patients.[1-3] No patients in any study developed deep vein thrombosis or pulmonary embolism [1-3] and only 1/222 patients in the randomised trial developed an injection site infection, successfully treated with oral antibiotics.[1]

There has been no research on the value of cyanoacrylate embolization in the treatment of patients with chronic venous insufficiency and ulceration. Venous leg ulceration costs the NHS £600 million per year and affect 1.7% of the elderly population[4,5], making it a significant health problem that justifies further study.

We propose to define whether cyanoacrylate embolization is a safe and effective method of occluding incompetent lower limb veins in patients with venous ulceration of the lower limb.

PRIMARY OBJECTIVES

Our primary objectives are to answer the following research questions:

1. Does VenaSeal™ cyanoacrylate occlusion of incompetent lower limb veins increase the rate of healing and shorten healing time in patients with an ipsilateral venous ulcer?

2. What is the incidence of venous recanalization following VenaSeal™ cyanoacrylate occlusion for the treatment of ipsilateral venous leg ulcer?

3. Does VenaSeal™ cyanoacrylate occlusion of incompetent lower limb veins improve quality of life and symptom severity scores in patients with venous leg ulcer?

4. What is the adverse effect profile of VenaSeal™ cyanoacrylate occlusion of incompetent lower limb veins for the treatment of venous leg ulcers?

The overall aim of the research is to determine whether VenaSeal™ cyanoacrylate occlusion of incompetent lower limb veins is an effective, safe and acceptable treatment in patients with ipsilateral venous leg ulcer.

STUDY DESIGN

This study is a randomised controlled trial comparing VenaSeal™ cyanoacrylate occlusion plus normal treatment with normal treatment alone in patients with ipsilateral venous leg ulceration and Duplex-detected lower limb vein incompetence.

Normal treatment in both groups is defined as nurse-led dressing of the ulcer using a low adherence dressing and four-layer compression bandaging. Patients randomized to the treatment arm will also undergo cyanoacrylate occlusion using the VenaSeal™ system.

The study will begin with 5 patients undergoing VenaSeal treatment as ‘roll in’ cases. Following these patients’ treatment, the study proper will begin. Randomisation software will be used to allocate patients who fulfil inclusion / exclusion criteria to either the treatment arm or the non-treatment arm. This will be done to a 1:1 ratio, with 25 patients in each arm.

Patients will be followed up via face-to-face consultations at 3, 6 and 12 months post-randomisation.

INCLUSION CRITERIA

1. Venous ulcer of the lower limb at least 2cm^2 (CEAP classification C6)
2. Ulceration present for >6 weeks and <6months despite treatment.
3. Ipsilateral lower limb vein incompetence of >0.5 seconds duration, confirmed by venous duplex imaging.
4. Aged ≥18 years.
5. Willing and able to provide informed consent.
6. Ipsilateral ankle-brachial pressure index ≥0.8 at the time of randomisation.

EXCLUSION CRITERIA

1. Non-venous cause of ulceration: peripheral arterial disease (ABPI < 0.8), vasculitis, neuropathy, recent lower limb trauma, chronic dermatitis, pyoderma gangrenosum, malignancy, chronic osteomyelitis or any other lower limb pathology that may be contributing to the ulceration, in the opinion of the investigator.
2. Inability to tolerate or comply with lower limb compression therapy
3. Inability to receive prompt endovenous treatment
4. Unwilling or unable to provide informed consent.
5. Current enrolment in another study pertaining to venous ulceration.
6. Primary or secondary immunosuppression.
7. Previous treatment of the target vein or other venous surgery that may compromise the study, in the opinion of the research team.
8. Patient has pre-planned surgical intervention or endovascular procedure scheduled up to 30 days after the index procedure.
9. Currently pregnant.
10. Duplex evidence of deep venous incompetence or occlusion.
11. Clinical evidence of post-thrombotic syndrome.
12. Incompetent vein considered too tortuous to allow VenaSeal™ treatment.
13. Inability to tolerate VenaSeal™ treatment.

PRIMARY ENDPOINTS

The primary outcome measure is the rate of healing in leg ulcer surface area. The margins of the ulcer will be traced onto an acetate sheet and measured using a planimeter[1]. From these weekly measurements (every 7 days +/- 2 days), it will be possible to calculate the

[1] The ulcer margins are traced onto a sheet of acetate. The acetate is then placed on a flat surface, and a planimeter is used to measure the surface area within the outlined margins. The planimeter is calibrated prior to use to ensure accuracy. For this study, a Planix 7 (Tamaya Technics, Tokyo, Japan) will be used.

rate at which the ulcer is healing. The time to healing (defined as complete overgrowth of the epithelial surface in the opinion of the researcher) will also be recorded. All measurements will be taken in duplicate by two members of the research team. The point at which the ulcer has healed represents the patient reaching the primary endpoint. Once healing has occurred, the patient will not be required to return to the clinic for weekly assessments, but will be asked to complete the questionnaires that measure the secondary endpoints at 3, 6 and 12 months (as described below), until the one year follow up period is complete.

Measuring rate of healing is important as it allows legitimate comparison between patients with differently sized ulcers. Time to healing is extremely important, as healing reduces the burden of symptoms and the impact on quality of life, and is the primary target for all patients and clinicians managing venous leg ulcer. Ulcer recurrence will not be assessed, as the follow up period is limited to 12 months.

PATIENT SAFETY

All patients will be treated in line with local and National Health Service (NHS) health and safety policies. All VenaSeal™ treatments will adhere to the Instructions For Use (IFU) supplied with the product. All patients will have immediate access to acute medical and surgical services provided by the University Hospital of South Manchester NHS Foundation Trust in the event of adverse effects or complications of treatment.

PROCEDURE / INTERVENTION DESCRIPTION

All patients will be randomised to receive standard venous leg ulcer management, or standard venous leg ulcer management plus VenaSeal occlusion of incompetent lower limb veins.

Patients randomised to the treatment arm will undergo cyanoacrylate treatment using the VenaSeal™ closure system (Medtronic, Dublin, Ireland), according to the Instructions for Use (IFU). The patient will lie supine on an examination couch, wearing a standard hospital gown. The skin will then be prepared using chlorhexidine gluconate 4% solution and a sterile field created with adhesive drapes. The operator will then use a portable ultrasound system to identify a target and will mark it using a sterile marker pen. The course of the target vein will also be assessed using the ultrasound probe. The skin over the target site will be infiltrated with 1% lidocaine with 1:200,000 adrenaline solution (maximum dose 7mg/kg) until sufficiently anaesthetised in the opinion of the operator and the patient.

Choosing the appropriate access site will depend on patient factors. Care must be taken to not enter the vein through an area of compromised skin, ulceration, and/or area of

infection. An access point near or at the ankle may be chosen, taking care not to choose a site immediately overlying bone. Regardless of access point, the goal is to treat as much of, if not the entire segment of pathologic vein. If the operator considers it possible to give additional injections over incompetent calf perforators with cyanoacrylate during the saphenous treatment, then that will be attempted. If low cannulation of the vein is not considered possible due to proximity with the ulcer, then this will not be attempted.

An additional aim of this study is to determine whether VenaSeal can be used as an office-based treatment without the requirement for adjunctive, theatre-based interventions. As such, foam sclerotherapy, phlebectomies and other adjuncts will not be used.

The operator will use Seldinger technique to gain access and position the VenaSeal™ delivery catheter into the target vein at the marked site. The catheter will be passed along the length of the target vessel that is required to be treated. The operator will confirm its position with the ultrasound probe. For GSV/AAGSV treatment, position the catheter 5 cm caudal from the saphenofemoral junction (saphenopopliteal junction for SSV treatment), and perform treatment according to the IFU.

Once the desired length of vein has been treated, the device will be withdrawn and the wound compressed manually until haemostasis has been achieved. A small dressing will be placed at the puncture site, followed by dressing of the venous ulcer with a low adherence dressing and four-layer compression bandaging applied by a specialist leg ulcer clinic nurse, aiming for a pressure of 40mmHg at the ankle and graduated towards the knee. Written advice will be provided to emphasise the need for patients to elevate their lower limb whenever possible, along with additional advice on how to manage the compression bandages. Patients will return to the leg ulcer clinic weekly to continue the usual leg ulcer treatment of wound care, dressings and compression bandaging.

Patients randomised to the non-treatment arm will receive the usual treatment for venous leg ulcer, specifically routine wound care, dressings, and the application of four-layer compression bandaging applied by a specialist leg ulcer clinic nurse, aiming for a pressure of 40mmHg at the ankle. The same written advice will be provided to this group. All compression bandages for patients in both arms will be applied by nursing staff who work in the specialist leg ulcer service.

If any participant requires further vascular surgical intervention, including treatment of perforators (e.g. treatment with ClosureFast™ RFS Stylet), then this will be arranged and offered as for any other non-research participant. The requirement for further interventions directly related to the patient's venous disease will be recorded by the research team, if it occurs within the 12 month follow up period.

SECONDARY ENDPOINTS

The secondary measures will be measured at baseline, 3, 6 and 12 months and are as follows:

1. The validated EQ-5D, SF-36 and VEINES-QoL scores[6,7] will be used to assess quality of life, self-assessment of health, and severity of symptoms in both groups. Venous leg ulcer is associated with reduced quality of life and prolonged, often severe symptoms, so this is an important assessment.

2. The rate of venous recanalization seen on duplex ultrasound is also important, to ensure that the venous occlusion has persisted.

3. Patient satisfaction scores

4. Adverse event recording will also take place, which is an important step in defining the safety of the procedure for this purpose. These will be described in the final report and in any other presentations of the work.

5. Health economic analysis:

a) Cost and frequency of visits to wound care and outpatient clinic.

b) District nurse visit costs

c) Inpatient treatment costs

d) Costs of complications of the treatment, or of non-healing ulcers (for example, acute or chronic infections).

STATISTICAL METHOD / RATIONALE

The main aim of the pilot study is to inform a larger, more definitive study by assessing feasibility and describing the main outcomes for the patients in the study. As such, the main analysis will be summary statistics. Simple statistical tests will be used to compare the groups, though these analyses are exploratory and non-definitive since the study is a pilot and has a limited sample size.

Time from intervention to healing, one part of the primary outcome, will be described in the two randomised groups using medians, interquartile ranges and ranges (minimum to maximum), assuming the data will be non-normally distributed. The other component of the primary outcome, the mean % ulcer healed per week[2], will be calculated for each patient

[2] The mean % ulcer healed per week will be calculated up to the point where the ulcer has fully healed (the primary endpoint). No further measurements will be calculated after this point.

and summarised in the two groups using means, standard deviations and ranges, assuming the data will be normally distributed.

The secondary endpoints will also be assessed using descriptive statistics. The composite VEINES-QOL/Sym score will be calculated using the intrinsic scoring method detailed in the Bland et al. validation paper.[7] The composite summary scores will be described at each point they are assessed using means, standard deviations and ranges.

The rate of venous recanalization in each group will be summarised using frequencies and percentages. The number of adverse events and percentage in each group will be presented.

The statistical analyses used to compare the groups will be independent samples t-tests, Mann-Whitney U tests, and chi-squared tests.

In addition to the quantitative analysis, images will be collected from each participant. These may be photographs of the ulcerated limb, pre- and post-treatment, and / or ultrasound images generated during the investigation or treatment. These images will be stored anonymously and securely by Medtronic for educational and product development purposes. The images may also be used in dissemination of the study report, either in presentations to learned societies or in peer reviewed journal articles.

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