Research Protocol
Foam Sclerotherapy for Venous Leg Ulcers

Protocol serial number: RCT2022-1

Rationale:
Venous leg ulcers (VLU) have been reported to affect 0.06-2% of the population[1]. They are known to cause significant physical and psychological disability[2].

VLU can be caused by reflux within the superficial venous system, by reflux and/or obstruction of the deep venous system, or a combination of these. A key component of the treatment of VLU is compression therapy, which has received a level 1A recommendation in the current SVS guidelines[3].

The EVRA trial showed that early ablation of superficial venous reflux plays a positive role in increasing the number of patients who reached complete ulcer healing and reduced the time to ulcer healing[4]. There have been a number of publications[5-9] describing the successful use of foam sclerotherapy to obliterate the refluxing network of veins in the vicinity of the VLU or underlying the VLU. However, it has not previously been shown whether the addition of this technique to the obliteration of superficial venous reflux, the latter being the focus of the EVRA trial, impacts upon VLU healing.

Furthermore, there is no consensus on how to treat VLU associated with post-thrombotic deep venous system reflux or obstruction. Many authors have reported on the beneficial use of foam sclerotherapy to treat VLU in cohort studies. There has been only one randomized study comparing compression alone versus compression and foam sclerotherapy for the treatment of VLU. The authors of this study concluded that it failed to recruit a sufficient number of patients for meaningful comparison (total number of recruited patients was 40)[10].

Therefore, we recognize the need to conduct a prospective randomized study to assess the effect on VLU healing of foam sclerotherapy of the network of veins in the vicinity of the ulcer as an adjunct to obliteration of superficial venous reflux in primary superficial venous reflux patients, and as an adjunct to compression in post-thrombotic patients.

This study will include patients with open VLU caused by primary superficial venous reflux or post-thrombotic deep venous disease.

For the purpose of this study, the refluxing network of veins in the vicinity of the ulcer or underlying the ulcer bed will be termed “ulcer veins”. These are to be distinguished from pathological incompetent perforators in the vicinity of the ulcer.

Objectives:
- Primary objective:
    - To assess the effect of foam sclerotherapy of the ulcer veins on time to complete VLU healing

- Secondary objectives:
    - To chart the rate of ulcer healing at 3, 6, 9 and 12 months
    - To assess the rate of ulcer recurrence
    - To determine the length of time free from ulcers (ulcer-free time) during the first year after randomization
    - To report health-related quality of life
    - To describe the side-effects and complications of foam sclerotherapy

Inclusion criteria:

- Patients with active venous leg ulceration, classified as C6 in the CEAP classification, who have duplex or venography criteria of primary superficial venous reflux, or criteria of post-thrombotic deep venous reflux and/or obstruction, and who show a refluxing network of veins in the vicinity of the ulcer; "ulcer veins", and/or pathologic incompetent perforators.
- Age >18 years

Exclusion criteria:

- Pregnant and lactating females
- Age <18 years
- Peripheral arterial disease confirmed by ABPI <0.8, or a duplex scan showing significant peripheral arterial disease
- Do not show evidence of a refluxing network of veins in the vicinity of the ulcer; "ulcer veins"
- VLU >2 years duration
- VLU size >20cm in any dimension
- Participant unable to give informed consent

End points:

- Complete VLU healing at 3, 6, 9 and 12 months from the time of randomization
- Rate of ulcer healing as measured by the reduction in ulcer size during the study period
- Time free from ulcers (ulcer free time) during the 12-month period after randomization
- VLU recurrence during the study period (12 months)

Study design:
Prospective randomized controlled study

Ethics committee approval:
Pending

Methods:

- Patients with open venous ulcers (C6) will be assessed by duplex ultrasound scan for
    - Superficial venous reflux, and identify its source
    - Evidence of post-thrombotic reflux and/or obstruction, and characterize this
    - Evidence of refluxing "ulcer veins" and/or pathologic incompetent perforators in the vicinity of the VLU

- Cross sectional or invasive venography +/- intravascular ultrasound at the discretion of the treating physician, based the upon suspicion of proximal venous outflow obstruction
- Patients with open VLU and/or refluxing ulcer veins and/or pathologic incompetent perforators will be eligible for admission to the study
- Individuals meeting inclusion criteria will be offered a participant information sheet
- Written informed consent will be obtained
- Consented patients will be randomized into two groups:
    - Group A: Foam sclerotherapy for ulcer veins in addition to appropriate therapy
    - Group B: Appropriate therapy alone without foam sclerotherapy for ulcer veins
- Appropriate therapy:
    - Superficial venous pathology only: will be treated by ablation of the superficial venous reflux by surgery or endovenous techniques, in addition to treatment of incompetent leg tributaries by phlebectomy or foam sclerotherapy.
    - Superficial venous reflux associated with deep venous obstruction or reflux: treatment of the superficial venous reflux will be individualized and left to the discretion of the vascular surgeon in charge.
    - Deep venous obstruction and / or reflux: patients with iliac vein obstruction may be considered for iliac vein stenting. Otherwise, patients with deep venous pathology will be treated by compression.

- In all participants, the VLU will be debrided as clinically indicated and, if there is evidence of infection, a course of antibiotics will be prescribed according to the local standard of care
- Compression therapy will be provided by trained personnel according to the local standard of care. Multilayer elastic compression (two to four layers), short-stretch compression, compression stockings, and adjustable compression wraps are all deemed to be acceptable. Details of compression types used will be recorded
- **Foam sclerotherapy:** ulcer veins are identified using a linear US probe 7-10Mhz; polidocanol 0.5-1% mixed with gas in a ratio of 1:4 is used to fill the network of refluxing ulcer veins. A total volume of 5-10ml of foam is used per session. Patients are reviewed after 1 week. Foam sclerotherapy may be repeated after one week if the ulcer veins remain patent and the ulcer is not healed. Only two sessions are permitted per lower limb. Following foam sclerotherapy, foam compression is applied
- Ulcer dressing and re-application of compression is performed on a weekly basis until the ulcer is healed
- Following ulcer healing, grade II compression stockings or adjustable compression wraps are prescribed
- After complete healing the patient is followed up monthly by telephone to enquire about ulcer recurrence, and compliance with compression hosiery
- At completion of the study, the patient is reviewed in person

Sample size calculations:
Sample sizes were calculated at 90% power with alpha of 5%

The sample standard deviation of healing time in days was 26, with the 'worst case' recorded standard deviation being 39.4
The weighted average of healing time for compression only was 75.4 (based on N=1787)

The weighted average of healing time for compression + intervention was 47.3 (based on N=758)
This represents a large effect size of treatment and, even with the 'worst case' SD, would require a sample size of 42 - I feel this is optimistic, likely overestimates the effect size of the intervention and would result in an underpowered study

If, like EVRA, a 15% effect size was considered this would make the healing time estimate for compression + intervention 64.1 days, giving a sample size of 255 (using the 'worst case' recorded standard deviation of 39.4)
Allowing for a dropout rate of 10% and protocol violations the target sample size can be 300 set at patients

With the more lenient SD of 26, and the EVRA effect size of 15%, the sample size is 112

Allowing for a dropout rate of 10% and protocol violations the target sample size can be 130 set at patients

Quality of life assessment:
QoL questionnaire SF-12 Arabic version and VCSS

Documentation:
- A secure cloud based digital platform will be created
- Upon randomization, the following data will be collected for each participant:
    - Unique participant number
    - **Initial visit clinical assessment:** date, age, gender, clinical center, ulcer size in 2 dimensions, ulcer size as measured by Lesionmeter software, ulcer depth (subjective), ulcer location, ulcer side (right or left lower limb), ulcer duration, presence of pedal pulses, ABPI, history of DVT(s), history of venous intervention(s), type of venous intervention (surgery, ablation, foam, stent), date(s) of venous intervention(s), history of diabetes, HbA1C, BMI (weight and height), cardiac failure (including ejection fraction and NYHA classification), other co-morbidities
    - **Dressings and compression:** type of ulcer dressing and type of compression used; both recorded at each visit
    - **Duplex ultrasound findings:** details of superficial and deep system reflux and obstruction
    - **Foam sclerotherapy:** drug used, concentration, gas used, number of injections, foam volumes injected, number of foam sclerotherapy sessions, perforator treatment
    - **Follow up visits:** date, ulcer healed?, ulcer size in 2 dimensions, ulcer size as measured by Lesionmeter software, ulcer depth (subjective), foam side effects/complications
    - **Final visit:** ulcer healed?, ulcer size in 2 dimensions, ulcer size as measured by Lesionmeter software, ulcer depth (subjective), foam side effects/complications
    - **Telephone follow up:** date of date, date of recurrence if any, compliance with compression hosiery
    - **Ulcer photography:** at least one ulcer photograph at the first visit, and one ulcer or ulcer site photograph during the last visit

- **Proof of data credibility:** ulcer photography

Exclusion from trial:
Patient non-compliant with protocol
Participant withdrawal of consent

Financial support:
Self-sponsored

Principal investigator: Rashad Bishara

Investigators (Alphabetical):

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10. Sherif Essam
11. Wael Shaalan
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Time periods:
See attached Gwent chart

Expected outcome:
Foam sclerotherapy of the ulcer veins is expected to increase the number of healed ulcers, reduce the time to achieve complete healing, and reduce recurrence rate

Safety:
Any adverse events should be recorded and reported to the PI

Statistical and health economic analysis:
A comprehensive statistical analysis plan will be produced by the study statistician
Kaplan-Mayer curves will be created for both Group A and Group B, and will be compared for significance
The total number of patients who achieved complete healing in both groups will be compared
Analysis of variance or logistic regression analysis could be used to assess the effect of each variable on healing (age, gender, DM, BMI, ulcer size, and method of treatment)

A health economist will support a health economic evaluation of the study results

Publication:
Publication of the study protocol and results expected in high impact factor journals
Authorship: all investigators are expected to be co-authors, however the international rules for authorship will be observed[11]

Expected problems:
Recruitment: patients meeting inclusion/exclusion criteria; patients refuse to consent to randomization
Loss to follow-up
Operators deviate from protocol
Patient non-compliance with compression

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