Study Title: Outcomes of sclerotherapy of the ulcer bed compared to a combination of ablation and injections

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Background:
Venous ulcers are the most common cause of ulcerations that affect the lower extremities and are estimated to effect 1% of the American population[1]. They are responsible for more than 80% of lower extremity ulcerations[2-4]. Venous ulcers are most common in the elderly and in patients with a history of diabetes, obesity, varicose veins, blood clots, and edema of the lower extremities. Treatment is extensive averaging 6 to 12 months of continual therapy. Healing rates for these ulcers are poor and more than 50% of these types of ulcers are still unhealed after 9 months[5,6]. Over 70% of those patients will end up developing another venous ulcer within 5 years[1]. With these astounding numbers, it is imperative for early diagnosis and prompt treatment. Any underlying causes should also be assessed and determined at the time of diagnosis to help with healing and prevention.

Management of these ulcers has historically been compression treatment, stripping of the superficial veins, elevation of the effected leg, and exercise. Ablative superficial surgery along with compression is another form of treatment. Endovenous ablation is where the problematic vein is sealed off (generally the great saphenous vein (GSV) in the thigh or the short saphenous vein (SSV) behind the knee and calf). A catheter is fed up the vein from the ankle or knee level. It is carefully fed, using the aid of ultrasound, to the junction between the GSV and SSV. An electrical current or laser energy is passed through the vein wall causing the vein to contract and seal itself off. This procedure is quicker and less painful compared to the traditional operation of vein stripping. Early endovenous ablation of superficial venous reflux in addition to compression has resulted in shorter ulcer healing time and a reduction in the 12-month reoccurrence rate versus compression therapy alone[7,8].

Another popular form of treatment is sclerotherapy. Either a foam mixture or a solution is injected into the effected veins causing inflammation and scarring. Over time this leads to destruction of the veins. This treatment is also commonly used with compression therapy. This technique promotes rapid healing usually occurring within 4 to 8 weeks after the initial treatment and long term recurrence rates[9]. This route is much less invasive, quicker, and less painful than the historical procedure of vein stripping.

Although there have been several studies performed on the significance of endovenous ablation and sclerotherapy, there is very little data or evidence to support the effectiveness of endovenous ablation in addition to sclerotherapy and compression in the treatment of venous ulcers and their reoccurrence. There is also very little data on whether receiving sclerotherapy and ablation together at the start of treatment, has any benefit over receiving sclerotherapy at the start of treatment and conducting ablation at a later time.

Research Question
Do outcomes of sclerotherapy of the ulcer bed alone, differ from a combination of ablation and injections?

Specific Aims
Our specific aims for this study are as follows:

Efficacy:

1. To determine if receiving sclerotherapy and ablation along with compression therapy at the start of treatment (arm 1) has any benefit over receiving sclerotherapy at the start of treatment and ablation 3 months later along with compression therapy (arm 2) in the treatment of chronic venous ulcers.
2. To compare and determine which arm has improved scores for quality of life (using the VEINES-QOL/Sym questionnaire).
3. To compare and determine which arm has improved venous clinical severity scores (VCSS).
4. To determine ulcer outcome and need for retreatment in arm 1 versus arm 2.

Safety:

1. To determine which arm puts patients at greater risk of increased healing times in the treatment of chronic venous ulcers.

Methods
Patients who are treated at Jobst Vascular Institute (JVI) will be evaluated for potential enrollment in this prospective study. Those who qualify, or their legally authorized representative (LAR), will be approached with study information and informed consent. Patients, or their LAR, who agree to participate will be consented and enrolled in the study.

This will be a randomized clinical trial. Subjects will be randomly allocated to each group. There will be roughly equal number of subjects in each arm. Arm 1 will be patients receiving sclerotherapy and ablation at the start of treatment along with compression therapy. The patients in arm 1 will not receive any further treatment during the duration of the study. Arm 2 will be patients who receive sclerotherapy at the start of treatment along with compression therapy, and ablation 3 months later. All patients in arm 2 will receive ablation at their 3 month appointment. After ablation, the patients in arm 2 will not receive any further treatment for the remainder of the study.

30 opaque envelopes, 15 indicating arm 1 and 15 indicating arm 2, will be prepared by the study coordinator. Patients who agree to participate will select an envelope and treatment will be initiated based off of the arm that is selected. In the event of a participants early termination from the study, up to 5 study participants will be replaced in each study arm to help ensure an adequate number of subjects for analysis. The purpose of this study is to see if one treatment is more effective over the other in treating chronic venous ulcers.

Patients who participate will have ultrasound-guided sclerosant injected into the affected area. Half of the patients will only receive injections (arm 2) while the other half of the patients will receive injections along with ablation (arm 1). Patients in arm 1 will not receive any further

treatment during the remainder of the study. All patients will fill out a quality of life questionnaire (using the VEINES-QOL/Sym questionnaire) and complete the venous clinical severity score (VCSS) questionnaire prior to treatment. All patients will undergo compression therapy.

Patients will be seen weekly after treatment. Safety assessments will take place during these weekly appointments to ensure patient safety. After 3 months, patients will be brought in for another follow up visit. The 3 month follow up is considered standard protocol after these procedures to monitor for adverse events. Ulcer size, symptoms, healing rate, quality of life (using the VEINES-QOL/Sym questionnaire), and venous clinical severity score (VCSS) will be assessed. All patients in arm 2, will receive ablation at this time.

All patients will continue to be seen weekly to assess healing progress and to ensure patient safety. Six months following initial treatment, the patients will return for another follow up visit where ulcer size, symptoms, healing rate, quality of life (using the VEINES-QOL/Sym questionnaire), and VCSS will be assessed. Participation in the study will be complete after the 6 month follow up appointment. Patients will continue to see their physician for treatment, if needed, after their participation has concluded.

All treatments and appointments are considered standard of care and will be billed to the patients insurance.

Following completion of data collection (see study variables on attached excel sheet), analysis will be completed to identify study results. We will be analyzing the differences between the two groups in A. ulcer healing rate (comparison of means, generalized linear model), and B. proportion of healed ulcers (Chi square).

Inclusion/Exclusion Criteria

Inclusion Criteria:

- Patients18 years of age and older
- Patients who have saphenous vein reflux and a single venous ulcer of any size

Exclusion Criteria:

- Patients under 18 years of age
- Patients with multiple venous ulcers

How Human Subjects will be involved

All enrolled subjects will have ultrasound-guided sclerosant injected into the affected area. At the start of treatment, half of the patients will receive injections at the start of treatment and ablation 3 months later (arm 2) while the other half of the patients will receive injections in addition to ablation at the start of treatment (arm 1). All patients will undergo compression therapy following treatment.

Risks/Side-effects
During the **sclerosant injections**, some people experience minor stinging or cramps when the needle is inserted into the vein. The risks associated with the injection include, but are not limited to, bruising, raised red areas, small skin sores, darkened skin in the form of lines or spots, and multiple tiny red blood vessels. These side effects usually go away within a few days to several weeks. Other more serious side effects include, but are not limited to, inflammation, blood clot, air bubbles and allergic reaction.

For **ablation**, if local anesthetic is used, the patient may experience slight pinpricks as the anesthetic is injected. They may also feel slight pressure when the catheter is inserted. The risks associated with an ablation include but are not limited to, infection, blood vessel damage, swelling, pain over the treated vein, nerve damage, and bruising or bleeding at the puncture site.

Benefits
Patients may or may not receive any personal benefits from being in this study. It is anticipated that other people may benefit from the results of this study in the future.

Number of Subjects
Up to 40 subjects. The goal is to enroll 15 subjects in each arm. In the event of a participants early termination from the study, up to 5 study participants will be replaced in each study arm to help ensure an adequate number of subjects for analysis.

Confidentiality
All data will be kept private. The study team has taken steps to protect participant privacy. The research investigators cannot guarantee absolute confidentiality. Only the authorized people described in this application will have access to participant information and results. The ProMedica Health System Institutional Review Board also may have access to study records. Data will be stored in a password protected computer at a secured location with access limited to research staff. Patients included with this study will be assigned a unique identifier to maintain confidentiality and the de-identified data set will be used for analysis. Any reports regarding outcome data will be presented in aggregate, without any patient identifiers.

Dissemination of Results
Pending results, it is anticipated that significant findings will be submitted to peer-reviewed journals for publication and may also be submitted as an abstract to appropriate scientific meetings.

References:

1. Terrie YC, (2017). Recognizing and Treating Venous Stasis Ulcers. *US Pharm.* 2017. 42(2):36-39.

2. Agale SV, (2013). Chronic leg ulcers: epidemiology, aetiopathogenesis, and management. *Ulcers*, 2013:413604.

3. de Araujo T, Valencia I, Federman DG, Kirsner RS, (2003). Managing the patient with venous ulcers. *Ann Intern Med*, 138(4):326-334.

4. O'Meara S, Al-Kurdi D, Ovington LG, (2008). Antibiotics and antiseptics for venous leg ulcers. *Cochrane Database Syst Rev*. 2008;(1):CD003557.

5. Gabriel A. Vascular ulcers. *Medscape*. http://emedicine.medscape.com/article/1298345-overview#a6. Accessed November 1, 2016.

6. Fishman TD, (2007). How to manage venous stasis ulcers. *Podiatry Today*. 20(5).

7. Barwell JR, Davies CE, Deacon J, Harvey K, Minor J, Sassano A, et al. (2004). Comparison of surgery and compression with compression alone in chronic venous ulceration (ESCHAR study): randomized controlled trial. *Lancet*. 363(9424):1854-9.

8. Gohel MS, Heatley F, Liu X, Bradbury A, Bulbulia R, Cullum N, et al. (2018). A Randomized Trial of Early Endovenous Ablation in Venous Ulceration. *The New England Journal of Medicine*. 378:2105-2114

9. Bush R, Bush P. (2013). Percutaneous foam sclerotherapy for venous leg ulcers. *J Wound Care*. 22(10 Suppl):S20-2.