Electrical Stimulation as an Adjunctive Therapy to Increase Vascular Perfusion in People With PAD or PVD

Study Protocol and Statistical Analysis Plan

NCT04313985

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Study Title
Electrical stimulation as an adjunctive therapy to increase vascular perfusion and enhance healing in patients with chronic wounds associated with peripheral arterial disease: A prospective case-controlled double-blinded randomized cross-over pilot study.

OBJECTIVES (Primary & Secondary Outcome measures)
Primary Objective:
This study is designed to test the effectiveness of the Tennant Biomodulator® PRO electrical stimulation device (Avazzia), which uses BEST™ (Bio-Electric Stimulation Technology), in enhancing short-term perfusion at the wound site in patients with chronic wounds associated with peripheral arterial disease. The perfusion will be examined using the HyperMed's HyperView device.

Secondary Objectives:
This study is also designed to test the effectiveness of Avazzia in reducing bacterial burden at the wound site, enhancing overall wound healing, and improving patient's pain level. The bioburden and bacterial load will be assessed using quantitative deep tissue swabs from the wounds. Wound healing will be assessed by percentage decrease in wound size. Pain will be assessed using a numerical 0-10 visual scale.

BACKGROUND
Study Disease:
Chronic cutaneous wounds are defined as wounds that have failed to proceed through an orderly and timely series of events to produce a durable structural and functional closure. The main etiologies include diabetes, pressure, venous insufficiency, and peripheral arterial disease. Those afflicted experience decreased quality-of-life, pain, restricted mobility, loss of limb, and loss of life. The incidence is on the rise due to aging population and growing prevalence of obesity and diabetes. Approximately, 2% of the population in developed countries suffer from chronic wounds, and the care costs in the United States alone exceed $50 billion annually. Peripheral arterial disease constitutes estimated 20% of the chronic wounds. Arterial ulcers, also referred to as ischemic ulcers, are caused by poor perfusion (delivery of nutrient-rich blood) to the lower extremities. The overlying skin and tissues are then deprived of oxygen, killing these tissues and causing the area to form an open wound. In addition, the lack of blood supply can result in minor scrapes or cuts failing to heal and eventually developing tissue necrosis and/or ulceration. The primary goal of the treatment for arterial ulcers is to increase circulation to the area, either surgically or medically. Surgical options range from revascularization in order to restore normal blood flow to amputation and rehabilitation in extreme cases. It is needless to say that the surgical options are invasive and associated with high risk. As for non-surgical measures, modifying contributing factors can slow or stop the progression of the local ischemia. Additionally, there are boots and pumps available to augment perfusion to the affected limb. There is an apparent lack of effective non-surgical modality to treat this crippling health condition.

Study Devices:
* Tennant Biomodulator PRO electrical stimulation device (Avazzia): This study is designed to test the effectiveness of the Avazzia device, which uses BEST™ (Bio-Electric Stimulation Technology), in enhancing short-term perfusion at the wound site. Avazzia device is a microcurrent transcutaneous electro-stimulation device with proprietary frequency sets specified by Jerry Tennant, MD within the BEST platform control options. It is an easy-to-use, hand-held, AA battery-operated portable device for use at home or clinic. It applies charge and power to the tissue through electrodes where maximum power delivered to the load is controlled and limited, and an automatic shut off is implemented. The user can passively place the electrodes where indicated and apply stimulation for a set period of time. The user controls the output by selecting the preset mode and power setting. BEST™ devices produce unique microcurrent impulses transmitted through the skin to interface with the internal peripheral nervous system for the purpose of therapeutic intervention. With each response, the electrical properties of the tissue change. These changes in the tissue characteristics result in changes in the output. The device detects changes and indicates relative tissue reaction responses in a cybernetic feedback loop. BEST products are controlled by a high-performance micro-computer chip, which uses Avazzia proprietary software. These hand-held devices are FDA-cleared for the symptomatic relief and management of chronic, intractable pain. Additionally, there is data to suggest their effect in improving perfusion, as well as their disinfectant properties.

* We will examine perfusion using the HyperMed's HyperView device: HyperView is a handheld, battery operated, portable diagnostic imaging device that is used to assess tissue oxygenation without contacting the patient. Patented technology uses a proprietary spectrometer to measure light absorption in blood molecules to determine levels of oxyhemoglobin and deoxyhemoglobin and oxygen saturation in superficial tissue. The product is intended for use by physicians and healthcare professionals as a non-invasive tissue oxygenation measurement system that reports an approximate value of oxygen saturation (O_2Sat), oxyhemoglobin level (Oxy), and deoxyhemoglobin level (Deoxy) in superficial tissue. The HyperView system displays two-dimensional, color-coded images of tissue oxygenation of the scanned surface. Images and data provide hyperspectral tissue oxygenation measurements for selected tissue regions. The product is indicated for use to determine oxygenation levels in superficial tissues for patients with potential circulatory compromise.

For Clinicaltrials.gov Compliance:
The devices used in our study are both FDA-cleared.

Rationale:
It has been proven that improving arterial supply in patients with peripheral arterial disease would enhance the healing process of the associated wounds in this patient population. The preliminary data suggests that electric stimulation may enhance vascularization. Therefore, we hypothesize that electric stimulation may be beneficial in healing the wounds associated with peripheral arterial disease. We hypothesize that, based on previous data, Avazzia would enhance short-term perfusion, decrease bioburden, decrease pain, and improve overall wound healing. The scientific premise is supported by previous literature including those published by

Dr. Harikrishna K.R. Nair.

Study Design:
* The primary purpose for the study is “treatment”.
* The interventional model is “cross-over” where participants will receive one of two alternative interventions during stage 1 and the other in stage 2.
* There will be “two” intervention arms in this study.
* The study will be masked in a “double-blind” fashion, as both parties will be unaware of intervention assignment.
* The study will be “randomized”.
* The primary outcome that the study is designed to evaluate is “efficacy”.

Inclusion Criteria
* Age above 18 years
* Ankle Brachial Index (ABI) ≤ 0.7
* Chronic wounds associated with peripheral arterial disease.
* Failure to demonstrate clinically-significant healing after 4 weeks of conventional therapy.
* Subjects must demonstrate ability to understand and the willingness to sign a written informed consent document.
* Wound size ≤ 5cm diameter at widest point.
* We will include patients with clinical malnutrition but subject this data to subgroup analysis.

Exclusion Criteria
* Age younger than 18 years
* ABI > 0.7
* Wound size > 5cm diameter at widest point
* Active malignancy
* Clinical signs of infection at the wound site.
* Patients in need for immediate surgical revascularization including those with critical limb ischemia and/or wet gangrene.

Informed Consent Process
All participants will be provided a consent form describing the study with sufficient information for participants to make an informed decision regarding their participation. Participants must sign the IRB approved informed consent prior to participation in any study specific procedure. The participant will receive a copy of the signed and dated consent document. The original signed copy of the consent document will be retained in the research file.

Randomization Procedures
Upon enrollment, each patient will be randomized via sealed envelopes to one of the two study groups, treatment group and control group. The randomization process will be conducted by an independent clinic staff. Both patients and primary investigators will be blinded to the randomization status.

Study Timeline
Primary Completion:
The study will reach primary completion 6 months from the time the study opens to accrual.

Study Completion:
The study will reach study completion 7 months from the time the study opens to accrual.

TREATMENT PLAN
Study Design
To validate our hypotheses, we will conduct a prospective case-controlled double-blinded randomized cross-over pilot study. We plan to enroll total of 30 patients, 15 in the study group and 15 in the control group. All subjects will be assessed during the screening period for inclusion and exclusion criteria. Patients will be followed for total of two weeks. Patients will visit the wound clinic twice during the follow-up period for assessing outcomes, one week and two weeks after the initial enrollment. Study protocol consists of 5 steps:

- Step 1 (Take BEFORE-treatment data): document the wound size; take perfusion data before-treatment (using HyperView device); take a wound swab for bacterial measurement (tissue samples will not be retained and will not be used for future research); document the pain level; take a photograph of the wound.

- Step 2 (Apply study treatment protocol therapy): First, test the device and equipment before treating the patient. Verify the device, conductive electrode pads, and lead wires connections by letting the patient feel what the stimulation will feel like by placing the electrode pads on the hands of the patient, powering on the device, and increasing the power until the stimulation is felt. Then, turn off the device and move the pads to the treatment area on the patient. Explain to the patient that it is normal for some patients to not feel the stimulation due to the chronic condition of their wound. It is also normal for some patient's skin to become more sensitive during therapy so that while they may not feel the stimulation at first, it is possible that they will begin to feel it, and it may even become too strong and need to reduce the intensity power settings. The patients can do this themselves if the output becomes uncomfortable. Treat the patient's wound area as the following. Place self-adhesive, conductive electrode pads on either side of the wound on the skin where the pads are not placed in the open wound itself, but rather in the surrounding area with one pad on each side of the wound. Connect the pads to the lead wire to the Avazzia device. There will be two different sets of lead wires marked as A or B where A is for "good" lead wires for therapy and B is for "broken" lead wires for the control group. Turn on the Avazzia device and change modes to the **RSI** mode. Allow to run unattended for 15 minutes. Change modes to **Blue Stimulation** mode without moving any of the pads. Allow to run unattended for 10 minutes. The total duration of each treatment session per day will be 25 minutes.

- Step 3 (Take AFTER-treatment data): take perfusion data after-treatment; take a wound swab for bacterial measurement; document the pain level; take a photograph of the wound

- Step 4: One week later, patient assigned groups will be switched. The study will be repeated with cross-over fashion so that the patients that had real treatment repeat the test, but with broken lead wires. And patients who had broken lead wires get treatment with good lead wires.

- Step 5 (Take final data one week later): document the wound size; take perfusion data; take a wound swab for bacterial measurement; document the pain level; take a photograph of the wound

Criteria for Removal from Study

In the case of following events, the patient will be removed from the study and his or her usual care will be restored based on the conventional therapy: disease progression; unacceptable adverse events; patient withdrawal from study.

Alternatives

Patients in both study and control groups will continue to receive the standard-of-care wound therapy throughout the course of study.

Potential Adverse Events

Potential risks associated with Avazzia device is minimal, being limited to pain at the site of probe application, and/or temporary numbness of the peri-wound area.

Potential risks associated with HyperView device is negligible.

Potential risks associated with wound swabs is minimal, being limited to pain and/or minimal bleeding.

STATISTICAL CONSIDERATIONS

Assuming a 1-2% drop out, the estimated sample size is 30. The sample size will include a cross-over study design. We recognize that this sample size may not be sufficient to validate all primary and secondary end-points but would be sufficient to estimate trend and determine a more-accurate sample size for the larger scale study. A sample size for long-term benefit has not been calculated yet. This is a pilot study assessing improved perfusion. If findings demonstrate favorable trend, Avazzia will consider a larger study with appropriate sample size calculations consistent with assessment of long-term benefits.

Publication plans envisioned for this work

Results will be disseminated in relevant conferences (e.g. Wound Healing Society Annual Meeting) and peer reviewed journals (e.g. Wound Repair and Regeneration)