Study Protocol with SAP

Title:
Evaluating the Safety and Efficacy of Fractionated Carbon Dioxide Therapy in Postoperative Lower Extremity Wound Healing

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Purpose: This study will evaluate the efficacy and safety of laser therapy on postoperative lower extremity wound healing over 12 weeks. We will include adult patients who have underwent Mohs Micrographic Surgery on their lower extremities. Patients with poor immune systems, current pregnancies, uncontrolled diabetes, lower extremity venous or arterial disease will not be included in this study. After surgery patients will be randomized into two groups. One group will receive a single laser treatment immediately after their surgery on their wound while the other will not. The group not receiving laser therapy will undergo a sham laser therapy treatment. Immediately after therapy and 4, 8, and 12 weeks postoperative patients will have a follow up visit. During these visits patients wound size will be recorded, whether the wound has healed, a photograph will be taken, and the wound temperature will be measured. Patient will be given a diary to record any adverse events related to the wound and will fill out a quality of life survey.

Objectives (specific aims and hypotheses): We hypothesize that the AFL carbon dioxide ablative laser is a safe and efficacious treatment for lower extremity wounds that result from skin cancer surgery. We plan to test this hypothesis in 2 specific aims:

Aim 1. We will establish the safety and tolerability of the carbon dioxide AFL for postoperative lower extremity wounds. Patients with postoperative lower extremity wounds will be randomized to sham laser versus laser therapy. At designated time points 0-12 weeks after sham or laser treatment, patients will return to clinic for assessment of safety endpoints, including the incidence of wound infection and tolerability using a patient diary and health-related quality of life measured using a standardized generic questionnaire such as EQ. A sample size of 48 is appropriate.

Aim 2. Determine the efficacy of the carbon dioxide AFL for healing postoperative lower extremity wounds. We plan to randomize n=48 patients with post-surgical lower extremity wounds to sham versus carbon dioxide fractional laser treatment. We will determine the time to complete ulcer healing over a 12 week course of follow up. Completion of these aims will likely improve care for hundreds of thousands of patients with lower extremity ulcers by extending the use of ablative fractional lasers to a new population of patients. Future studies will be needed to address the efficacy of ablative laser technology in ulcers of other etiologies, and have the potential to impact the lives of many patients.

Study Design: Our study is a prospective, double-blinded, randomized, placebo-controlled trial evaluating the efficacy of fractionated carbon dioxide therapy in postoperative lower extremity wound healing. This study, including analysis and submission for publication, will occur from September 2018 to November 2020. Eligibility criteria will include patients older than 18 years, those with a lower extremity wound as a result of Mohs Micrographic Surgery at Saint Louis University Dermatology Des Peres, and a postoperative wound greater than 5mm in diameter. Patients must be able to understand the informed consent, willing to come to the office for treatments and capable of following posttreatment instructions. Exclusion criteria will include pregnancy, immunosuppression, uncontrolled diabetes (defined as >7% A1c in the last 3 months), peripheral vascular disease, venous insufficiency, or no desire/unable to undergo laser therapy. After informed consent is obtained, a screening visit will be performed on their Mohs surgery day and patient eligibility will be determined. Then, patients will be randomized 1:1 to a treatment or control group via computer software. One arm will receive carbon dioxide AFL

immediately postoperatively on the wound base. The second arm, which will serve as control, will receive sham laser therapy. Both patients will be given identical postoperative wound care instructions, including vaseline applied to the wound, nonstick pad to overlay the wound, and paper tape to secure the dressing. Additionally, patients will be advised to avoid baths and application of any other products to their wound. Patients will be given a diary to record observations about their postoperative wound and to note any adverse events.

Blinding: There will be one unblinded member of the team in this study which will be the clinician performing laser therapy or sham therapy, who will therefore not be involved in any data collection, but will be responsible for reporting any adverse events per IRB protocols at our institution. Other members of the research team member will be blinded to patient group assignment, and these members of the research team will collect data (see below) at subsequent visit. Additionally, patients will be blinded to treatment group. This will be achieved by having patients wear safety glasses which blind them and the wound site still anesthetized from the operation. Data collection will be done by a separate research team member who is blinded to the treatment groups.

Inclusion Criteria: Eligibility criteria will include patients older than 18 years, those with a lower extremity wound as a result of Mohs Micrographic Surgery at Saint Louis University Dermatology Des Peres, and a postoperative wound greater than 5mm in diameter. Patients must be able to understand the informed consent, willing to come to the office for treatments and capable of following post-treatment instructions.

Exclusion Criteria: Exclusion criteria will include pregnancy, breast feeding, immunosuppression, uncontrolled diabetes (defined as >7% A1c in the last 3 months), peripheral vascular disease, venous insufficiency, decompensated heart failure (NYHA class IV), peripheral neuropathy involving the treatment site, active cancer at the time of study enrollment excluding curatively treated skin cancer, and any underlying or current medical condition which, in the opinion of the Investigator, would interfere with the evaluation of the subject. or no desire/unable to undergo laser therapy. Immunosuppression will be defined as patients with HIV, AIDS, who have received an organ transplant, allogeneic bone marrow transplant, or peripheral stem cell transplant, and any other patients taking chronic doses of systemic immunosuppressive medication within 6 months prior to randomization. Examples of immunosuppressive medications include Tacrolimus, Azathioprine, Prednisone, or Methotrexate.

Patient Visits and Data Collection:
Patients will be seen at 4 separate visits to monitor safety and efficacy endpoints (4, 8 and 12 weeks post-operatively). The patient's initial visit will include preoperative screening for eligibility, informed consent procedure, and recording of past medical history and physical exam. Once the patient is deemed eligible, enrolled, and signed informed consent, they will be randomized to either carbon dioxide AFL therapy or sham laser therapy. After the patient undergoes Mohs surgery with the resultant ulcer (the defect that typically forms after Mohs), the patient will undergo either carbon dioxide laser versus sham laser therapy. We will determine presence or absence of complete healing, wound temperature, a digital photograph, quality of life, and adverse events at each visit. Healing will be determined by one of the licensed research team members and will be defined by complete epithelialization in the absence of scab/eschar.

Wound temperature will be recorded by noninvasive infrared thermographic camera. A digital photograph will be taken with a camera that has an attachment ensuring the same distance and angle at every visit. Quality of life will be determined by ED-5Q questionnaire. Adverse events will be recorded by eliciting an oral history and review of the patient's diary. Adverse events will be recorded as presence of absence of specific outcomes. Outcomes that patients will be directly questioned about include: crusting (scaly or thickened scar), swelling, burning sensation, xerosis at treatment site, pruritus at treatment site, infection, bleeding, hypertrophic or keloid scarring, burns, or color changes at treatment site. These data points will be collected at every visit, and adjudicated by a member of the research team blinded to the treatment group. Placebo treatment will consist of directing the laser system at the floor instead of the patient's wound site. The patients will be wearing safety glasses and will have their wound site still anesthetized from the operation therefore unaware if they are receiving the therapy. This group will serve as the control group to the treatment arm in the study.

Statistical / Data analysis: We estimate that 48 participants will be required to show a significant difference in time to 100% epithelialization between treatment and control during the 12 week study. A power analysis conducted in R(1) using the powerSurvEpi package(2) with alpha = 0.10 and beta = 0.20 suggested 24 participants per group or 48 total were required. We will employ various statistical techniques in addressing our study aims. For our first aim, efficacy: time to epithelialization will be modeled in a Cox regression as a function of covariates and treatment status. Temperature will be similarly modeled, but for these outcomes we will examine effects across time via a linear mixed model. For our second aim, safety: we intend to model incidence of infection as well as quality of life again across time using linear mixed models but this time based on non-inferiority comparisons. To address any attrition, we will employ per-protocol analysis. In the interest of safety, we plan to perform interim analyses at one month and discontinue the study if warranted.