A single center, double-blinded randomized placebo-controlled trial to evaluate surgical scars after treatment with fractional carbon dioxide rejuvenation laser therapy

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Table of Contents

Synopsis

This study evaluates the effect of a fractionated carbon dioxide laser on surgical scars of the face and neck over 12 months. Anyone with a surgical scar on the face and neck who has not had laser therapy may be eligible. The visits occur every three months for up to 12 months. Subjects will be randomly assigned to receive two high energy treatments or two low energy treatments. During the study visits, the scars will be photographed pre-treatment and the subject will complete a questionnaire to rate the scar. Three physicians will also evaluate the scar: one as a live assessment and the other two will evaluate the scars after each visit using photographs. Patients will receive their assigned treatment, obtain post-treatment instructions, and a diary to record redness, swelling, pain, itching, or other skin changes after treatment. Patients and raters will be blinded to which therapy level the patient receives until the 9-month visit (Visit #3) at which time patients will be unblinded and offered to have a third high energy treatment if in the high energy treatment group or to have two high energy treatments if in the low energy treatment group.

Study Timeline

The study will occur over 14 months. Our tentative timeline consists of recruitment and screening to occur in November 2016-September 2017. Study visits and data collection would occur between November 2016 and September 2017. Preliminary data analysis and publication of preliminary results would occur between August 2017 and March 2018. Final data analysis and publication would be between October 2018 and January 2019.

Introduction

In dermatology, the use of Light Amplification by Stimulated Emission of Radiation (laser) has revolutionized the management of various conditions including angiomas, vitiligo, wrinkles, and scars. (Omi, 2014 and Chapas, 2008) Scars result from sub-optimal collagen production during wound healing leading to topographical irregularities. In addition to impairing body image, these scars may limit functional recovery, compromise activities of daily living, and prevent return to work. To effectively modify these defects, any treatment must be capable of penetrating the epidermis and eliciting dermal remodeling at a depth of at least 1 mm. (Chapas, 2008) Laser ablation removes 20 to 60 µm of epidermis and heats a zone of connective tissue approximately 120 µm wide, resulting in vaporization of the upper layers of the dermis to create a wound bed optimal for new collagen and elastin formation. Re-epithelialization occurs over 7-to-14 days, thus rejuvenating the patient's skin. (Omi, 2014; Bordenorf, 2009; Chapas, 2008) The 10,600 nm carbon dioxide (CO_2) laser utilizes high energy at short durations to vaporize intra- and extra-cellular water, resulting in tissue ablation causing a substantial thermal injury to the dermis, reducing the likelihood of additional scarring (Chapas, 2008). The incorporation of fractional photothermolysis, first introduced by Manstein et, al. facilitates a controlled area of dermal injury creating cylindrical microscopic treatment zones (MTZ) of necrosis (Hong Li, 2010, Manstein et al, 2004). Sparing uninvolved normal healthy tissue, each wound is surrounded by healthy cells that can migrate towards the wound, allowing for faster healing by secondary intention (Manstein et al, 2004). The fractionated CO_2 laser is selective in that segments of tissue are effected, which translates into decreased recovery time (downtime) for the patient (Bordenorf, 2009). Therefore, by causing selective thermal injury in the skin, the CO_2 laser can stimulate collagen production and theoretically improve scar thickness, pliability, and texture.

The utility of the CO_2 laser was first examined in patients with wrinkles. In a split face

prospective cohort study of 20 Chinese women, blinded evaluators and patients agreed at one and three months post-CO2 laser resurfacing that the deep wrinkles on the faces of subjects were more shallow, pores smaller, texture more smooth, and skin appeared brighter compared to the untreated side. Additionally, there was a perpetual decrease in the roughness of treated skin by 9.72% on day 7 post treatment, 18.92% at 1 month follow-up, and 24.40% at 3 months assessed by a 3-D in-vivo imaging system (Hong Li, 2010). Likewise, CO2 laser resurfacing for acne scars yielded similar positive outcomes. Chapas et al performed an unblinded cohort study of 13 patients with moderate to severe acne scarring to evaluate change in acneiform scars following two to three treatments with ablative laser resurfacing with a 30 W CO2 Fraxel re:pair laser. She observed that subjects and investigators rated 26-50% improvement in atrophy and cheek scarring three months after laser treatment. Use of the Phaseshift Rapid In Vivo Measurement (PRIMOS) topographical skin imaging system demonstrated that the mean depths of scars improved by 66.8%. With higher energy levels (70-100 mJ) on deeper scars on the cheek after the second and third treatment, scars improved by 51-75% three months after the final treatment (Chapas et al, 2008). In another study using a cohort of 60 patients with various morphologies of acne scars over three years with 3-4 sessions, a blinded evaluator rated 67% of patients with good-to excellent improvement in their overall appearance compared to images of their pre-treatment status (Majid, 2014).

Our study is a prospective, randomized double-blinded placebo-controlled trial to evaluate the efficacy of fractionated carbon dioxide laser in improving surgical scars on the head and neck. Scar assessments will be based on objective changes identified with the Canfield Vectra M3 3D Imaging System and subjective changes identified with the Patient and Observer Scar Assessment Scale (POSAS), a validated scar scale.

Study Objectives/Primary and Secondary

The primary objective is to assess the efficacy of fractionated carbon dioxide laser in improving surgical scars. Objective assessment of the scars will involve the Vectra microtopographic imaging system to measure changes in the length of the scar. The Patient and Observer Scar Assessment Scale (POSAS) is a validated survey that will be utilized for subjective assessments of the vascularity, pigmentation, thickness, pliability, surface area, relief, pain, and pruritus.

The secondary objective will be to evaluate the tolerability of the laser, by assessing the severity and duration of known side effects of laser therapy such as erythema, edema, burning sensation, post-inflammatory pigment changes, infection, scarring, xerosis, pruritus, bronzing, and any other adverse events that arise following treatment. Patients will be given a 30-diary after each treatment to document this information.

Selection and Withdrawal of Study Subjects

Study Population

The study population will consist of 50 adult patients 18 years of age or older with surgical scars located on the head and neck.

Minors are not included due to the Mohs patient population being adults only who have undergone surgical excisions of skin cancers on the head or neck. Although participants are not

required to be patients in the Mohs clinic, scars and healing may be significantly different in children, making the data less reliable and difficult to interpret.

Inclusion and Exclusion Criteria

For the inclusion criteria, adult patients of all Fitzpatrick phototypes who have surgical scars of the head and neck will be screened for this study. There is no data to suggest that there is a difference in the appearance of older (more than 1 year old from the initial injury) and newer scars (at least 8 weeks after surgery) post-therapy. Most scars are fully mature at exactly 1 year from the date of the initial injury, so in the "older scar" cohort one may presume (in the absence of any confirmed findings in the medical literature) that any changes to these scars post-therapy will be an effect from the laser. The minimum age of the scar will be eight weeks from the initial surgery, as the scar has healed enough to determine if additional fine tuning may be helpful. In addition, standard practice is to allow a scar to heal for 8 weeks before laser treatment. Therefore subjects may be enrolled in the younger scar group if the scar is 8 weeks – 51 weeks from occurrence, and enrolled in the older scar group if the scar is 52 weeks or older from time of occurrence. We will aim to recruit 20 patients with old scars (10 of which will be in the high energy treatment group, and 10 of which will be in the low energy treatment group). In terms of statistical analysis, we will review whether there is a difference between the post-treatment measurements and appearance of older scars and newer scars. Patients must be able to understand the informed consent, willing to come to the office for treatments and capable of following post-treatment instructions.

In terms of exclusion criteria, patients who have had prior laser treatments to the face and neck, have a history of keloid formation, scars resulting from non-surgical etiologies (i.e. minor trauma), isotretinoin use in the last 6 months prior to study enrollment, and allergy to topical lidocaine will not be eligible for the study.

Minors are not included due to the Mohs patient population of adults only who have undergone surgical excisions of skin cancers on the head or neck. Although participants are not required to be patients in the Mohs clinic, scars and healing may be significantly different in children, making the data less reliable and difficult to interpret. Any patient who has a condition that the PI assesses may put the subject at significant risk, may confound the study results, or may interfere significantly with the subject's participation in the study will be excluded from the study. Pregnant subjects are not included in the study due to insufficient data on the safety of lasers in pregnant patients.

Subject Discontinuation or Withdrawal from Study Participation

Subject Discontinuation

At any time within the trial, subjects may discontinue participation. Subjects who do not complete the trial will be asked to identify the reason for discontinuation and this information will be documented. If the date that they elect to discontinue from the trial occurs shortly after a treatment (within minutes to 30 days after treatment), patients will be asked to return for a follow-up 3 months to evaluate for any significant adverse events. No treatments will be performed. Only photographs of the scar and rating of the scar by the patient and evaluators will be performed at this visit. Also, collection of the diary will occur at this visit. If subjects discontinue from the trial after 30 days, patients will be followed up via phone for the reason of their discontinuation and asked to return the diary as soon as

possible. In either case, subjects will be given the contact information for the research office in case they have further concerns regarding their participation in the trial.

There are no guidelines or endpoints by which early decisions regarding efficacy or lack of efficacy will be made for this FDA approved device. However, the PI could stop the study early if significant unexpected adverse events occur, or enrollment and retention is not adequate.

Screen Failures

Subjects who do not meet the eligibility criteria will be considered screen failures. Any documentation completed prior to the determination of their status will be placed in one of the containers for shredding in our facility. The reason for the disqualification will be noted and the subject will be included in the count for screened subjects for publication purposes.

Study Device: CO2RE Laser

This fractionated ablative laser is FDA approved for the revision of surgical scars. Access to this laser may also be obtained outside of the study.

Mechanism of Action

The 10,600 nm carbon dioxide (CO2) laser utilizes high energy at short durations to vaporize intra- and extra-cellular water, resulting in tissue ablation causing a substantial thermal injury to the dermis, reducing the likelihood of additional scarring (Chapas, 2008). The incorporation of fractional photothermolysis, first introduced by Manstein et, al. facilitates a controlled area of dermal injury creating cylindrical microscopic treatment zones (MTZ) of necrosis (Hong Li, 2010, Manstein et al, 2004). Sparing uninvolved normal healthy tissue, each wound is surrounded by healthy cells that can migrate towards the wound, allowing for faster healing by secondary intention (Manstein et al, 2004). The fractionated CO2 laser is selective in that segments of tissue are effected, which translates into decreased recovery time (downtime) for the patient (Bordenorf, 2009). Therefore, by causing selective thermal injury in the skin, the CO2 laser can stimulate collagen production and theoretically improve scar thickness, pliability, and texture.

Dose Regimen

Subjects will be randomized to either a high energy treatment (CO_2RE Mid treatment mode [45-257 mJ] or CO_2RE Deep treatment [30-70 mJ] mode) or a low energy treatment (CO_2RE Light treatment mode [18-74.5 mJ] mode).

Study Device: Canfield Vectra M3 Imaging System

This body imaging is utilized in several clinical trials to capture 3-D photographs of subjects. Subjects will have images and dimensions of their scars measured in a non-invasive manner at each visit using photographs taken with the Canfield Vectra M3 3D Body Imaging System. Detailed step-by-step instructions for executing the images and measuring the scars will be a separate document.

Study Procedures

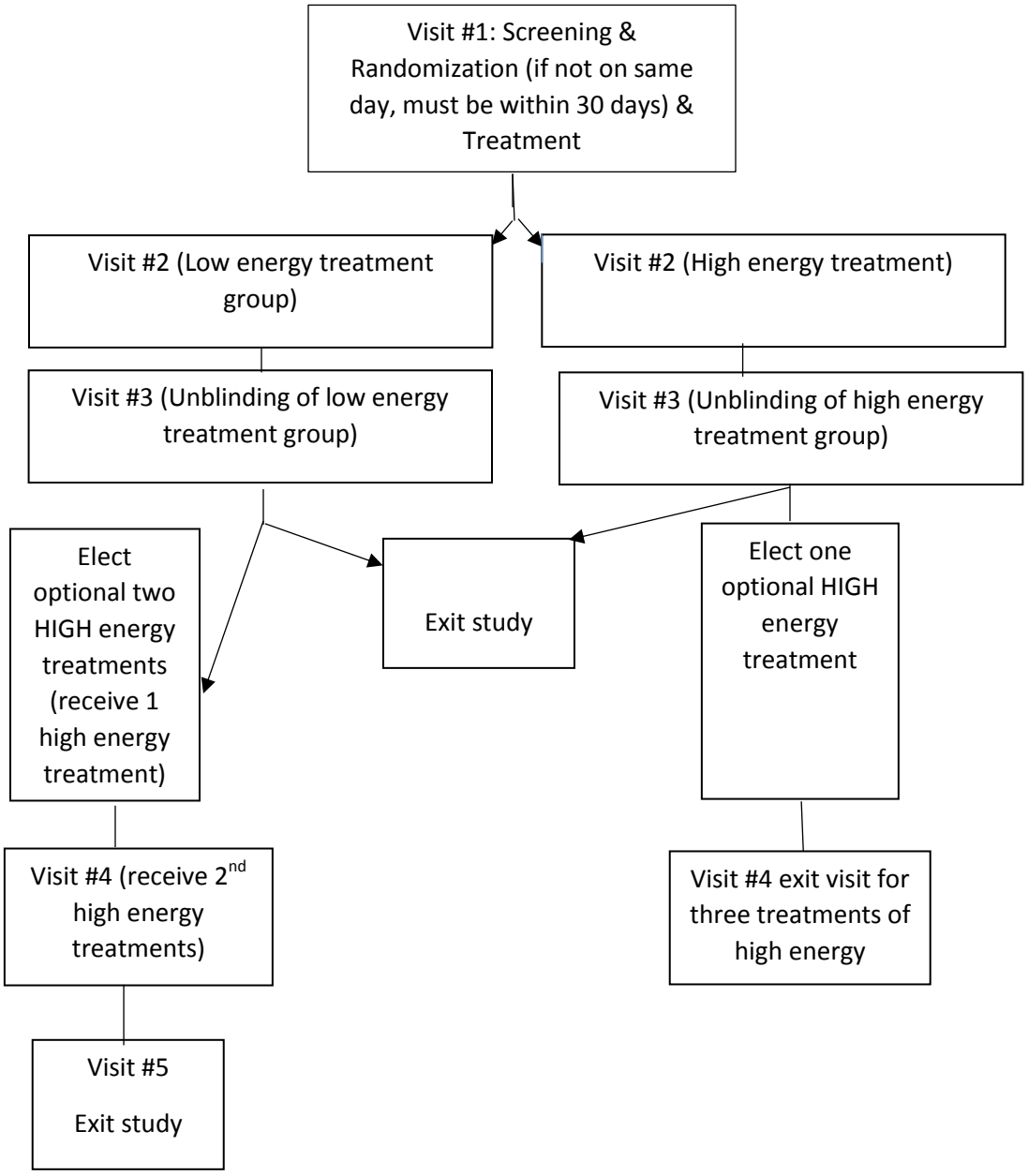
A screening visit will occur whereby patients deemed appropriate for the study will have the segment of the scar with the most deformity defined for objective evaluation at each session. Baseline photographs of this area will be obtained and demographic data about the surgery that created the scar, associated wound healing complications, age of the scar, and the Fitzpatrick skin phototype will be collected. Randomization will occur at this visit and patients will receive their first treatment at this visit. Prior to treatment application, subjects will cleanse their face with a gentle cleanser, such as Cetaphil, provided in the office in order to remove all lotion, creams, make up, and sunscreen. An optional topical or local anesthetic medication will be offered to the subject and if desired by the subject will be applied to the treatment area approximately 20 minutes prior to the procedure. If the scar is deeper, an injection of numbing medicine (lidocaine with epinephrine) may be used as well. Once this time passes and the numbing medicine is working, the subject will be escorted to the procedure room. The treatment areas will be wiped clean of the numbing cream prior to the procedure. Just prior to the procedure, the subject's eyes will be covered with eye shields to protect their eyes. The treatment time may vary, but generally takes 10 minutes or less. During this time, subjects will hear the laser, which sounds like a bee buzzing, and will feel some warmth. Most patients report minimal discomfort during the procedure. There may be pinpoint bleeding, bruising, and crusting depending upon the area and extent of the treatment. After the treatment, patients will be provided with a 30-day diary to daily record treatment-related reactions: redness, swelling, pain, itching or color changes following treatment. If the subject has a history of recurrent fever blisters/cold sores on the lips or face, the subject will be offered a three day prescription for an antiviral medication that the subject can fill at the subject's pharmacy to prevent a recurrence since laser treatments may increase the chance of recurrent episodes. The subject would take one pill every twelve hours the day prior to treatment, on the treatment day, and the first day post-treatment. The subject or their insurance plan must cover the cost of the medication. This may delay the treatment to a later date within 30 days of the screening visit. If antibiotic/antiviral medications are needed, you and/or your insurance company will be responsible for covering this cost.

If a patient prefers not to have treatment at this visit, they will be asked to return to clinic for this first treatment within 30 days from the screening and randomization visit. Subjects will return for a second treatment 3 months later. With 10 min allotted for treatment, as well as completing the patient questionnaire (5-7 minutes), assessment of adverse events and updating medications and procedures, along with performing photographs (10 min) and having an evaluation by the blinded evaluator, the entire visit may take up to 30-40 min. The diary entries will take 5 minutes each day. Subjects will return again 3 months following the second treatment and will undergo the follow up photos and assessments. Subjects will be unblinded at the third visit to the treatment received and given three options. One option is to exit from the study. The second option is if the subject received the high energy laser treatments, the subject may elect one additional treatment that day. The third option is subjects with low energy treatments have the option to receive two high energy treatments at this visit and a subsequent visit. Those in the high energy group who receive the third optional high energy treatment will return in 3 months for an exit visit and follow-up assessment of the scar (photos, patient POSAS, and observer POSAS) and exit at visit #4. Those in the low energy group who elect the two high energy treatments will follow up in 3 months after Visit #3 for the final high energy treatment, photos, and assessments (patient POSAS and observer POSAS). After receiving the last optional high energy treatment at Visit #4, patients in this low energy treatment group will return to the clinic in 3 mos for the last study visit where pictures will be obtained, survey assessments of the scar will occur, and the

subject will exit from the study. This allows comparison of all subjects following 2 treatments, and adds further data to the high energy laser treatment group for subjects who cross over.

The subjects' participation may be up to 14 months.

Visit Flowchart



Study Visit #1

The subject will verify information regarding the subject's name and contact information. The subject cannot take part in this study if the subject has a history of prior laser treatment to the face or neck, or if

the subject tends to form keloid scars or scars from minor trauma. Also, the subject should not participate in the study if the subject has taken oral isotretinoin medication within the past 6 months. In addition, the principle investigator may exclude the subject from the study if she determines that the study may put the subject at risk. The subject will provide written consent (permission) to be a participant in the study and for the research team to access the subject's health information to learn more about the surgery that resulted in the scar and the original features of the scar. Immediately before any study visit, the subject will be asked to not wear any make-up or use facial moisturizers (or moisturizers on the neck). The subject will be asked to cleanse their face with a gentle cleanser, such as Cetaphil, provided in the office prior to treatment.

Other procedures at this visit:

- The subject will have photographs taken of the scar that will be shared confidentially with two other research physicians in the study for them to answer questions about the scar.
- The subject will complete a questionnaire about the scar and another research physician will see the subject at this visit to evaluate the scar.

If the subject qualify for study treatment the following may occur at the same visit or at a return visit within 30 days. The following will occur:

- If the subject has a history of recurrent fever blisters/cold sores on the lips or face, The subject will be offered a three day prescription for an antiviral medication that the subject can fill at the subject's pharmacy to prevent a recurrence since laser treatments may increase the chance of recurrent episodes. The subject would take one pill every twelve hours the day prior to treatment, on the treatment day, and the first day post-treatment. The subject or their insurance plan must cover the cost of the medication. This may delay the treatment to a later date within 30 days of the screening visit.

- The subject will complete a pre-treatment questionnaire.
- The subject will receive laser treatment as randomized to either high energy or low energy treatment which includes:
    - Prior to treatment, the subject will be asked to cleanse his or her face with a gentle cleanser, such as Cetaphil, provided in the office in order to remove all lotion, creams, make up, and sunscreen.
    - A topical anesthetic medication will be applied to the treatment area approximately 20 minutes prior to the procedure. If the scar is deeper, an injection of numbing medicine may be used as well. Once this time passes and the numbing medicine is working, the subject will be escorted to the procedure room. The treatment areas will be wiped clean of the numbing cream prior to the procedure.
    - Just prior to the procedure, the subject's eyes will be covered with eye shields to protect their eyes.
    - The treatment time may vary, but generally takes 10 minutes or less. During this time, the subject will hear the laser, which sounds like a bee buzzing, and will feel some warmth. Most report minimal discomfort during the procedure. There may be pinpoint bleeding, bruising, and crusting depending upon the area and extent of the treatment. . After the treatment, the subject will be provided with a diary to daily record treatment-related reactions: redness, swelling, pain, itching or color changes following treatment.
    - The subject will be given a paper diary to record possible reactions such as redness, swelling, pain, itching or color changes following treatment

- You will be given post-treatment instructions:
    - Thoroughly wash your hands prior to touching the treatment area.
    - Gently clean the treated area with a mild cleanser 3 times per day. Splash the face with tepid water and pat dry with a paper towel or a clean soft washcloth. The goal is to lightly remove the exfoliating skin and crusting that develops after the laser procedure. This is a GENTLE process with NO scrubbing. Avoid picking or scratching at the treatment site, as the skin is very friable and sensitive. Picking or scratching can lead to pigmentation changes or further scarring.
    - After each cleaning, apply a coat of Vaseline with a cotton tipped applicator (i.e. Q-tip)
    - As the skin heals, it is common to see little dots ("peppering") all over the treated skin. These will come off with the cleansing process.
    - You will continue the wound care for 7 - 10 days, at which time you should begin applying sunscreen instead of Vaseline.
    - You can shower the next day and wash hair, but avoid very hot water
    - Do not expose the treated area to sun or wind for at least two weeks after treatment. If you go outside, use sunscreen with zinc (SPF 30+) and wear a hat. Protecting your skin and limiting sun exposure ensures the best results.
    - Expect the treated area to be red for several weeks. You can use makeup starting three days after the treatment, but it is best to wait until the skin has fully exfoliated and becomes pink to red shiny, smooth skin. This usually takes 7 to 10 days.
    - Some swelling may develop, and generally lasts 1-2 days. It is recommended that you sleep in a slightly elevated position to help relieve swelling.
    - It is common to feel a heat or sunburn sensation in the treated areas. This heat will dissipate over the next few hours. Cold compresses, such as ice, may help soothe the heat and can be gently applied to the skin.
    - Pain is uncommon after the first few days, and usually subsides with Tylenol and cooling the skin. Itching can be seen, and will usually last a few days or less. You can press on the clean itchy skin with a cotton tipped applicator (i.e. Q-tip) to relieve the itching. Avoid scratching the skin.
    - Normal daily activities may be resumed immediately after treatment. Avoid strenuous exercise, bending, straining, stooping or lifting heavy objects for 48 hours. These activities may cause swelling and pain in the treatment area. If a patient is not able to receive the treatment on the same day as the screening and randomization visit (possibly due to an ongoing oral herpetic infection), they may return to the office within 30 days for their first treatment.

Study Visit #2

The subject will be asked to return in 3 months for a second treatment visit with the following activities:

- The subject will complete a pre-treatment questionnaire
- The subject will receive laser treatment as randomized to high energy or low energy treatment
- The subject will obtain post-treatment instructions
- The subject will obtain a paper diary to record possible reactions such as redness, swelling, pain, itching or color changes following treatment
- If the subject has a history of recurrent fever blisters/cold sores on the lips or face, the subject will be offered a three day prescription for an antiviral medication that the subject can fill at the subject's pharmacy to prevent a recurrence since laser treatments may increase the chance of recurrent episodes. The subject would take one pill every twelve hours the day prior to

treatment, on the treatment day, and the first day post-treatment. The subject or their insurance plan must cover the cost of the medication. This may delay the treatment to a later date within 30 days of the screening visit.

Study Visit #3

This visit occurs 3 months after the subject's second treatment with the following activities:

- The subject will return the diary
- The subject will complete a questionnaire
- The subject will undergo scar evaluation by the research physician
- The subject will have photographs taken
- The treating investigator will let the subject know which treatment the subject received
- If the subject received the high energy laser treatment, the following will occur:
    - The subject will be offered the option to receive a third high energy treatment.
    - If the subject accepts treatment today, the subject will return in 3 months for the final follow up visit and to exit the study
- If the subject declines further treatment, the subject will be exited from the study at this visit.

If the subject received the low energy laser treatment, the following will occur:

- The subject will be offered the option to receive two high energy treatments.
    - If the subject accepted treatment, the subject will receive one treatment today and return in 3 months for the second treatment (Visit 4); the subject will then be asked to return 3 months later for a follow up final study visit (Visit 5).
- If the subject declined further treatment, the subject will be exited from the study.

Study Visit #4

If the subject were originally treated with the high energy laser, and elected a third treatment at Visit 3, this visit occurs 3 months after the subject's Visit 3 treatment with the following activities:

- The subject will return the subject's diary
- The subject will complete a questionnaire
- The subject will undergo scar evaluation by the research physician
- The subject will have photographs taken
- The subject will be exited from the study

If the subject were originally treated with the low energy laser, and elected treatment with the high energy laser, this visit occurs 3 months after the subject's Visit 3 treatment with the following activities:

- The subject will complete a pre-treatment questionnaire
- The subject will receive the last high energy laser treatment The subject will obtain post-treatment instructions
- The subject will obtain a paper diary to record possible reactions such as redness, swelling, pain, itching or color changes following treatment
- If the subject has a history of recurrent fever blisters/cold sores on the lips or face, the subject will be offered a three day prescription for an antiviral medication that the subject can fill at the subject's pharmacy to prevent a recurrence since laser treatments may increase the chance of recurrent episodes. The subject would take one pill every twelve hours the day prior to treatment, on the treatment day, and the first day post-treatment. The subject or the subject's insurance plan must cover the cost of the medication. This may delay the treatment to a later date within 30 days of the screening visit.
- The subject will be asked to return in 3 months for a final follow- up visit

Study Visit #5

This visit occurs 3 months after the subject's last treatment if the subject received the low energy laser treatment followed by the high level laser therapy as a final study visit. The subject will not be offered treatment at this follow up visit. The following will occur:

- The subject will return the subject's diary
- The subject will complete a questionnaire
- The subject will undergo scar evaluation by the research physician
- The subject will have photographs taken.

At any time, the subject may choose to not participate in the study. If the date that they elect to discontinue from the trial occurs shortly after a treatment (within minutes to 30 days after treatment), patients will be asked to return for a follow-up 3 months to evaluate for any significant adverse events. No treatments will be performed. Only photographs of the scar and rating of the scar by the patient and evaluators will be performed at this visit. Also, collection of the diary will occur at this visit. If subjects discontinue from the trial after 30 days, patients will be followed up via phone for the reason of their discontinuation and to assess for AE/SAEs and asked to return the diary as soon as possible. In either case, subjects will be given the contact information for the research office in case they have further concerns regarding their participation in the trial.

Unscheduled Visits

Patients who require evaluation outside of the three month windows +/- two weeks due to a related adverse event will be evaluated by the research team at the earliest convenience. If the nature of the evaluation is in regards to an adverse event/significant adverse event, a severe cutaneous reaction to the laser, or having an unrelated cosmetic procedure involving the study scar during the study, staff will evaluate the patient accordingly, document the event, and report any serious adverse events to the SLU IRB within a 24 hour window.

Completion of Study

At the completion of the study, the data obtained will be reviewed and analyzed with the aid of the Saint Louis University Center for Health Outcomes Research. This data will then be presented in the form of a paper and/or scientific poster. At the completion of the study, the data obtained will be presented in the form of a scientific paper and/or scientific poster.

Methods of Assigning Subjects to Treatment Arms

In terms of randomization, a spreadsheet will be created by the principle investigator with the aid of the research staff to predesignate the treatment assignment. For each patient that comes in, the principle investigator will use that as a guide to dictate the treatment arm assigned for that subject.

Blinding

Other than the investigating physician performing the laser treatment, no one (including the subjects, study coordinators, and the physicians who will be evaluating the response to treatment) will know who is receiving the high energy treatment or the low energy treatment until Visit #3.

Unblinding

At the Visit #3, subjects and the investigating physician performing the treatments will know the type of treatment that the subject in question received.

Concomitant Treatments

Prohibited

Patients will be prohibited from obtaining any additional cosmetic procedures during the study (i.e. dermabrasion, chemical peels) that may interfere with the interpretation of the results of the study.

Permitted

Patients will be permitted to continue using the moisturizers and cleansers that they have been using for the last 6 months. Patients will be allowed to take all oral medication (except isotretinoin) throughout the study.

Benefits and Alternatives

Benefits

Participants will not receive compensation for their time or travel. They may not receive benefits related to the treatments either, however society may benefit from the findings derived from this study. The investigational product, study-related procedures and study visits that are not otherwise part of the standard of care for this condition will be provided at no charge to the subject or to the subject's insurance company.

Alternatives

Participants may receive standard of care treatments (corticosteroids injections, ablative laser, non-ablative laser, and dermabrasion) in lieu of being a part of this study. A participant's choice of whether or not to participate will not affect their clinical care.

Fractional ablative laser resurfacing may be superior to the other currently available treatments. Treatment with corticosteroid injections alone has known side effects of atrophy, striae development, injection site-related reactions that are not caused by ablative laser treatment. The literature demonstrates that non-ablative laser therapy is not potent enough to generate the changes necessary to alter the dimensions and features of the scar. Microdermabrasion removes the strateum corneum and superficial spinous layer, which are not the layers where the collagen remodeling is active in the scar formation. It also has mixed results in improving scars. Manual dermasanding is labor intensive and the results from motorized dermabrasion are operator-dependent. Additionally, only particular scars (i.e. fibrotic scars, ice pick scars, scars with significant tissue loss) are most amenable to this motorized dermabrasion. Additionally, dermabrasion involves aerosolized particle formation, which may or may not be infectious.

Safety

The safety of subjects will be maintained. Subjects will be provided with information about the risks associated with laser therapy, severity, and time course for resolution will be addressed during the consent process. Such risks include the following: infection (days, mild, reversed with topical antivirals), pinpoint bleeding (occasionally occurs, resolves with application of pressure dressing), scarring (uncommon, varies, may be ameliorated with different laser settings), erythema (very common, severity varies, resolves over a few days to months with sun avoidance and sunscreen use), postinflammatory hyperpigmentation (occasionally occurs, varies, reverses with sunscreen use), and delayed-onset hypopigmentation (occasionally occurs, varies, self-resolves with sunscreen use), bronzing (common, varies, reverses with daily sunscreen use and time), exposure to laser smoke, visible skin patterns, damaged skin, distortion of anatomic features, acute pain, crusting (very common, severity varies, resolves over days), pruritus (common, varies, ameliorated with neutralizing moisturizer and self-resolves), edema (common, varies, self-resolves days to weeks) xerosis (commonly occurs, mild-to-moderate, reverses with neutralizing moisturizer cream), allergic reactions, delayed healing, surgical anesthesia, additional treatment or surgery may be necessary.

Topical and/or local medication used to numb the treatment area prior to the laser treatment may be offered. Adverse reactions associated with use of topical lidocaine cream and injectable lidocaine include skin rash, redness, itching, hives, burning, stinging, swelling, tenderness, and transient (temporary) loss of skin color, lightheadedness, anxiety, dizziness, vomiting, local erythema, local edema, abnormal sensations, hypersensitivity reactions, anaphylactoid reactions, central nervous system excitation or depression, cardiac arrest, irregular heart rhythms, and familial malignant hyperthermia exacerbation. The adverse reactions are anticipated to occur rarely due to the small doses required for laser treatment pain control. Some anesthetic agents contain epinephrine, which may cause short-term moderate anxiety, fear or an uneasy feeling, restlessness, shaking, weakness, dizziness, sweating, rapid or abnormal heart beats, increased blood pressure, pale skin, nausea and vomiting, headache, and/or difficulty breathing. These symptoms are more likely in people with high blood pressure or an overactive thyroid. Excessive doses of epinephrine may cause severe high blood pressure, stroke, and irregular heartbeats, which can lead to death.

Adverse reactions associated with acyclovir include nausea, vomiting, diarrhea, headache, malaise, dizziness, arthralgia, rash, seizures, hallucinations, psychosis, anaphylaxis, angioedema, renal failure, and blood dyscrasias. The adverse reactions are anticipated to occur rarely due to the low dose short term prophylactic dose. During the treatment, subjects will be provided with eye protection during the treatment. Additionally, subjects will be provided with the contact information of the principle investigator, the research team, and IRB office should they experience any unforeseen adverse effects or develop questions regarding the severity of the adverse effects they experience.

Early Study Termination

There are no guidelines or endpoints by which early decisions regarding efficacy or lack of efficacy will be made for this FDA approved device. However, the PI could stop the study early if significant unexpected adverse events occur, or enrollment and retention is not adequate.

Definition of Adverse Events

An adverse event is any untoward medical occurrence associated with the use of a study drug in humans, whether or not considered device related. An AE can, therefore, be any unfavorable and

unintended sign (including an abnormal laboratory finding), symptom or disease temporally associated with the use of the study device, whether or not related to the study device.

Reporting of Adverse Events

Only AEs that occur during or following study treatment with the drug will be reported in the AE section of the source documents. Events recorded prior to study treatment with the drug will be reported in the Medical History section of the source documents as appropriate. All AEs occurring during the course of the study will be individually recorded in the source documents. A condition that is present prior to administration of study drug and that worsens after administration of study drug should be reported as an AE. Information regarding the onset, duration, severity, action taken, outcome, and relationship to study drug will be recorded. New or worsening abnormal laboratory values and/or vital signs are to be recorded as AEs if they are considered to be of clinical significance by the PI or meet the criteria of an SAE (see below). Unless a diagnosis is available, signs and symptoms must be reported as individual AEs in the source documents; a diagnosis is preferred.

Adverse events (AEs) will be monitored throughout the study. Subjects will be instructed to inform the Principal Investigator (PI) and/or study staff of any AEs. At each visit, subjects will be asked about AEs in a non-specific manner using open-ended questions so as not to bias the response (e.g., Has the subject had any changes since the last visit?). Specific inquiry regarding reported AEs will be conducted when applicable. All adverse events will be documented and recorded in the source documents.

Any subject who has an AE (whether serious or non-serious) or clinically significant abnormal laboratory test value will be evaluated by the PI and will be treated and/or followed up until the symptoms or values return to normal or to clinically acceptable levels, as judged by the PI. A physician, either at clinical site, or at a nearby hospital emergency room, will administer treatment for any serious adverse events (SAEs), if necessary. When appropriate, medical tests and examinations will be performed to document resolution of event(s).

Intensity Grading of AEs

The severity of an AE will be designated as mild, moderate or severe. The term “severe” is used to describe the intensity of an adverse event; the event itself, however, may be of relatively minor clinical significance (e.g. ‘severe’ upper respiratory infection). Severity is not the same as “serious”. Seriousness of AEs is based on the outcome/action of an AE.

Causality and Relatedness

The relationship of the AE to the study treatment will be based on the following two definitions:

Not related: An AE is defined as “not related” if the AE is not judged to be associated with the study treatment and is attributable to another cause;

Related: An AE is defined as “related” where a causal relationship between the event and the study treatment is a reasonable possibility (possibly or probably related). A reasonable causal relationship is meant to convey that there are facts (e.g., evidence such as dechallenge/ rechallenge) or other clinical arguments to suggest a causal relationship between the AE and study treatment.

Serious Adverse Events

Definition of Serious Adverse Events

An SAE is defined as any untoward medical occurrence that, at any device setting or dose:
• Results in death;
• Is immediately life-threatening (i.e., in the opinion of the PI, the AE places the subject at immediate risk of death; it does not include a reaction that, had it occurred in a more severe form, might have caused death);
• Requires inpatient hospitalization or results in prolongation of an existing hospitalization;
• Results in persistent or significant disability or incapacity;
• Is a congenital anomaly or birth defect;
• Is an important medical event that may not be immediately life-threatening, results in death, or require hospitalization, but may be considered an SAE when, based upon appropriate medical judgment, it jeopardizes the subject or may require medical or surgical intervention to prevent one of the outcomes listed above.

Reporting Serious Adverse Events

As soon as the PI becomes aware of an AE that meets the criteria for an SAE, the SAE should be documented to the extent that information is available. A report must be submitted by the study site to the SLU IRB, within 24 hours. Forms for reporting SAEs will be provided to the study site. SAEs will be recorded from the time of informed consent, through the end of the study. If in the opinion of the Investigator, an SAE occurring outside the specified time window (i.e., following subject completion or withdrawal from the study), is deemed to be device related, then the event should be reported with 24 hours as outlined above. The Investigator should institute any clinically necessary supplementary investigation of SAE information.

Death

In the case of subject death, any post-mortem findings/reports will be requested and a report (even if a preliminary diagnosis/cause of death is available) will be submitted to the SLU IRB within 24 hours of learning about the death.

Reporting of Pregnancy

In the case of subject pregnancy, the subjects will be discontinued from the study and will be followed leading up to delivery.

Data Analysis and Statistical Considerations

At the completion of the study, the data obtained will be reviewed and analyzed with the aid of the Saint Louis University Center for Health Outcomes Research. A chi-square test along with the Wilcoxon signed rank test will be performed to assess significant difference between clinical improvement scores between study visits. There is no data to suggest that there is a difference in the appearance of older (more than 1 year old from the initial injury) and newer scars post-therapy. We will aim to recruit 20 patients with old scars (10 of which will be in the high energy treatment group, and 10 of which will be in the low energy treatment group). In terms of statistical analysis, we will review whether there is a difference between the post-treatment measurements and appearance of older scars and newer scars.

Quality Control and Quality Assurance

Quality control and assurance for this study will be performed by an internal review every 3 months to ensure that the data collected is in accordance with the goals of this study and to address any issues with data collection or performance of any study procedures.

Direct Access, Data Handling and Record Keeping

Access to all study materials will be kept in a locked facility within the SLU Dermatology Des Peres Office. Only staff members will have access to this room. With respect to the randomization spreadsheet, only the principle investigator will have access to this information. This information will be kept in a locked file cabinet in her office. The source documents created by the study site will be the primary forum for recording study data. When the study is completed, these documents will be placed in a long term storage facility owned by SLU.

Confidentiality

Interested subjects will sign a HIPPA form allowing access to relevant medical records. All study data will remain confidential, unless it is deemed by the principle investigator and/or research team members that it is important for the patient's health for study participation to be disclosed to appropriate parties (i.e. other medical providers). Study materials for each subject will have a deidentified code, such as subject Jane Doe is subject 001.

Data Protection

The master list, which will be password-protected, will be kept confidential to all research staff except the principle investigator. She will be the only unblinded individual in this study who will set the password for this document and will have access to the master list. Study materials for each subject will have a deidentified code, such as subject Jane Doe is subject 001.

Records Retention

Records will be retained within a locked office within the SLU Dermatology Des Peres Office

Posting to Clinical Trials Register and Publication

Information about this study will be posted to the Clinical Trials Register (accessible via http://www.clinicaltrials.gov). Recruitment for the study will be open until the study has obtained 50 patients. All recruitment information posted to the Clinical Trials Register will be reviewed and approved by the SLU IRB. Final data analysis and publication will be between July and August 2017.

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