

Date: May 27,2016

Principal Investigator: Ginette Okoye, M.D.

Application Number: IRB00082453



JOHNS HOPKINS
M E D I C I N E

Fractional laser assisted steroid therapy vs intralesional steroids in the treatment of keloids

IRB no.: IRB00082453

NCT no.: NCT02996097

PI: Ginette Okoye, MD

CTReP Derm: #150

Cutaneous Translational Research Program (CTReP)

Johns Hopkins Outpatient Center, Room 8033C

Department of Dermatology

(410) 502-SKIN

JHM IRB - eForm A – Protocol

Fractional laser assisted steroid therapy vs intralesional steroids in the treatment of keloids

1. Abstract:

The purpose of this study is to compare the effects of fractional CO₂ laser therapy immediately followed by intralesional steroid therapy against intralesional steroid therapy alone for the treatment of keloids. Intralesional corticosteroids remain the gold standard treatment for keloids. However, more effective therapies are desperately desired. Ablative fractional laser (AFL) treatment facilitates delivery of intralesional steroid more deeply and uniformly into the skin by creating vertical channels. Recent studies have showed that fractional laser assisted steroid therapy can be effective in the treatment of keloids.⁵ However the studies are lacking in comparing this treatment modality to the gold standard of intralesional steroids.

2. Objectives:

Primary objective: To compare fractional CO₂ laser ablation immediately followed by intralesional steroids to the gold standard of intralesional steroids for the treatment of keloids.

3. Background (briefly describe pre-clinical and clinical data, current experience with procedures, drug or device, and any other relevant information to justify the research)

Keloids are a form of aberrant scar formation usually at the site of healing skin injury. They present clinically as firm, hyperpigmented to skin colored rubbery shiny nodules that are usually very distressing to patients and are often a source of both physical and psychological morbidity. During the normal wound healing process, extracellular matrix consisting of Collagen I or III are deposited by fibroblasts to fill in a defect. The extracellular matrix also is constantly being broken down and remodeled with the help of matrix metalloproteinases (MMPs). With keloids, there is a poorly understood excessive deposition of scar tissue during this wound healing process resulting in firm, irregularly shaped, fibrous, hyperpigmented, or even rope-like nodules.^{1,2,3}

Extensive research has been performed regarding further elucidating the pathophysiology of this condition and various treatment options. Investigated treatment options that have become part of the mainstay of treatment include massage therapy, pressure garments, adhesive tapes, silicone gel sheets, intralesional corticosteroids, topical corticosteroids, and surgical resection. Poorly investigated treatment options include use of cryotherapy, radiotherapy, intralesional 5-fluorouracil and bleomycin, imiquimod 5% cream, and Tranilast.^{1,3}

The CO₂ laser has been used extensively in dermatological surgery over the past 30 years and is now recognized as the gold standard for soft tissue vaporization. CO₂ laser beam heats and vaporizes the skin tissue, instantly removing the superficial layers of the skin. Each fractional micro-spot creates a thermal zone.

Intact cells around the treated area help during the healing process which in turn, induces cell regeneration⁴. The laser beams can assist delivery of topical drug deeply into the skin by creating vertical channels.

A recent study published in April 2015 in *Dermatologic Therapy* assessed the ablative erbium laser in fractionated mode, combined with topical high potent corticosteroid cream for treating resistant keloid scars. It was performed in the laser center of the Department of Dermatology (University Hospital of Nice, France), from January 2010 to June 2012, on patients with keloids who were resistant to a first-line of treatment. A 2940-nm ablative fractional erbium laser was used and topical betamethasone cream was applied twice a day under occlusion with transparent film dressings. A total of 23 patients with 70 keloids were treated and the median percentage of improvement was 50% (range -43 to 84).⁵ The paper supports the interest of the laser-assisted delivery of steroids for treating keloids scars and the authors admit that a prospective comparative evaluation is warranted.

We hypothesize that laser assisted intralesional steroid therapy will be superior to intralesional steroid alone in the treatment of keloids. We also hypothesize that treatment with laser assisted intralesional steroid therapy will give a more uniform treatment result since there are more even amounts of steroid spread throughout the treatment site with the laser assisted steroid method.

4. Study Procedures

a. Study design, including the sequence and timing of study procedures:

In order to be eligible for the clinical study, subjects must have been seen in the dermatology clinic at Johns Hopkins Hospital or from patient populations participating in Johns Hopkins Cutaneous Translational Research Program (CTReP) research studies. Interested study participants will be evaluated after their routine clinical care visits. Participants will also be recruited from other Johns Hopkins patient populations via the use of fliers. Study procedures will be conducted at the CTReP office located at the Johns Hopkins Outpatient Center. Recruitment may include Johns Hopkins University employees or students, but these populations will not be specifically targeted for recruitment. Interested individuals will be interviewed to ensure they meet basic criteria for participation.

We will enroll up to 40 subjects in this study.

Power calculation: an n of approximately 33 would be needed to obtain statistical power at the recommended .80 level (assuming a 50% improvement expected in the keloids treated with intralesional injections plus laser vs a 25% improvement in the keloids treated with intralesional injections alone).

During the first visit, the expected timeline will be discussed. We will also discuss in detail the laser procedure and expectations with regards to healing time and symptoms in the post-procedure period. We will attempt to answer all questions to the subject's satisfaction. If the subject is agreeable, documentation will be obtained of their consent to participate in the study and the subject's agreement to be contacted in for future research studies. After informed consent is obtained, subjects who are currently receiving treatment for their keloids will undergo a washout period of 4 weeks.

Once this washout period has elapsed, subjects will return to the study site to undergo baseline procedures. Patients with more than one keloid on the trunk or back would be selected for participation in the trial. Two keloids of comparative size and texture located on the same general anatomic location (trunk or

back) would be selected for intervention on each patient. Topical anesthetic compound with EMLA or tetracaine 24%/ lidocaine 7% will be applied to both keloids using standard protocol. One lesion would be treated with fractional CO2 ablative laser followed with intralesional triamcinolone acetonide at 4 weeks intervals while the other lesion would be treated with intralesional triamcinolone acetonide alone at 4 week intervals. Patient would be treated 4 times with each treatment modality for a total of 16 weeks. Digital photographs may be obtained at each study visit. The Patient and Observer Scar Assessment Scale (POSAS) would be used to evaluate each treated lesion prior to and at completion of the treatment duration. Measurement of keloid size and thickness will be also be performed prior to and at completion of the treatment duration. Each patient will serve as his or her own control, as we will compare the keloid treated with the laser assisted steroid therapy to the keloid treated with ILK alone.

Laser treatment: During the treatment visit, topical EMLA cream or tetracaine 7%/lidocaine 23% will be applied to the both treatment sites and after sufficient anesthesia is attained, one keloid will be treated with the fractional CO2 laser using standard protocol as practiced in our clinics followed by intralesional triamcinolone acetonide.

Photography: Standardized digital photographs will be obtained by study staff using a digital camera and software under standard photographic conditions. Photograph files will be coded to remove personal identifiers and stored on a secure hard drive in CTReP.

Clinical assessment: Clinical assessments will be performed to 1) record baseline skin findings, 2) assess treatment progress prior to each subsequent treatment 3) and assess results at the end of the study

The Patient and Observer Scar Assessment Scale: The POSAS includes subjective symptoms of pain and pruritus and expands on the objective data captured in the Vancouver Scar Scale. It consists of 2 numerical scales: The Patient Scar Assessment Scale and the Observer Scar Assessment Scale. It assesses vascularity, pigmentation, thickness, relief, pliability, and surface area, and it incorporates patient assessments of pain, itching, color, stiffness, thickness, and relief. The POSAS has been applied to postsurgical scars and used in the evaluation of linear scars following breast cancer surgery, demonstrating internal consistency and interobserver reliability when compared to the VSS with the added benefit of capturing the patients' ratings.⁶ We will use this rating system for the analysis of the keloids in our study.

STUDY TIMELINE AND EXPECTATIONS

b. Study duration and number of study visits required of research participants.

The study consists of 4 on-site visits over approximately 16 weeks. We will allow up to 2 years to complete the study.

c. Blinding, including justification for blinding or not blinding the trial, if applicable.

NOT APPLICABLE

d. Justification of why participants will not receive routine care or will have current therapy stopped.

Participants will be asked to stop treatment with all topical and intralesional steroids as this may alter the normal expected dynamics of wound healing¹, altering not only the healing process but also possibly cell-signaling pathways.

e. Justification for inclusion of a placebo group or non-treatment group.

NOT APPLICABLE.

f. Definition of treatment failure or participant removal criteria.

Any clinical findings determined by the Investigator to be important and/or unusual will be referred to as an adverse event (AE). Study participants are asked to contact clinic staff immediately if they experience a reaction at any time during the study. Expected reactions may be documented in a problem events log. The Investigator will use his discretion to remove participants from the study and all problem events will be reported to the IRB.

g. Description of what happens to participants receiving therapy when study ends or if a participant's participation in the study ends prematurely:

NOT APPLICABLE.

Participants must fulfill all of the criteria listed below:

5. Inclusion/Exclusion Criteria

Inclusion criteria

Subjects who meet the following inclusion criteria will be included in the study:

1. Male or female older than 18 at the screening visit;
2. The subject is healthy, as determined by the investigator based on a medical evaluation including medical history;
3. The subject has at least two keloids of comparative size and texture located on the same general anatomic location (trunk or back);
4. The subject is willing and able to comply with the requirements of the protocol. In particular, subject must adhere to the visits schedule and concomitant therapy. The subject is willing to comply with the 4 week washout period;
5. The subject has understood and signed an Informed Consent Form approved by the IRB prior to any investigational procedure

Exclusion criteria

Any subject who is meeting one or more of the following exclusion criteria at the screening visit and/or at the baseline visit will not be included in this study:

1. The subject has an underlying known disease, a surgical or medical condition that in the opinion of the investigator might put the subject at risk
2. The subject is pregnant or breastfeeding at the time of enrollment or is planning to become pregnant at any point during the study period
3. The subject has a past history of coagulopathy
4. The subject has an underlying dermatological disease that in the opinion of the investigator could interfere with the study evaluations
5. The subject has used prohibited topical or systemic treatments without sufficient protocol-defined wash-out period prior to Baseline (checked at Screening and Baseline) or is unwilling to refrain from use during the study

6. The subject is treated with anticoagulants or antiplatelet therapies
7. The subject has a known allergy or sensitivity to any local anesthetic drug (e.g. EMLA or tetracaine 7%/lidocaine 23%) or a local antiseptic planned to be used for the laser.
8. The subject is in an exclusion period from a previous study or is participating in another clinical trial
9. The subject is an adult under guardianship or is hospitalized in a public or private institution, or is deprived of freedom
10. The subject is unable to communicate or cooperate with the Investigator due to language problems, poor mental development, or impaired cerebral function

6. Drugs/ Substances/ Devices

EMLA cream or tetracaine 7%/ lidocaine 23% is the topical anesthetic used in the study and will be the same drug provided to the entire Johns Hopkins Dermatology Department. There will not be a separate batch of this drug for the sole purposes of this study as the purpose of this study is unrelated to the use of the drug and is unlikely to interfere with study results.

EMLA cream (lidocaine 2.5% and prilocaine 2.5%) is an emulsion in which the oil phase is eutectic of lidocaine and prilocaine in a ratio of 1:1 by weight.

The fractional CO₂ laser treatment will be administered using standard settings on the eCO₂ Plus laser system, Lutronic Inc. The Lutronic eCO₂ Plus laser system will be obtained by the Johns Hopkins Dermatology department and will be evaluated and approved by the department of Clinical Engineering.

Intralesional triamcinolone acetonide (Kenalog) will be used in the study.

7. Study Statistics

The data collected in this study will be used to inform the design of future study related to the use of laser therapies for keloids.

8. Risks

There are risks associated with ablative laser therapy. The most common local side effects are discomfort during the procedure, temporary swelling, acute sensitivity to sun exposure, increased sensitivity to use of cosmetic products and erythema. There is also an associated risk of both hyper- and hypopigmentation of the skin in the treated area. There is risk that the laser could make the keloid larger. This is unlikely but if this was to happen, laser treatment on this lesion would be discontinued and only intralesional keloid would be used from that point on. Finally, there is a risk of eye injury related to the CO₂ laser therapy. Exposure to the invisible carbon dioxide laser beam (10,600 nm) can cause damage to the cornea or sclera. For this reason, the operator, participant and all other parties within the secured treatment room will wear protective eyewear provided by CTReP. The provided eyewear has wrap-around shields, meets ANSI/ISEA Z87.1-2003 standards, and offers protection from CO₂ lasers (10,600 nm).

Other potential complications of this treatment are infection, activation of herpetic lesions, and scar formation. Preventative measures are taken to minimize these risks. Standard precautions will be taken using the same protocol used in our clinics for patients undergoing therapies using ablative laser. Caution and

careful attention to settings is paramount in performing the technique safely and all treatments will be performed by trained providers.

The potential complications of intralesional steroid include the known risks of skin atrophy and hypopigmentation of the applications sites. There are minimal risks with regards to confidentiality as all participant information will be de-identified. Since this is an exploratory study, no confidential nor protected information would be taken outside the standard. There is slight financial risk to the participants in the rare event that the aforementioned complications occur requiring additional medical care.

9. Benefits

It is unclear whether there will be direct benefit to the participant as a result of this study. In theory, the participant may enjoy keloid improvement with both the laser assisted steroid therapy as well as the intralesional steroid therapy. This, however, cannot be guaranteed.

10. Payment and Remuneration

Participants will not be paid for this study

11. Costs

All other costs will be covered by Johns Hopkins Department of Dermatology.

Bibliography

1. Arno AI, Gauglitz GG, Barret P, Jeschke MG. Up to date approach to manage keloids and hypertrophic scars: A useful guide. *Burns* 2014. 40 (7) 1255-1266.
2. Jin R, Huang X, Li H, Yuan Y, Li B, Cheng C, Li. Laser therapy for prevention and treatment of pathologic excessive scars. *Plast Reconstr Surg*. 2013; 132 (6): 1747-58.
3. Monstrey S et al. Updated scar management practical guidelines: non-invasive and invasive measures. *J Plast Reconstr Aesthet Surg*. 2014. 67(8): 1017-25.
4. Prignano, F. et al. A study of fractional CO₂ laser resurfacing: the best fluences through a clinical, histological, and ultrastructural evaluation. *Journal of cosmetic dermatology* 10, 210–6 (2011).
5. Cavalié M, Sillard L, Montaudié H. Treatment of keloids with laser-assisted topical steroid delivery: a retrospective study of 23 cases. *Dermatology Therapy*. 2015 Mar-Apr;28(2):74-8.
6. Draaijers, Lieneke J. M.D.; Tempelman. The Patient and Observer Scar Assessment Scale: A Reliable and Feasible Tool for Scar Evaluation. *Plastic & Reconstructive Surgery*: June 2004