Official title: The effects of fractional CO2 laser on Poikiloderma of Civatte

NCT number: NCT04581330

IRB Approved date: 09-09-2020

The University of Texas Southwestern Medical Center at Dallas
Institutional Review Board

Protocol Template (for Investigator Initiated Studies)

Title: The effects of fractional CO2 laser on Poikiloderma of Civatte
Principal investigator: Heather W. Goff, M.D.
Funding Sponsor: UTSW Dept of Dermatology
IND Number (if applicable):
Version number and date: Version 1; 7/19/2020

Introduction and Purpose: This study will assess the safety and efficacy of fractional CO2 laser treatment for Poikiloderma of Civatte (POC). POC is a chronic vascular and pigmentary disorder typically involving the lateral and inferior neck region, as well as the chest area. Clinically, poikiloderma appears as a combination of telangiectasia, irregular pigmentation, and atrophic changes[1]. Previously studied effective treatments of POC include pulsed dye lasers and IPL devices.[2,3,4,5] Ineffective treatments include hydroquinone, electrosurgery, argon laser photocoagulation, and cryotherapy.[6] Although PDL and IPL laser technologies are relatively safe, there have been a few reports of PDL treatment with subsequent complications, which may include ulceration developing immediately after treatment as well as scarring.[7,8,9,10]Additionally,

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[2] Haywood RM, Monk BE. Treatment of poikiloderma of Civatte with the pulsed dye laser: a series of seven cases. J Cutan Laser Ther. 1999;1(1):45-48. doi:10.1080/14628839950517093
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[9] Sommer S, Sheehan-Dare RA. Atrophie blanche-like scarring after pulsed dye laser treatment. J Am Acad Dermatol. 1999;41:100-102.
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PDL and IPL laser treatments require multiple sessions before seeing a clinically significant effect and do not address textural issues.[11] Therefore, alternative safe and effective options for management of POC are still needed. Fractional CO2 laser has been widely used for photoaging due to its effectiveness and high safety profile.[12,13] Clinically evident improvement can be appreciated even after only one session of treatment.[13]

One previous study showed that ablative fractional laser resurfacing was both safe and effective for the treatment of the vascular, pigmentary and textural components of POC.[14] Little data exist regarding the use of fractional CO2 laser for management of POC. This study hopes to fulfill this purpose.

2. Background

Poikiloderma of Civatte (POC) is characterized by vascular and pigmented lesions consisting of linear telangiectasias, mottled dyspigmentation and superficial atrophy in a reticular pattern found on sun-exposed areas of the face and neck, often sparing the shaded, submental area.[15,16] Fair-skinned women in their 4th and 7th decades of life are predominantly affected.[15] Most cases are benign and asymptomatic, however, some report symptoms of pruritus, burning sensation and flushing triggered by sun exposure.[15] The cosmetically unappealing lesions can be distressing to affected individuals. The cause of POC is multifactorial. Chronic sun exposure,

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[12] Tierney EP, Hanke CW. Fractionated carbon dioxide laser treatment of photoaging: prospective study in 45 patients and review of the literature. Dermatol Surg. 2011;37(9):1279-1290. doi:10.1111/j.1524-4725.2011.02082.x
[13] Tierney EP, Hanke CW. Ablative fractionated CO2, laser resurfacing for the neck: prospective study and review of the literature. J Drugs Dermatol. 2009;8(8):723-731.
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[15] Katoulis, A.C., et al., Poikiloderma of Civatte: a clinical and epidemiological study. J Eur Acad Dermatol Venereol, 2005. 19(4): p. 444-8.
[16] Errichetti, E. and G. Stinco, Dermoscopy in Facilitating the Recognition of Poikiloderma of Civatte. Dermatol Surg, 2018. 44(3): p. 446-447.

photoallergy, and contact dermatitis to perfumes and cosmetics are implicated.[15,17] While the disease has a chronic and unrelenting course, effective treatments have not been fully established. The goal of treatment is to target both the vascular and pigmented lesions to improve symptoms and appearances. Current treatments that yield satisfying results include pulse dye laser, fractional non-ablative photothermolysis, and intense pulsed light.[15, 18,19,20,21,22] However, these therapies may induce crusting, purpura, blisters, hypopigmentation and postinflammatory hyperpigmentation. [18, 20,21,23,24] Multiple sessions are often needed to achieve desired cosmetic results.

Carbon dioxide laser was introduced for skin resurfacing in the mid-1990s. It has a wavelength of 10,600 nm, has an absorbing chromophore of water, and is used to vaporize tissue. It was initially used as a full-field laser resurfacing device which removes the entire skin surface in the area being treated. In 2004, Manstein et al. introduced the concept of fractional photothermolysis in which only small fraction of the skin would be treated at each session, leaving skip areas in between.[25] For the traditional full field laser resurfacing, healing occurs from deeper structures alone; however, fractionated laser resurfacing has the advantage of healing from deeper

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[19] Bernstein, E.F., et al., Treatment of poikiloderma of Civatte using a redesigned pulsed dye laser with a 15 mm diameter treatment spot. Lasers Surg Med, 2019. 51(1): p. 54-58.
[20] Meijs, M.M., F.A. Blok, and M.A. de Rie, Treatment of poikiloderma of Civatte with the pulsed dye laser: a series of patients with severe depigmentation. J Eur Acad Dermatol Venereol, 2006. 20(10): p. 1248-51.
[21] Behroozan, D.S., et al., Fractional photothermolysis for treatment of poikiloderma of civatte. Dermatol Surg, 2006. 32(2): p. 298-301.
[22] de Medeiros, L.M., A.R. de Luzuriaga, and R. Tung, *Treatment of Poikiloderma with Chemical Peeling*, in *Body Rejuvenation*, M. Alam and M. Pongprutthipan, Editors. 2010, Springer New York: New York, NY. p. 39-45.
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structures as well as adjacent untreated structures.[26] This approach avoids open wound as well as lowers risk of pigment disturbance or scarring.[11] Non-ablative fractional devices such as the 1,550 nm wavelength Erbium fiber laser was used for treatment of POC which showed some clinical improvement in the degree of erythema, dyschromia, and overall texture of the neck with very little adverse effects.[21] Fractional ablative resurfacing with carbon dioxide intends to provide more significant results than non-ablative systems, while achieving shorter healing times and complications when compared with full-field ablative systems. While fractional CO2 laser has been used for successful management of acne scars, facial skin rejuvenation, benign nevus, seborrheic keratosis, syringoma, xanthelasma, recalcitrant warts, its efficacy has not been widely proven for management of POC.[27] This study hopes to fill that knowledge gap in order to best optimize treatments for future patients.

3. Concise summary of project

The study subjects' neck and décolletage area will be divided into two equal halves. The line of division will be from the mid mental protuberance to manubriosternal junction. One half of the neck and upper chest area will be treated with ablative fractional CO2 laser while the other half will be untreated and used as a control. If desired after the study endpoint, patients may have the other side of their neck treated at no additional charge.

Primary Outcome Measures:

Physician's Global Aesthetic Improvement Scale at 12- and 24-weeks post treatment. Photographs will be presented to a panel of independent dermatologists. The panel will be blinded to treatment parameters and the treatment laterality at each photograph time point. Each

[26] Ramsdell WM. Fractional carbon dioxide laser resurfacing. Semin Plast Surg. 2012;26(3):125-130. doi:10.1055/s-0032-1329414

[27] Omi T, Numano K. The Role of the CO2 Laser and Fractional CO2 Laser in Dermatology. Laser Ther. 2014;23(1):49-60. doi:10.5978/islsm.14-RE-01

dermatologist will be asked to identify the baseline and post-treatment images from randomized, paired images for all subjects. Reviewers will rate improvement in POC in 10% increments on a 10-point scale (0% no improvement to 100% or complete clearance)

Secondary Outcome Measures

Subject Satisfaction Assessment at 12- and 24-weeks post treatment. Subjects will assess overall satisfaction with improvement of poikiloderma of civatte using an 5-point satisfaction and aesthetic scale.

Study subjects will be followed for 24 weeks post-laser treatment to assess incidence and severity of all procedure-related adverse events.

4. Study procedures

Patients with a clinical diagnosis of POC defined by a skin change with atrophy, hypopigmentation, hyperpigmentation, dilation of the fine blood vessels (telangiectasia) will be recruited. Ten patients will be consented. Before the initial visit, all patients will complete a one-month preoperative daily use of SPF 50+ sunscreen. The sun protection is to reduce further sun damage and protect skin from increased photosensitivity that may occur after laser resurfacing. At the initial visit, high resolution photographs of the affected area on the neck and décolletage area will be taken. All patients will fill out a form with demographic information. Patients will be instructed to come to their appointment with clean skin and without any lotions or moisturizers on the neck or décolletage area. Laser-specific eyewear will be provided to practitioners, patients, and all other people in the treatment room. A blue skin marking pen will be used to draw a line from mid mental protuberance to manubriosternal junction to divide tested area into two equal halves. Compounded benzocaine, lidocaine, and tetracaine (BLT) cream in a 20:8:4% concentration will be applied to the treatment area for 40 minutes prior to the procedure. Before

the treatment, topical anesthesia will be thoroughly washed off with chlorhexidine gluconate and distilled water. One pass with a 1-mm spot density and a 60micron depth will be performed followed by a 1mm spot density and a 200-micron depth will be used. The other half of the testing area will be left intact and used as the control for easy comparison. The side that undergoes treatment will be selected randomly. Forced cold air (Zimmer cooler) will also be used in conjunction with the laser device for better patient comfort.

Cold compresses with refrigerated distilled water can be used to reduce swelling and to soothe the skin with frequent reapplication of white petrolatum to keep the skin coated for days 1-5 post-procedure with strict sun avoidance for the first week post-procedure. Daily use of broad-spectrum sunscreen with SPF50+ will be required after the first week.

Given the current pandemic, limited in-person follow-ups will be scheduled (once at baseline before treatment, then at 12 and 24-weeks post-treatment. Participants will communicate immediate post-treatment issues or concerns along with selfies through MyChart on day 2, 3, 7, 10, 14 to track progress and to identify any post procedural complications in a timely fashion.

There will also be no costs to the patients for the laser procedures as funding will be supplied by the UT Southwestern Dermatology department via an educational grant. Patients desiring treatment of the control side after the study end-point (24 weeks) will be provided at no cost for the participants.

5. Sub-Study Procedures: N/A

6. Criteria for Inclusion of Subjects

- Male and female subjects, English and non-English speakers, and subjects more than 18 years old
- Clinical diagnosis of poikiloderma of Civatte affecting the neck and chest

- Agree to not undergo any other procedures on the neck and chest area during the study
- Agree to refrain from tanning for 6 months post-procedure
- Willing and able to read, understand, and sign the consent form
- Willing and able to adhere to the treatment and follow-up schedule as well as post-treatment care

7. Criteria for Exclusion of Subjects

- Patients under 18 years old
- Active skin infection, dermatitis, or a rash on the treatment area
- Pregnant or lactating patients
- Patients on immunosuppressive medications
- Any laser procedures or chemical peel procedures on the neck or chest area within the past 6 months
- Patients with multiple comorbidities such as diabetes mellitus, cardiovascular diseases, neurologic disorders, internal malignancies
- Personal history or family history of forming keloids or hypertrophic scars, or abnormal wound healing
- Patients with known bleeding disorders or taking more than one anticoagulation medications
- Undergoing any surgery in the treatment area within the past 12 months
- History of radiation to the head, neck, and chest area
- Systemic use of isotretinoin within 6 months
- Any use of gold therapy
- Current smoker or history of smoking within 12 months of study

- Any physical or mental condition in which the investigators deem unsafe for the subject to participate in the study.
- History of recurrent herpes simplex on the neck or chest.

8. Sources of Research Material

Sources of materials used during this study will include data collected from patient surveys, data collected from blinded dermatologists' assessment, and pictures taken of the participants. These materials and data will be obtained at each patient visit. Given the current pandemic, only limited in-person follow-ups will be scheduled (once at baseline before treatment, then at 12 weeks, 24 weeks). Participants will communicate immediate post-treatment issues or concerns along with selfies through MyChart on day 2, 3, 7, 10, 14 to track progress and to identify any post procedural complications in a timely fashion. Materials and data gathered will be obtained specifically for research purposes, and no existing records or specimens will be used.

9. Recruitment Methods and Consenting Process

Subjects will be identified from patients presenting to the dermatology department at UT Southwestern. When a patient with POC is identified, they will be offered inclusion in the study. Informed consent will be obtained. Both English and non-English speaking patients will be included. If the patient is non-English speaking, a certified translator will be used to obtain consent. Each patient will be informed that he or she has the right to withdraw consent and terminate participation in the study at any point if he or she so desires. No vulnerable populations (cognitively impaired, institutionalized, children) will be included in the study to minimize the risk of undue influence or coercion.

10. Potential Risks:

- Ocular – severe ocular complications such as corneal ulceration and cataract could happen with any laser devices. Therefore, CO2 laser specific eyewear will be provided to everyone in the treatment room. Ocular complication for this study should be low since we are mainly targeting the neck and upper chest area instead of the facial area.
- Pain – Topical anesthesia, and a forced-air cooling device will be used to help patients tolerate the procedure. Prolonged severe pain postoperatively may indicate other complications such as infection infection and patient should contact the investigators and will be examined in-person to determine the cause.
- Infection – patients will be counseled on signs of infection such as increased erythema, purulence, oozing and crusting. Patients will submit electronic selfies of the treatment area electronically to investigators on day 2, 3, 5, 7 and 10. Investigators will contact patients if any signs of infection are identified. For patients with skin infection within the past 6 months, topical mupirocin ointment TID applied to the nares will be prescribed to prevent staph colonization.
- Post-inflammatory hyperpigmentation: This usually happen less frequently in lighter skin types which are the groups most commonly affected by POC. However, should this occur, hydroquinone and topical retinoids can be prescribed for the patient at the study end-point to alleviate the dyschromia.
- Prolonged erythema: if erythema lasts more than 3 weeks postoperatively, a mid-potency topical steroid will be prescribed to the patient.
- Scarring: patients with personal and family history of keloid disease and hypertrophic scar formation will be excluded from the study. If hypertrophic or keloidal scars happen, intralesional steroids will be used to flatten the scars.

11. Subject Safety and Data Monitoring

All treatments will be completed at the Dermatology clinics at UT Southwestern where there are adequate resources for medical intervention in case of an adverse event such as increased bleeding, pain, or infection. The risk of severe bleeding is minimal and does not warrant the need for spare blood products or type and screening.

12. Procedures to Maintain Confidentiality

The study materials will not be disclosed to any outside persons or entities. Patient surveys collected will be stored securely in files in the dermatology offices and will not be removed from campus.

13. Potential Benefits

- Improved overall dyschromia and telangiectasia of the chest and neck area
- Overall increased patient satisfaction and quality of life
- Provide patients safe and effective alternative for treatment of discoloration and atrophy of neck and chest area which hopefully can be generalized to similar patient populations.

14. Biostatistics

Descriptive statistics will be used to summarize patient demographics. Count (%) will be used for categorical variables; and mean, standard deviation (SD), and range (min/max) will be used to summarize continuous variables with approximately normal distributions. Skewed continuous variables will be summarized by median and interquartile range (IQR). Outcome data will be collected on patient satisfaction assessment scores and physician's global aesthetic improvement scores, as well as assessment of adverse events. The Wilcoxon signed rank test will be used to compare the magnitude of change between the baseline scores and post-intervention scores. The Wilcoxon signed rank test will also be used to compare the magnitude of change of the treated

area and the control area. A p-score of <0.05 will be considered statistically significant. The target sample size is 10 people.

Outcome Measurement:

Global Aesthetic Improvement Scale`

	Degree	Description
1	Exceptional improvement	Excellent corrective result
2	Very improved patient	Marked improvement of the appearance, but not completely optimal
3	Improved patient	Improvement of the appearance, better compared with the initial condition, but a touch-up is advised
4	Unaltered patient	The appearance substantially remains the same compared with the original condition
5	Worsened patient	The appearance has worsened compared with the original condition

Patient Satisfaction Assessment