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Improvement of disfiguring skin conditions by laser therapy

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A RANDOMIZED CONTROLLED PILOT STUDY ON ABLATIVE FRACTIONAL CO₂ LASER FOR CONSECUTIVE PATIENTS PRESENTING WITH VARIOUS SCAR TYPES

AM van Drooge, C Vrijman, JPW van der Veen, A Wolkerstorfer

Submitted
ABSTRACT

Background: although ablative fractional laser is the gold standard for acne scars, evidence is still lacking for other types of scars.

Objectives: to evaluate the efficacy and safety of the ablative fractional 10600 nm CO₂ laser in the treatment of various scar types.

Methods: we performed an intra-individual single-blinded randomized controlled split lesion trial. Adult patients received 3 laser treatments at 8 week intervals for scars existing at least one year. Primary endpoints were the Physician Global Assessment (PhGA) and the assessment of adverse effects.

Results: twenty-five consecutive patients with atrophic (52%) or hypertrophic (48%) scars located mainly on the body (84%) were included in the study. At 6 months follow up of 21 patients, the PhGA showed no statistically significant difference between treated and untreated side of the scar (p = 0.70). Persistent erythema, post-inflammatory pigmentary changes, and scarring after ulceration (n=3) were observed as side effects.

Conclusion: in this trial involving various types of scars, the efficacy of ablative fractional CO₂ laser could not be confirmed. We presume that different types of scars have a different response to treatment. Future studies should aim to identify the type of scars that may benefit from ablative fractional laser therapy.
INTRODUCTION

Scars are a common phenomenon as they develop after skin injury in patients of all ages. Although most scars do not pose a health risk, they can be highly disfiguring, resulting in decreased quality of life. Also, pruritus, pain and functional impairment do occur in certain cases. Various therapies have been proposed in the treatment of different scar types, such as corticosteroids, 5-fluorouracil, bleomycin, silicone gel sheeting, pressure therapy, radiation, cryotherapy and surgery. However, little evidence on the efficacy is available due to a lack of (randomized) controlled trials, and outcomes are usually disappointing. Since the introduction of lasers in dermatology, many studies have been performed showing lasers to be effective in the treatment of scars. In the treatment of hypertrophic scars, most evidence is available for pulsed dye laser therapy, but also non-ablative fractional lasers have shown efficacy. For atrophic acne scars, multiple randomized controlled studies have shown the ablative fractional carbon dioxide (CO₂) laser to be effective. For the treatment of non-acne scars, evidence for ablative fractional laser therapy (AFLT) is lacking. The aim of our study was to assess the efficacy and safety of ablative fractional 10600 nm CO₂ laser therapy in the treatment of various types of scars. We present the first randomized controlled trial evaluating AFLT versus no treatment, in various scar types of different etiology encountered in dermatological practice.

METHODS

Patients

During the period January 2010 – September 2010 consecutive patients with scars were evaluated for study eligibility and recruited from the outpatient clinic of the Department of Dermatology and the Netherlands Institute for Pigment Disorders of the Academic Medical Centre (AMC) Amsterdam. The study was approved by The Medical Ethical Committee of the AMC, University of Amsterdam (METC 10/026 # 10.17.0623) and was registered on http://clinicaltrials.gov (NCT01358838). Written informed consent was obtained from all study participants. Inclusion criteria were age 18 and older, Fitzpatrick skin types I-IV, scars existing at least 1 year and allowing demarcation of two similar test regions of 2x2 cm, and willingness and ability to comply with the requirements of the protocol. Exclusion criteria were keloidal scars, suspected allergy to lidocaine, use of isotretinoin in the past 6 months, pregnancy or lactation, concomitant skin disease at the site of treatment, high exposure to sunlight or UV light, and patients not considered to be able to follow the treatment protocol. Previous scar treatment was not an exclusion criterion. A herpes simplex infection, formation of blisters larger than 3 mm and clinical deterioration of the treated scar as a result of the treatment were also exclusion criteria.
Intervention
The study was a prospective single (observer) blinded randomized controlled split lesion trial. Two test regions similar in size and appearance were randomized to receive treatment or no treatment. For randomization we used a digitally generated random list (Graphpad Software Inc., La Jolla, CA, USA) executed by an independent individual (EW). Opaque sealed envelopes containing cards indicating the allocation were numbered and opened in ascending order. The allocation was only revealed to the physician performing the laser treatments. This physician was not included in the pre- or post-treatment assessments and patients were instructed not to inform the assessor which area had been treated.

Before treatment, scars were mapped with a permanent marker on a flexible transparent sheet using natural landmarks such as moles as reference. A single physician (AMvD) performed three laser treatments at 8 weeks interval with the UltraPulse Encore 10600 nm CO$_2$ laser (Lumenis Inc., Santa Clara, CA, USA) using the Deep FX hand piece with a spot diameter of 120 µm and a scan size of 10 mm. The laser procedure was performed in a single pass at 600 Hz and with 15% coverage. Microbeam energy used was 40 mJ on the face and 30 mJ on the body, each lowered with 10 mJ in skin types III and higher. The skin was prepared with chloorhexidin solution and anesthetized by subcutaneous infiltration with lidocaine 2% and epinephrine 1:80000. Directly after laser treatment silver sulfadiazine cream was applied under occlusion. Post treatment care involved thrice daily application of fucidic acid cream during 5 days and the use of a sunscreen (SPF 50).

Measurements
Primary endpoint was the assessment of the Physician Global Assessment (PhGA) by a blinded physician (CV or IN). They scored 0-25%, 26-50%, 51-75% or 76-100% improvement of the scar. The presence of adverse effects like persistent erythema, hyperpigmentation, hypopigmentation and scarring, was reported by both investigator and patients. To assess pain, a visual analogue scale (VAS, scale 0-10) was used.

Secondary endpoints were the Patient Global Assessment (PGA), scoring no, moderate, good or excellent improvement of the scar and the Patient and Observer Scar Assessment Scale (POSAS). This is an evaluation tool in which both patient and assessor score the appearance of the scar on six dimensions, on a scale of 1-10 with 10 corresponding to the worst possible scar appearance. The melanin and erythema index, using reflectance spectroscopy (Derma-Spectrometer, Cortex Technology ApS, Hadsund, Denmark) were used to quantify pigmentation and vascularization. The mean of three MI and EI measurements taken from the treated scar, the untreated control, and the normal surrounding skin was calculated at baseline and 6 months after the final treatment.

Digital photographs were taken for documentation with a Powershot G7 Canon Digital Camera (Canon Inc., Lake Success, NY, USA). Photos were standardized with respect to magnification, lighting, exposure and positioning.

Statistical analysis
All data were collected and transferred to Microsoft Excel. The statistical analysis was performed using Statistical Package for the Social Sciences 19.0 software (SPSS, Chicago,
RESULTS

Patient demographics
Twenty-five consecutive patients (36% male, 64% female) visiting our outpatient department with atrophic (52%) or hypertrophic (48%) scars were included in the study and received treatment. Most patients had scars located on the body (84%), resulting from surgery (52%) or trauma (20%). Only two patients had acne scars in the face (Table 1). Nine patients received only 1 of 3 laser treatments; three of them were withdrawn because of ulcer formation due to the laser treatment, 1 patient discontinued treatment because of illness not related to the treatment, and 5 patients discontinued due to a lack of motivation. A total of 21 patients was seen at 6 months follow up.

Primary endpoints
At 6 months follow up, according to the PhGA, mild improvement (26-50%) of the treated side of the scar was found in 7 patients and in 2 of these patients the control side had improved equally. Two other scars showed mild improvement of the control side only. One scar had improved with >50% but this was on both sides of the scar. There was no statistically significant difference ($p = 0.70$) between treated and untreated side on the PhGA score (Figure 1).

Thirty percent of patients experienced mild pain during treatment (median VAS score of 3). Participants reported erythema (87%), crusts (61%), burning sensation (39%), edema (30%), bruising (30%), and vesicles (22%) in the first 5 days after treatment. At 6 months follow up, persistent erythema (48%), post-inflammatory pigmenitary changes (24%), and scar formation after ulceration (14%) were observed by the physician as long-term side effects.
Table 1. Patient characteristics

<table>
<thead>
<tr>
<th>Patient</th>
<th>Sex</th>
<th>Age*</th>
<th>Skin type</th>
<th>Scar type</th>
<th>Scar location</th>
<th>Scar etiology</th>
<th>Scar type</th>
<th>Previous treatment</th>
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<td>PDL, PS</td>
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<td>Atrophic</td>
<td>PDL</td>
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<td>Atrophic</td>
<td>CO2</td>
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<td>Hypertrophic</td>
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<td>IV</td>
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<td>Atrophic</td>
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<tr>
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<td>5</td>
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<td>Surgery</td>
<td>Atrophic</td>
<td>No</td>
</tr>
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</table>

A total of 16 female and 9 male patients with a median age of 30 years (IQR 23-32.5) participated in the study. Median scar age was 6 years (IQR 3.5-15). A total of 11 patients had received previous treatment of their scar. IQR = inter quartile range.

CDLE = chronic discoid lupus erythematosus, PDL = pulsed dye laser, PS = plastic surgery, IC = intralesional corticosteroids, cryo = cryotherapy, CO2 = fractional CO2 laser, Laser = laser therapy, not specified, No = no previous treatment

*Age & scar age in years.

Secondary endpoints

At 6 months follow up, the PGA score indicated a significant difference (p = 0.02) between treated and untreated control sides. Six patients scored moderate to good improvement on the treated side with no improvement on the control side, 2
patients scored equal improvement on both sides, and the other patients scored no
improvement on either side of the scar.
Statistical analysis showed no significant difference in the total POSAS score for both
the observer part of the scale (p = 0.09) and the patient part of the scale (p = 0.19).
Also, skin reflectance spectroscopy measurements after 6 months follow up were
not significantly different in treated and untreated control sides for both the melanin
(p = 0.40) and the erythema (p = 0.65) index.

DISCUSSION
This is the first randomized controlled trial evaluating the effect of ablative fractional
laser therapy in the treatment of scars other than atrophic acne scars.
Strikingly, none of the treated scars in this trial showed good improvement, and
spontaneous improvement of the untreated scars was observed. These findings are not
in line with previous randomized controlled trials on AFLT, where atrophic acne scars
and striae distensae were treated.\textsuperscript{15-17, 19,20} For AFLT of other types of scars, such as
posttraumatic, postsurgical, and burn scars, only anecdotal reports or uncontrolled trials
are available. Shumaker et al. showed that range of motion and overall skin functionality
of traumatic scars of 4 patients improved after 2-4 treatments with ablative fractional
CO\textsubscript{2} laser.\textsuperscript{5} Haedersdal reported a thermal burn scar to improve after a single session
of AFLT, comparing two different laser settings with no treatment.\textsuperscript{21} In a non-controlled
study, Weiss et al. treated 15 patients with atrophic postsurgical scars with a fractional
CO\textsubscript{2} laser. Six months after the final of 3 laser treatments, skin texture, pigmentation,
atrophy and overall appearance had improved in all scars, as scored by both patients
and investigators.\textsuperscript{22} Recently, improvement of mature burn scars was reported in 10
patients, 2 months after 3 sessions of fractional CO\textsubscript{2} laser treatment, as assessed by
both patients and physician using the Vancouver Scar Scale and POSAS assessment.\textsuperscript{23}
Most of the above mentioned papers with positive results are uncontrolled studies without
blinding of observers. Aside from the difference in study design that may account for
less positive outcomes in our study, other factors may have contributed. Location, type
and scar age can be reasons for the poor improvement. The majority of the scars (84%)
treated in our study was located on the body. We hypothesize that scars located on the
face respond better to treatment than scars on the body.\textsuperscript{15-17,22} Scar type and etiology
may also influence the outcome. To date, successful AFLT has been reported in atrophic
(acne) scars and burn scars.\textsuperscript{15-17, 21-23} In our study, only 2 patients with facial atrophic scars
and only one burn scar patient were included. Scar age can influence the results. Fresh
scars are assumed to improve faster and better after laser therapy. Our median scar age
was 6 years with an IQR of 3.5-15 years. Follow up periods of most studies differ from
ours. When follow up is as short as 2 or 3 months, short term side effects like erythema
or hyperpigmentation can be mistaken for repigmentation of hypopigmented scars.
Laser settings may also attribute to poor outcomes, since cautious treatment usually
results in less improvement, while aggressive treatment can cause side-effects. We
used a relatively high energy per microbeam, adjusted for skin type and location. The
coverage (15%) and the treatment interval (8 weeks) are comparable to other studies. Ozog et al. and Shamsaldeen et al. used average energy settings of 20 mJ/mb and 18.9 mJ/mb respectively and reported only minor adverse effects of AFLT.\textsuperscript{23,24}

Side effects were frequently reported in our study. Of the patients that developed post-inflammatory hyperpigmentation, only one had a skin type IV and he was treated with lower energy settings. The 3 patients who unexpectedly developed a wound all

**Image 1.** Hypertrophic scar located on the left ankle of a male patient. Six months after 3 treatments with the fractional 10600 nm CO\textsubscript{2} laser (30 mJ/mb, 600Hz, 15% coverage), this scar was scored with 51-75% improvement on both sides of the scar. Thickness and pliability of the scar had improved in particular.

**Image 2.** Hypertrophic scar located on the right forearm of a female patient. Six months after 3 treatments with the fractional 10600 nm CO\textsubscript{2} laser (30 mJ/mb, 600Hz, 15% coverage), this scar was scored with no improvement. Post-inflammatory hyperpigmentation on the treated side of the scar (side A) was still visible at 3 months follow up, but had almost completely resolved at 6 months follow up.
had skin types II and were treated with 20-25 mJ/mb. Their scars were located on the torso and extremities. Previously, ulceration was reported after AFLT in the neck, which is known to be a susceptible location for side effects.\textsuperscript{25,26} Recently, Chuang et al. reported ulceration after non-ablative fractional laser therapy in 2 patients and suggested that the 1% lidocaine with epinephrine injections were the culprit.\textsuperscript{27} Other factors that can account for the side effects in our study, are all of the above mentioned factors like location, type and age of the scar, and laser settings used.

Patients judged that the treated side of their scar had a significantly better appearance than the untreated control side, although none of them scored the improvement as excellent. The positive results scored by one third of our patients, are in contrast with the results as scored by the physician. This stresses the importance of controlled studies with blinded observers.

This study is subject to several limitations. First of all, the study population is small. We included consecutive patients with divergent etiology, location and type of scars. This resulted in a very heterogeneous patient population. Since the subgroups were so small, comparison of results in scars of different etiology or different location was precluded. Also, the number of patients who dropped out after the first treatment was higher than expected. Reasons for drop out were the lack of direct clinical improvement and the effort to come to the clinic. The fact that we used semifixed energy settings may also be regarded as a limitation. If we had used individualized settings, outcomes might have been better with fewer side effects.

In summary, ablative fractional laser therapy is not effective in every type of scar encountered in dermatological practice. Optimization of laser settings in the presence of scar characteristics such as location, age and etiology may improve outcomes and prevent side effects. More studies with scars of other etiology than acne in higher patient numbers are necessary to identify the type of scars that may benefit from ablative fractional laser therapy.

**ACKNOWLEDGEMENTS**

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