Low Density, Non-Ablative Fractional CO_2 Laser Rejuvenation

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Background and Objectives: Fractional skin rejuvenation has gained increased interest since its introduction in 2003. Both non-ablative and ablative lasers as well as different treatment techniques have been devised. Recent clinical studies indicate that a paradigm of low spot density combined with high fluences tend to produce better clinical results and less risk of post-inflammatory hyperpigmentation in darker skin types. The present study is focused on investigations of the clinical outcome by non-ablative fractional CO_2 treatments with a single pass with low spot density.

Methods and Materials: A CO_2 laser was equipped with a scanner enabling it to perform fractional treatments with 36, 64 or 100 microthermal zones (MTZ)/cm^2. Twelve patients participated in the study. The perioral area was treated three times with 1-month intervals using a spot density of 64 MTZ/cm^2, a spot diameter of 0.5 mm, a microbeam energy of 36–60 mJ, and a pulse duration of 3–5 milliseconds. Follow-up was performed 3 months after the last treatment.

Results: At the 3-month follow-up 72.7% of the volunteers had obtained improvement in ultrasonographically determined dermal density, and the average improvement was 40.2% (SD: 48.0%). This improvement was statistically significant ($P<0.006$). Eighty percent of the volunteers rated the reduction in visible perioral wrinkles to be fair, good or excellent. For reduction of irregular pigmentation, fair, good or excellent clearance was reported by 62.5% of the volunteers.

Conclusions: The present study demonstrates subjective improvements in wrinkles, skin texture and mottled pigmentation as well as statistically significant objectively measured improvements in ultrasonographical dermal density after three non-ablative fractional CO_2 laser treatments. Lasers Surg. Med. 40:454–460, 2008.
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Key words: fractional; CO_2 laser; photo rejuvenation; skin rejuvenation; wrinkle reduction

INTRODUCTION

Fractional optical skin thermolysis techniques were first used to apply argon laser energy to the skin in order to treat vascular malformations more uniformly. Single spots of 2 mm diameter were arranged in a linear fashion leaving alternate 2–3 mm wide untreated bands, from which the skin would heal by controlled scar formation using either a manual technique or by a scanner (Hexascan) [1–3].

Microfractional photothermolysis, which is a further development of the technique using spot sizes of less than 1 mm, has proven to be efficient for treatment of wrinkles, melanocytic pigmentation, melasma, acne scars as well as photodamaged skin [4–8].

The first microfractional skin rejuvenation system was based on a 1550-nm glass fiber laser which was introduced in 2003 (Fraxel®, Reliant Technologies, Mountain View, CA, USA). This laser system applies arrays of microscopic spots, which induce microthermal zones (MTZ) in the skin tissue. The density of these microspots could be selected to be either 125 or 250 MTZ/cm^2, and due to an overlapping and multiple pass technique the treated areas would in total receive 1,500–2,500 MTZ/cm^2. The energy used varied typically between 6 and 12 mJ per microspot. The spot size was 50–70 μm resulting in a MTZ about 70–100 μm diameter due to lateral heat conduction in the tissue and the damage extended to a depth of 250–750 μm, depending on the amount of energy per pulse [9].

A newer equipment (Lux1540™, Palomar, Burlington, MA, USA) takes advantage of a stamping technique, in which 100 or 320 MTZ/cm^2 are delivered in a single shot. The area of skin exposed to this shot has a diameter of 10 or 15 mm, and the maximum delivered energy per MTZ is 70 or 15 mJ, respectively. The pulse duration is 5 or 10 milliseconds leading to a damage depth of up to 1 mm. Due to the relatively low absorption of the 1540 nm (Palomar) and 1550 nm (Fraxel) wavelengths, damage to the stratum corneum is reduced.

The Er:YAG laser operates at a wavelength (2940 nm) where tissue water absorbs maximally. It is used for ablative skin rejuvenation [10–12], and therefore it was obvious also to utilize this laser in a fractionated manner for treating rhytids, fine lines and for skin resurfacing.

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In a newly introduced piece of equipment (Pixel, Alma Lasers, Caesarea, Israel) the stamping technique is also used to create either 40 or 67 MTZ/cm^2 within an area of 11 mm×11 mm. Each MTZ has a diameter of 700 μm. Maximum pulse energy per micropulse is 24 and 13 mJ, respectively. The penetration depth is 20–50 μm, but a pulse stacking technique can be used to obtain deeper penetration.

The CO_2 laser [13–15] emitting a wavelength of 10.6 μm is the state of the art for ablative skin rejuvenation. CO_2 lasers operated in a fractional mode might therefore be expected to achieve more efficient fractional treatments than the near-infrared fractional laser types described previously. Four manufacturers have now released fractional CO_2 lasers. The technical specifications differ considerably; the micro-beam spot size varies from 100 μm (Fraxel®, Reliant) to 1.3 mm (Active FX, Lumenis, Yoknema, Israel) and the spot density from 30 to 1000 MTZ/cm^2. Released energy per microspot also varies substantially from 10 to 80 mJ. The very first results with fractional CO_2 lasers were presented at the ASLMS meeting in 2007 by Rahman et al. [16], Weiss et al. [17], Fournier et al. [18] and Hale et al. [19]. Three-month follow-ups showed promising result with 50–75% improvements in wrinkles and acne scars. However healing time was substantial, and the reported down-time was between 4.5 and 10 days.

To obtain better and more consistent results it is important to investigate the influence of the different treatment parameters on clinical treatment efficacy and side effects. In a split face study with a laser (Fraxel SR 750) emitting a wavelength of 1550 nm, Kono et al. [20] investigated the efficacy as function of used fluence and density in 33 Asian females. One group was treated with 8 passes and a fixed fluence of 8 mJ; one half-face was treated with 125 MTZ/cm^2 and the other side with 250 MTZ/cm^2. A second group had 8 passes with a fixed density of 125 MTZ/cm^2; one side was treated with 8 mJ, the other with 16 mJ. The last group had 8 passes performed; one side was treated with 8 mJ and 250 MTZ/cm^2, the other with 16 mJ and 125 MTZ/cm^2. The highest efficacy was obtained in patients treated with high fluence and low density. Pain, erythema, and swelling were more frequently observed and persisted longer in patients treated with higher densities and higher energy.

Side effects after fractional laser treatments for skin rejuvenation with a laser emitting 1550 nm have been investigated in 60 follow-up visits of patients with skin types I–IV by Fisher and Geronemus [21]. All patients had transient post-treatment erythema. Transient facial edema occurred in 82%, dry skin in 86.6% and flaking of skin in 60% of the patients.

Post-inflammatory hyperpigmentation (PIH) after fractional resurfacing is a commonly noted side effect, especially in darker skin types. In a prospective study of 18 Chinese patients Chan et al. [22] treated forearms with a CO_2 laser using nine different densities and energy levels. Both the density and energy of the treatment influences the risk of PIH in dark-skinned patients. It was found that patients who underwent a high-energy but low-density treatment had a lower risk of getting PIH, than those who underwent a low-energy and high-density treatment. Skin surface cooling to prevent bulk skin tissue heating may also be important, and it was concluded that, by using adequate laser parameters, the risk of PIH in dark-skinned patients can be significantly reduced.

As the clinical data up to now indicates that low spot density combined with higher energy levels tend to give more efficient fractional treatments, and less risk of PIH, we focused this study on investigations of the clinical outcome by fractional CO_2 treatments with a single pass with 64 MTZ/cm^2 and a micro-beam energy of 36–60 mJ corresponding to 12 W laser output with pulse durations of 3–5 milliseconds.

METHODS AND MATERIALS

Volunteers

The study included 12 healthy female volunteers (mean age: 54.2 years, SD: 8.3 years, range: 38–63 years), with Fitzpatrick photo skin types I–IV (mean: 2.4; SD: 0.9) all with photo-damaged skin with substantial perioral wrinkles. Their actual degree of pigmentation varied from light to medium.

Sun tanned volunteers and volunteers who were exposed to sun or sun beds in the week before the study were excluded. Also, filler treatments of the upper lip within 3 months prior to treatment, or a history of keloids or hypertrophic scarring were exclusion criteria.

Laser System

All treatments were performed with a flexible optical fiber based CO_2 laser (MedArt 610, MedArt, Hadsund, Denmark), equipped with a scanner specially developed for fractional skin resurfacing (MedArt 457, MedArt, Denmark). The density of the microthermal zones, which had a fixed diameter of 0.5 mm, can be adjusted to 36, 64 or 100 MTZ/cm^2. The pulse duration can be adjusted between 2 and 10 milliseconds.

Ultrasonic Measurements

Skin density and skin thickness were measured prior to first treatment and at the follow-up visit in a blinded fashion on ultrasonograms, obtained with a 20 MHz ultrasonic equipment (DermaScan, Cortex Technology, Denmark). This device is FDA cleared for general purpose skin scanning and provides a 60 μm×200 μm resolution and 15 mm penetration depth, performing a B-scan with a length of 15 mm. All scans were performed on the right side of the upper lip immediately medial to the nasolabial fold and with the ultrasound transducer aligned with the nasolabial fold and touching the ala nasi.

The measurements of skin thickness and density were performed on a volume of dermis by placing two lines on the B-scan indicating the epidermal–dermal junction and the dermal–subcutaneous border, respectively (Fig. 1). The ultrasound system automatically calculated the distance between these two lines as well as the average density of echoes in the skin volume defined by these two lines and the ultrasound beam width, which equals 0.2 mm.

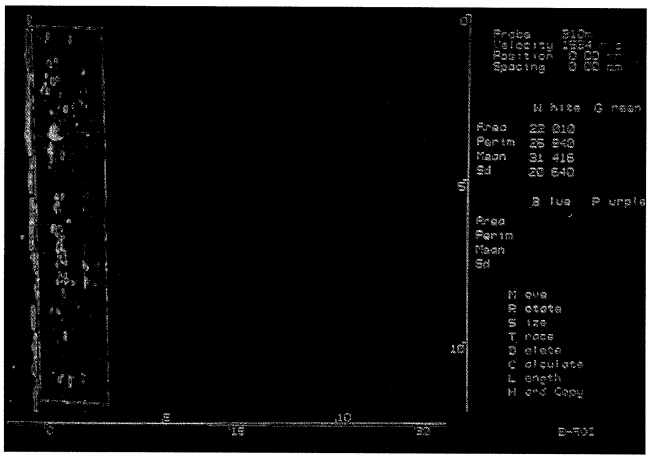


Fig. 1. The ultrasonographical measurement of skin thickness is defined by the distance between the two vertical white lines indicating (left) the lower border of the epidermis and (right) the lower border of the dermis, respectively. The dermal collagen density is automatically calculated based on the volume defined by these two lines and the ultrasound beam width, which equals 0.2 mm.

Photo Documentation

All photographic documentation was performed with an analog Nikon F601 camera. Frontal as well as 45° facial photographs were taken before each treatment and at the follow-up visit.

Local Anesthesia

Nerve blocks and local infiltration analgesia was performed with 2% carbocaine without epinephrine.

Laser Treatment Procedure

The fractional CO_2 laser treatments were performed only on the upper lip. A single pass with a spot density of 8 × 8 spots/cm^2 was used. The spot size was 0.5 mm and laser power was fixed to 12 W during the entire study. For the first treatment, pulse duration of 5 milliseconds was used in all volunteers. At the second and third treatment the pulse duration was reduced to 3 or 4 milliseconds and individually chosen in accordance with the obtained skin reaction. Care was taken neither to overlap nor to leave areas untreated.

Cicaplast® cream (La Roche-Posay, France) was applied to the treated skin immediately after treatment and the patients were instructed to wash the face with lukewarm water twice daily for 2 days post-treatment and to apply Cicaplast® cream at least twice daily for the following 3 days. Thereafter a standard moisturizing cream was used until 1 month after the last treatment.

All volunteers have had three treatments with 1-month intervals and a follow-up was performed 3 months after the last treatment.

Clinical Evaluation

Efficacy. The clinical outcome was evaluated 3 months after the last of three treatments by objective ultrasonographic measurements of changes in skin density and thickness as well as a blinded evaluation by a certified dermatologist, experienced in cosmetic dermato-surgery, who did not participate in the treatment of the volunteers. These evaluations were based on ranking the close-up photography taken prior to the first treatment and at the follow-up visit.

Safety. Any side effects were evaluated and registered by each treatment and by the follow-up.

Volunteer Evaluation

The volunteers' evaluation of efficacy were performed by ranking the treatment results into five groups: 0%, 1–24%, 25–49%, 50–74% and 75–100% wrinkle clearance, which corresponded to the following grouping of the subjectively evaluated effect: none, poor, fair, good and excellent (Scores 0, 1, 2, 3 and 4). The evaluations were performed individually for each of the following parameters: reduction of visible wrinkles, improvements in skin texture and clearance of irregular pigmentation.

Also the degree of redness was evaluated by the volunteers and was ranked into four groups: no redness, faint redness, moderate redness and strong redness (Scores 0, 1, 2 and 3).

Histological Investigation

In order to determine the sizes of the microthermal zones, a histological investigation was performed on abdominal skin from a single patient scheduled for abdominal plastic surgery. Standard haemotoxylin/eosin and Van Giesson stains were used.

Statistical Evaluation

The Student's t-test was used, and statistical significance was accepted at the 5% level.

RESULTS

Improvements in Skin Tightness and Density

The ultrasonographically based skin density measurements before the first treatment were between 11.8 and 37.4 (mean: 25.5; SD: 8.8). At the 3-month follow-up 72.7% of the volunteers had obtained improvement in the skin density, now ranging from 15.6 to 54.2 (mean: 34.0; SD: 11.7). This improvement was statistically significant ($P<0.006$). The average improvement in skin density was 40.2% (SD: 48.0%) and the distribution of the individual relative improvements can be seen in Figure 2. An example of the increased ultrasonographic dermal density after each treatment is shown in Figure 3.

Six out of 11 volunteers also obtained a slight increase in skin thickness by the 3-month follow-up. For four volunteers no difference was registered and a single volunteer obtained a decrease of 2% in skin thickness (Fig. 4). The average skin thickness increased from 1.79 to 1.93 mm, and even though this increase is much less dramatic than the skin density, the difference is statistically significant ($P<0.02$).

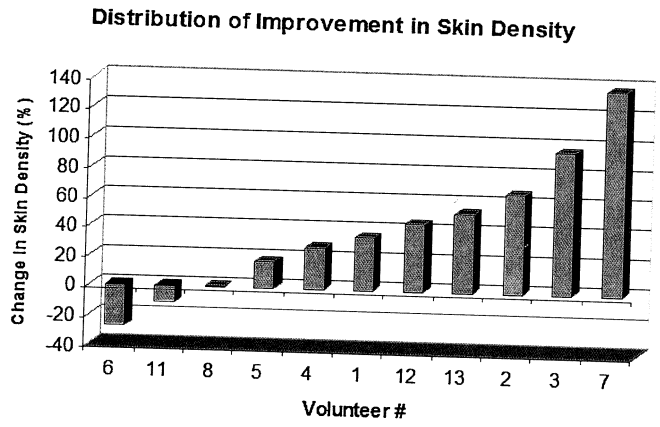


Fig. 2. Improvement in ultrasonographically determined skin density was statistically significant ($P<0.006$) and occurred in 8 out of 11 volunteers.

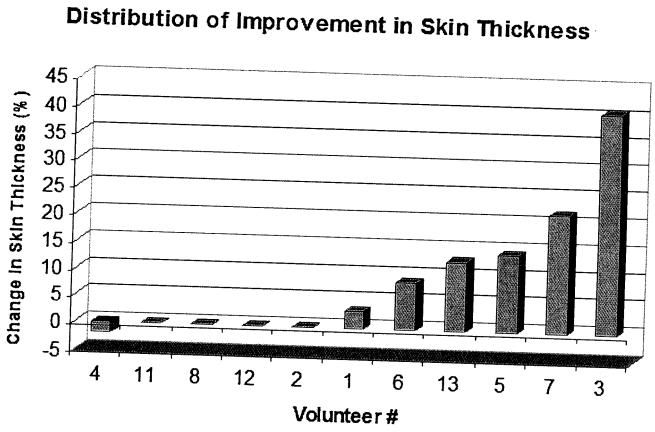


Fig. 4. Improvement in skin thickness is statistically significant ($P<0.02$) and occurred in 6 out of 11 volunteers.

Clinically Evaluated Side Effects

No signs of pinpoint bleeding or purpura were registered during the treatment or during the days following treatment. No skin atrophy, scarring, or pigment disturbances were registered by the 3-month follow-up.

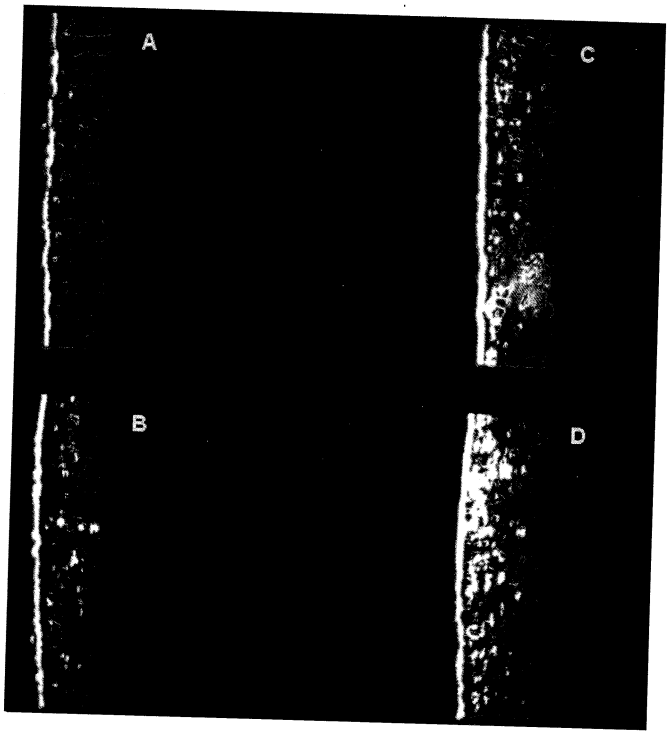


Fig. 3. Typical ultrasonographically determined progression in skin density by CO_2 laser treatments. Observation **A**: taken before treatment, **B**: taken 1 month after 1st treatment, **C**: taken 1 month after 2nd treatment and **D**: taken 3 months after 3rd treatment.

Clinically Evaluated Wrinkle Reduction

The clinical blinded evaluation 3 months after last treatment was based on analog photographs. In nine out of 11 cases the clinical evaluator was not able to see any difference in visible perioral wrinkles. For only one of the remaining two volunteers, the before and after photo was evaluated correctly.

Volunteers' Evaluation

At the second and third treatment and at the follow-up visit all volunteers were placed in front of a mirror and asked to evaluate improvements in skin texture, reduction in irregular pigmentation and reduction wrinkles based on a comparison with photos taken before treatment. Ninety percent of the volunteers noted increasing beneficial effects during the period of the study. By the 3-month follow-up, fair, good or excellent reduction in visible perioral wrinkles (Fig. 5) was reported by 80% of the volunteers and the average improvement score was 2.25 (SD: 0.86).

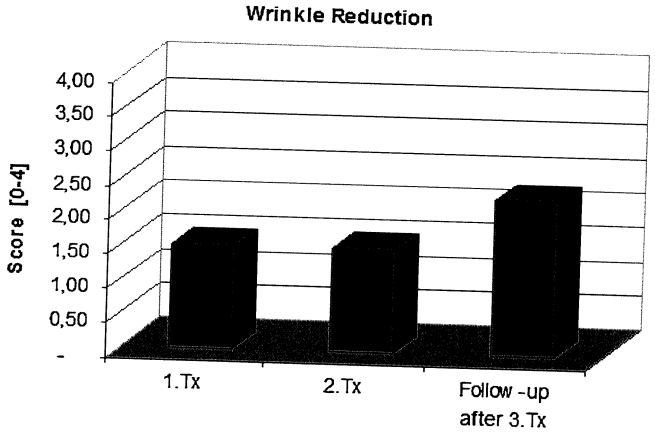


Fig. 5. Volunteer-reported reduction in perioral wrinkles 1 month after one and two treatments and 3 months after the last of three treatments.

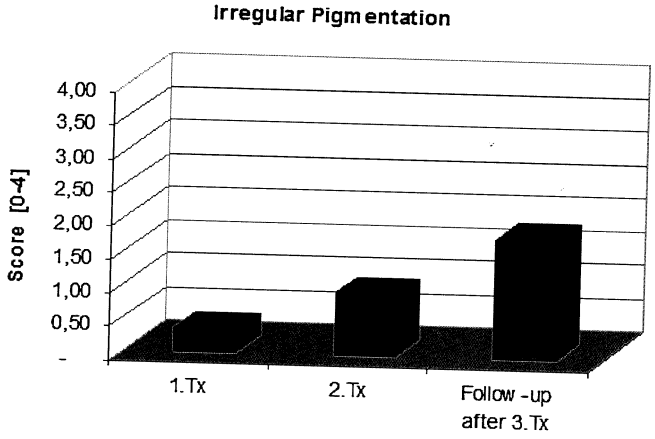


Fig. 6. Volunteer-reported improvement of mottled pigmentation 1 month after first and second treatments, and 3 months after third treatment.

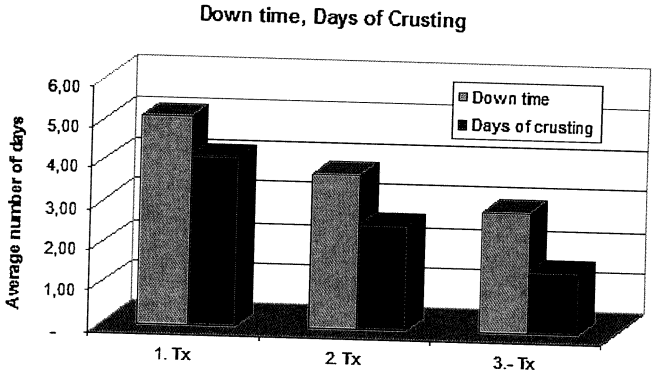


Fig. 8. Volunteer-reported down-time and days of crusting after first, second and third treatments.

For reduction in irregular pigmentation (Fig. 6) fair to excellent clearance was reported by 62.5% of the volunteers and the average improvement score was 1.75 (SD: 1.16).

Improvement in skin texture (Fig. 7) was reported as being fair, good or excellent by 60% of the volunteers. The average score was 2.05 (SD: 1.01).

Side Effects

One to four days after each treatment, all volunteers reported crusting lasting up to 15 days. The average duration of crusting decreased after the second and third treatment. After the first treatment the crusting lasted for on average 4.13 (SD: 4.12) days; after the second and third treatments: 2.56 (SD: 1.63) days and 1.50 (SD: 1.62) days, respectively. The duration of down-time varied from 2 to 10 days after the first treatment (mean: 5.08; SD: 3.6), dropping to 1–6 days after the second (mean: 3.75, SD: 1.3) and third treatment (mean: 2.9; SD: 2.0) (Fig. 8).

The intensity of skin redness as reported by the volunteers decreased after the second and third treatments and reached on average 1.46 (SD: 0.84), 0.83 (SD: 0.61) and 0.94 (SD: 0.56) after the first, second and third treatments. The duration of the skin redness after each treatment lasted 1.64 (SD: 0.92) weeks, 1.11 (SD: 0.78) weeks and 1.25 (SD: 0.89) weeks, respectively. Three out of 10 patients felt a burning sensation lasting for up to 4 days after the first treatment. Three patients noticed a temporary skin darkening after second and third treatment, which had subsided by the follow-up visit.

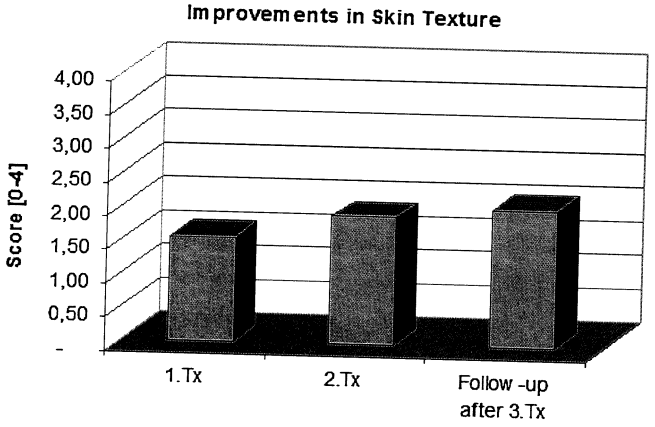


Fig. 7. Volunteer-reported improvement in skin texture 1 month after first and 1 month after the second treatment, and 3 months after the third treatment.



Fig. 9. Microthermal zone (MTZ) after CO_2 laser, 48 mJ, spot diameter 0.5 mm, biopsied immediately after exposure. The injury is characterized mainly by tissue coagulation and ablation is not visible (Masson's stain, original magnification 400×).

Histological Investigation

Histology (Fig. 9) shows that ablation only has taken place in the outer stratum corneum and the tissue injury is due to heat damage (thermal coagulation) of the epidermis and papillary dermis.

DISCUSSION

After three fractional CO_2 laser treatments performed with single passes, the present study shows an average increase in skin density of 40.2% (SD: 48%). This result was obtained with a microspot density as low as 64 MTZ/cm^2 and a microspot energy of 36–60 mJ (spot size 500 μm). In none of the 12 treated patients was PIH registered at the follow-up visit. This absence of PIH supports the observations by Chan et al. [22] where a reduced risk of PIH was found for the combination of low density and high intensity CO_2 laser treatment. The high efficacy also corresponds to results obtained by Kono et al. [20] in Asian female patients treated with a laser emitting 1,550 nm, where highest efficacy was registered in patients treated with high fluence and low density.

The volunteers reported increasing improvements in wrinkle, skin texture and irregular pigmentation during the entire study. By the 3-month follow-up, improvements in wrinkles were rated to be fair, good or excellent by 80% of the volunteers. Improvements in skin texture and improvements in irregular pigmentation were, in the same manner, rated to be fair to excellent by 60% and 62.5% of the volunteers, respectively. The high improvements in skin texture and wrinkle reduction scored by the volunteers were supported by the objectively measured improvements in ultrasonographically measured skin density. On the other hand no improvements were found by the blinded clinical evaluation of photographs; however the ambient lighting of the photographs was not absolutely standardized, which made the evaluation very difficult. Also previous studies have pointed out the difficulties in documenting three-dimensional clinical improvements on two-dimensional photographs.

The relatively large spot size (500 μm) in combination with spot energies of 36–60 mJ results in fluences of 18–30 J/cm^2. These are low compared to the fluences used in two fractional CO_2 laser in vivo and ex vivo histological investigations reported by Hantash et al. [23,24]. In these two studies a 100 μm spot size in combination with spot energies of 5–30 mJ were used, leading to spot fluences of 63–380 J/cm^2. The low fluences used in the present study may explain the heat damage with lack of direct ablation in the histological investigation (Fig. 9).

It is generally assumed that the efficacy of CO_2 laser fractional resurfacing, with only 20–35% of the skin cross-section being treated, is dependant on the depth of the MTZ; i.e. deeper damage results in larger treated volume and hence better clinical efficacy. These zones of coagulated and tightened collagens induce a long-lasting wound healing process resulting in skin shrinkage and thereby wrinkle reduction. Hantash et al. hypothesize that for a constant treatment density the depth of the lesions becomes the dominant predictor of final tissue shrinkage, but they state that further investigations are needed to substantiate this.

In the present study the fractional treatment was performed with dwell times and an energy level which did not lead to tissue ablation (Fig. 9). However tissue ablation does not seem to be a prerequisite for efficacy as objectively measured improvements in skin density were found in eight out of eleven volunteers with levels ranging from 17.8% to 138%. This strongly indicates that not only ablated MTZ are responsible for neoformation of collagens, but also heat-denatured collagens and cellular necrosis play important roles in the efficacy of the fractional resurfacing process.

In a comparison of tissue damage obtained by non-ablative fractional resurfacing and ablative fractional resurfacing Hantash et al. found that the shorter dwell time with higher power and smaller spot size used in the treatments ablated larger volumes, penetrated deeper, and generated less thermal diffusion into the surrounding tissue and hence created a thinner layer of denatured collagen or necrosis. This modality might not be optimal, as the present study showed significant subjective improvements and significant objective increases in skin density by heat denaturation of collagens without ablation. The lesion depth for fixed spot size and dwell time can be controlled by the laser energy setting. Heat diffusion to the surrounding tissue depends mainly on the dwell time and the spot size.

CONCLUSIONS

The present study showed patient self reported improvements of wrinkles, skin texture and mottled pigmentation as well as objectively measured improvements in skin ultrasonographical density after three non-ablative fractional CO_2 laser treatments. No post-inflammatory hyperpigmentation or other adverse effects were observed. The basic mechanism of fractional resurfacing is yet not fully understood and it still remains to be discovered if the treatment effect can be further improved by optimizing the CO_2 laser parameters in order to modify the shape of MTZs and hence the ratio of ablated/denatured collagens.

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