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Fractional carbon dioxide laser resurfacing of skin grafts: long-term results of a prospective, randomized, split-scar, evaluator-blinded study

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The clinical trial was conducted at the Department of Dermatology of the University Medical Centre Regensburg.
Conflict of Interest Disclosures: All authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest and have disclosed the following: The authors have stated explicitly that there are no conflicts of interest in connection with this article.

Abstract

Background

Fractional ablative resurfacing is frequently used for treating atrophic and acne scars as well as for the early improvement of scars after surgery. No evidence-based clinical data on improving the appearance of skin grafts by fractional CO_2-laser resurfacing have been available so far.

Objectives

The primary outcome parameter was the adaptation of the skin graft to the surrounding skin 2, 6, and 12 months after the second laser treatment. Secondary outcome parameters

Methods

The randomized half of the skin graft was treated with the fractional CO_2-laser two times in a 4-week interval, whereby the first laser treatment was conducted 3–8 weeks after surgery. Two independent dermatologists assessed the adaptation of the treated area and the untreated control of the skin graft to the surrounding skin using follow-up pictures and an 11-point scale (0 representing no adaptation at all and 10 complete adaptation).

Results

Adaptation to the surrounding skin was significantly improved after laser therapy. The mean investigator ratings showed poor adaptation to the surrounding skin before the first treatment (treatment: 2.24 ± 1.00; control group: 1.95 ± 1.27; $P < .001$; $n = 26$) but significant improvement at the follow-up visits (8 weeks: treatment: 6.38 ± 1.47; control group 5.29 ± 1.27; $P < .001$; 6 months: treatment: 7.31 ± 1.24; control group 6.04 ± 0.91; 12 months: treatment: 7.6 ± 1.26; control group: 6.57 ± 1.02; $n = 26$). After fractional ablative laser treatment, appearance of the skin grafts was significantly improved for all time points. Profilometric analysis showed significantly reduced skin roughness 1 year after laser treatment compared to control ($P = .003$). Pigmentary irregularities were improved. Melanin distribution was significantly more uniform 1 year after laser treatment compared to control ($P = .034$). Patients were reasonably satisfied with both sides of the skin graft before treatment but more satisfied with the laser-treated side at the other time points ($P < .001$).

Conclusions

Adaptation of the skin graft to the surrounding skin was significantly improved after ablative fractional skin resurfacing. Skin roughness and melanin variation were also improved. Patient satisfaction with the appearance of the skin graft was significantly higher after graft resurfacing. Thus, this treatment modality can be recommended for patients wishing to improve the appearance of their skin graft. Lasers Surg. Med. 50:1010–1016, 2018. © 2018 Wiley Periodicals, Inc.

INTRODUCTION

Fractional laser therapy has been intensively investigated over the past few years 1-6. Many controlled clinical trials have proven the efficacy of fractional CO_2-laser resurfacing for treating photoaged skin and rhytides 7, 8, atrophic acne scars 9-11 as well as postoperative and traumatic atrophic scars 12. No randomized controlled studies are yet available on the treatment of hypertrophic scars, but there is evidence that fractional CO_2-laser resurfacing

fractional CO_2-laser resurfacing in a prospective randomized, comparative split-scar study.

Dermabrasion has been used for improving the appearance of skin grafts several months after grafting 17. However, this procedure is relatively difficult to conduct, needs sterile conditions, requires local anesthesia and is associated with considerable side effects such as weeping and crusting. Because dermabrasion may require prolonged recovery and involve post-procedural complications, this procedure is less frequently applied. Patients often rate the success of surgery and the skill of the surgeon on the basis of the appearance of the scar. For this reason, an additional resurfacing procedure may be required in difficult cases or for patients with ambitious aesthetic demands. Fractional CO_2-laser resurfacing could be used as an alternative and less elaborate treatment to improve the appearance of skin grafts by texture remodeling and neocollagenesis 18-20. Because no clinical trial has been focused on fractional laser therapy of skin grafts so far, this clinical study investigated the cosmetic outcome of split-thickness and full-thickness skin grafts. As the blending of the skin graft is a key outcome measure and the treatment goal of post-surgical laser therapy, this split-graft study evaluated the adaptation of skin grafts to the surrounding skin by comparing the investigator ratings of laser-treated with control sites. We also objectively measured skin pigmentation, skin roughness and resizing of the treated graft area and untreated control. Furthermore, we assessed patient satisfaction with the cosmetic outcome and the side effects.

MATERIALS AND METHODS

Study Design

In a prospective, mono-centric, one-armed study, 29 skin grafts of 26 patients were compared regarding treatment efficacy before and after laser therapy. The study was conducted as a side-by-side comparison, in which one half of the skin graft served as untreated control. The study protocol was approved by the Ethics Committee of the University of Regensburg (approval number: 11-101-0206). Written informed consent was obtained from each patient before enrollment.

Primary outcome parameter was the adaptation of the skin graft to the surrounding skin at visits three to five. Secondary outcome parameters were melanin variation and skin roughness measured *in vivo* with an Antera 3D™ (Miravex, Dublin, Ireland) skin imaging device, resizing of the skin graft and the patient satisfaction score.

In addition, safety parameters were documented (adverse events [AE] and serious adverse events [SAE]).

ethnicity aged ≥18 years and presence of a split-skin or full-thickness skin graft measuring ≥2 cm in diameter that had been transplanted during the preceding 3–8 weeks. Exclusion criteria were completely or partially necrotic skin grafts, pregnancy, Fitzpatrick skin type IV–VI, presence of a skin disease influencing the evaluation of the study treatment and suspected lack of compliance.

Study Treatment

Each patient received two treatments at a 4-week interval, whereby the first treatment was conducted 3–8 weeks after surgery. Skin grafts were divided into two equally large and identically looking halves with a white adhesive stripe and a template consisting of self-adhesive foil. The allocation of the treatment and control areas was randomized. A randomization list was generated by the Centre for Clinical Studies with the software program SAS 9.2. The treatment allocation within each patient was concealed for the investigator by using closed and opaque envelopes.

The skin grafts were photo-documented with a FotoFinder mediscope for skin grafts on the face (FotoFinder Systems GmbH, Bad Birnbach, Germany) and a Canon Powershot G10 (Canon Deutschland GmbH, Krefeld, Germany) before each treatment as well as 8 weeks and 6 and 12 months after the last treatment. Besides, skin topography and the distribution of melanin was measured *in vivo* using an Antera 3D™ (Miravex, Dublin, Ireland) skin imaging device. The skin grafts were cleaned with an alcoholic disinfectant (Softasept® N, B. Braun Melsungen AG, Germany) directly before photo-documentation and *in vivo* measurements. Each skin graft and separation line was marked on a self-adhesive transparent foil (OpSite Flexigrid, Smith and Nephew, Hamburg, Germany) to ensure that the *in vivo* measurements at each visit were conducted in the identical area. Fractional CO_2-laser treatment was conducted in the randomized half with an additional margin of 1 cm of surrounding skin by the same clinician. The clinical trial was conducted at the Department of Dermatology of the University Medical Centre Regensburg.

Technical Data

We used a fractional CO_2-laser (Exelo$_2$, Alma Lasers, Germany, 10.6 μm, microbeam spot size 250 μm) with adjustable parameters for the density of microspots, pulse width, and energy. A round laser scanning pattern of variable diameters was applied in the “Soft Random Mode,” in which laser spots are randomly placed in the treatment area with the borders gently fading out. Therefore, no geometric patterns were visible on the skin after treatment. Using a spot density of 25 or 50 cm^2 and conducting four to eight rounds achieved a homogenous distribution of microspots. Pulse duration and pulse energy were slightly altered for each

the laser scanner (Zimmer Cryo 6, Zimmer MedizinSysteme GmbH, Neu-Ulm, Germany). We used airflow setting 1 during the treatments. Treatment parameters are shown in Table 1.

Table 1. Average Treatment Parameters (n = 29) (mean ± SD)

	First laser treatment	Second laser treatment
Pulse duration [ms]	2.6 (SD 0.5)	2.7 (SD 0.5)
Pulse energy [mJ]	55.3 (SD 7.1)	58.5 (SD 8.0)
Microspots per cm^2	283 (SD 60)	312 (SD 56)

Data are presented as mean (SD).

Skin topography and distribution of melanin were measured *in vivo* with the Antera 3D™ (Miravex, Dublin, Ireland) imaging system, consisting of a handheld imaging device and a connected laptop with a pre-installed proprietary software. Details about this skin imaging device have been published elsewhere 21.

Outcome Assessment

Clinical evaluation

Adaptation of the skin grafts to the surrounding skin—defined as the primary endpoint—was assessed by two experienced dermatologists for the treated areas as well as for the control areas. Adaptation was defined as the blending of color and texture between the graft and the surrounding skin. The dermatologists were not involved in the study and made their ratings independently of each other. Pre-treatment pictures and follow-up pictures taken 8 weeks and 6 and 12 months after the last treatment were evaluated. Ratings were made on an 11-point scale, in which 0 represented no adaptation at all and 10 complete adaptation to the surrounding skin.

In vivo skin measurements

The skin grafts were measured *in vivo* before the first treatment and at each follow-up visit. For measuring skin roughness, we marked the respective side in the pre-treatment image. Subsequently, the identical area was automatically marked in the follow-up images. Skin

For measuring melanin, we marked the respective side in the pre-treatment image. The identical area was automatically marked in the follow-up image, and the concentration and distribution of melanin were calculated by the software. The average of melanin is calculated as the sum of melanin values at each point within the selected area divided by the number of points. The absolute melanin variation is defined as the mean of the deviation of all melanin values from the melanin average.

For measuring resizing of the skin graft, we used the public domain image processing program ImageJ. In case of clearly identifiable margins of the skin graft before treatment and 12 months after the second treatment, the treatment side and the control side were marked in the picture. The size of the two halves of the skin graft was assessed by determining the number of the pixels in the image. Resizing was identified by comparing the marked areas in the pre-treatment and post-treatment images.

Patient-reported outcomes

We also asked the patients about their level of satisfaction with the overall appearance of the skin graft separately for both sides (4 = very satisfied, 3 = satisfied, 2 = somewhat satisfied, and 1 = dissatisfied).

Sample Size

Sample size was calculated by means of the primary endpoint (cosmetic outcome defined as skin grafts matching adjacent skin) and assessed by using an 11-point scale ranging from 0 (no adaptation) to 10 (complete adaptation). We considered a mean difference of $\Delta = 1.0$ between the two treatment areas clinically relevant (assuming a standard deviation of SD = 1.5). Because every patient served as their own control, the correlation between the two areas had to be considered and was conservatively estimated as $r = 0.3$. A sample size of 27 patients achieved 80% power to detect a mean difference of 1.0 between the two treatment regimens, assuming a standard deviation of 1.5 with an estimated correlation of 0.3 and a significance level α of 0.05 using a two-sided paired t-test. With an estimated lost-to-follow-up rate of 10%, a total of 30 patients were required. The sample size was calculated with SAS 9.2.

Statistical Analysis

All analyses were conducted with the software program SAS 9.4 (SAS Institute, Cary NC). Data are presented descriptively as mean ± standard deviation (SD) for continuous variables or as absolute and relative frequencies for categorical data. Inter-rater agreement was assessed using the inter-class correlation coefficient (ICC). All further analyses were done by means of

Bonferroni method. All *P*-values of the secondary endpoints were exploratory and therefore not adjusted for multiplicity. A *P*-value of <0.05 was considered statistically significant.

RESULTS

Patient Characteristics

We screened 42 patients and included 28 patients, who met all inclusion criteria and none of the exclusion criteria. A total of 14 screened patients could not be included because they did not meet each of the inclusion criteria or met one of the exclusion criteria. Patients were recruited between October 2011 and January 2012. Two patients dropped out, one after the first treatment without giving any reasons and the other one due to tumor recurrence. Two patients did not appear at the follow-up visit 6 months after the last treatment but did present at the last visit. Thus, data analyses were based on $n = 26$ patients. The mean age was 60.1 ± 11.7 years (Table 2). Altogether, 29 skin grafts were examined in the study, as three study participants had received two skin grafts. A total of 27 full-thickness skin grafts were located in the face and two split-thickness skin grafts on the shoulder and the lower leg. A total of 19 full-thickness skin grafts had been taken from supraclavicular and eight from retroauricular and the two split-thickness skin grafts from the thighs.

Table 2. Patient Characteristics

Age	**60.1 (SD 11.7)**
Sex	Men: 10
	Women: 16
Skin type	I: 16
	II: 9
	III: 1
Type of graft	Full-thickness skin graft: 27 (93%)
	Split-thickness skin graft 2 (7%)
Graft removal site	Retroauricular: 8 (28%)
	Supraclavicular: 19 (66%)

Thigh: 2 (7%)

Treatment Results

Primary endpoint

Clinical evaluations were made by two investigators independently of each other using an 11-point scale, in which 0 represented no adaptation to the surrounding skin at all and 10 complete adaptation. Comparing the mean investigator ratings ($P < 0.001$), time ($P < 0.001$) and the interaction of treatment*time ($P < 0.001$) showed significant main effects. Comparing the two treatment areas at each visit, adaptation to the surrounding skin was poor in both groups before the first treatment (treatment: 2.24 ± 1.00; control group: 1.95 ± 1.27; mean diff: 0.29 (95%CI: −0.20, 0.79); $P = 0.547$). A 8 weeks after the last treatment, adaptation had significantly increased (treatment: 6.38 ± 1.47; control group 5.29 ± 1.27; mean diff: 1.09 (95%CI: 0.59, 1.58); $P < .001$). A 6 and 12 months after the last treatment, adaptation had further improved in both groups: in the experimental group, adaptation to the surrounding skin was rated 7.31 ± 1.24 (6 months) and 7.6 ± 1.26 (12 months); in the control group, adaptation to the surrounding skin was significantly lower at 6.04 ± 0.91 (6 months, mean diff: 1.28 (95%CI: 0.77, 1.79); $P < .001$) and 6.57 ± 1.02 (12 months, mean diff: 1.03 (95%CI: 0.54, 1.53); $P < 0.001$) (Fig. 1). The inter-rater agreement calculated for all four time points was 0.816, which is regarded as excellent.

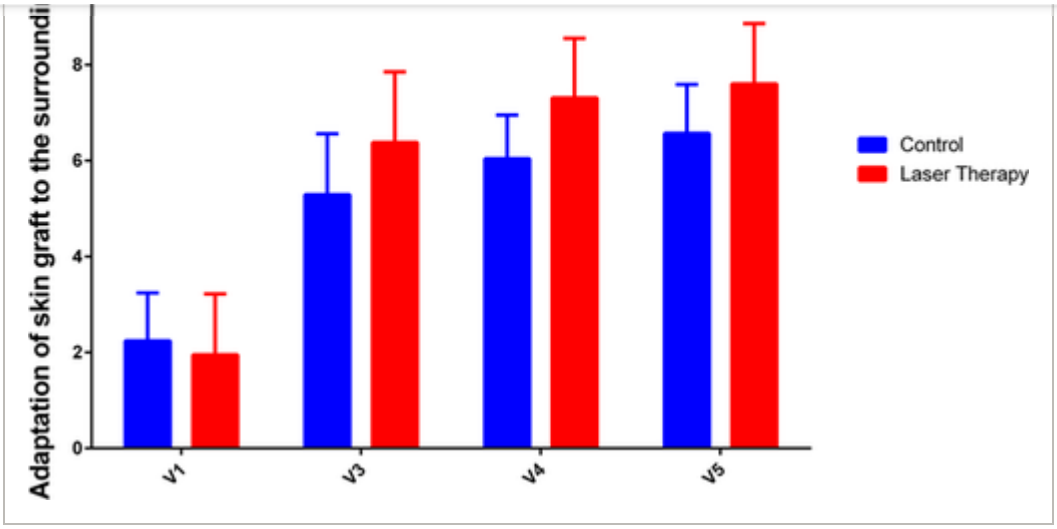

Figure 1

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Adaptation to the surrounding skin. The ratings showed poor adaptation to the surrounding skin before the first treatment (V1) (treatment: 2.24 ± 1.00; control group: 1.95 ± 1.27; $P = 0.130$). Eight weeks after the last treatment (V3), adaptation had significantly increased (treatment: 6.38 ± 1.47; control group 5.29 ± 1.27; $P < 0.001$). Six months (V4) and 12 months (V5) after the last treatment, adaptation had further improved in both groups. Adaptation to the surrounding skin was rated as follows: 7.31 ± 1.24 (treatment); 6.04 ± 0.91 (control group) (V4, $P < 0.001$) and 7.6 ± 1.26 (treatment); 6.57 ± 1.02 (control group) (V5, $P < 0.001$).

Secondary endpoints

Profilometric analysis showed reduced skin roughness in both groups over time. A total of 2 months, 6 months, and 1 year after the last treatment, skin roughness was significantly lower after laser treatment in the treatment area than in the control area ($P = 0.009$; $P = 0.016$; $P < 0.001$) (Table 3).

Table 3. Profilometric Analysis of Skin Graft: Skin Roughness (Sa)

	Laser therapy	Control group	Mean diff (95%CI)	*P*-value
Before first treatment ($n = 29$)	42.8 (SD 11.3)	43.3 (SD 13.4)	0.5 (−3.4, 4.4)	0.800
Before second treatment ($n = 29$)	34.7 (SD 11.8)	38.6 (SD 13.2)	3.8 (−0.04, 7.7)	0.053

6 months after the last treatment (n = 27)	31.7 (SD 12.3)	36.7 (SD 13.4)	4.95 (0.9, 9.0)	**0.016**
12 months after the last treatment (n = 29)	30.4 (SD 11.0)	37.8 (SD 12.8)	7.45 (3.6, 11.3)	**<0.001**

Results are based on a linear mixed model. Main effects: time $P < 0.001$; treatment, $P < 0.001$; time*treatment, $P = 0.159$. Data are presented as mean (SD). The significanct P-values are in bold.

Pigmentary irregularities were also improved. Before the first treatment, the distribution of melanin measured as melanin variation was worse in the laser therapy group than in the control group. After 1 year, the laser treatment group showed significantly better improvement than the control group (interaction term: $P = 0.020$). The melanin distribution was also more uniform ($P = 0.034$) (Table 4).

Table 4. Melanin Variation

	Laser therapy	Control group	Mean diff (95%CI)	P-value
Before first treatment (n = 29)	0.085 (SD 0.019)	0.081 (SD 0.021)	−0.004 (−0.011, 0.003)	0.232
12 months after the last treatment (n = 29)	0.054 (SD 0.020)	0.062 (SD 0.023)	0.008 (0.001, 0.014)	**0.034**

Results are based on a linear mixed model. Main effects: time $P < 0.001$; treatment, $P = 0.501$; time*treatment, $P = 0.020$. Data are presented as mean (SD). The significanct P-value is in bold.

The size variation of the respective halves of the skin grafts was determined by means of the images of 18 skin grafts. The other skin grafts could not be evaluated, because their margins could not be clearly identified. A 1 year after laser treatment, the number of pixels had decreased by −9.9% (SD 20%) in the treated grafts but increased by 4.4% in the control group (SD 26%) (mean difference: 14.3% (95%CI: 7.0%; 21.5%), $P < 0.001$).

Pain during treatment was assessed with a visual analog scale (0 represented no pain, 10 the worst possible pain). Patients reported a score of 4.6 ± 2.2 for the first treatment and 4.4 ± 1.9 for the second treatment, which may be considered moderate pain. At each visit, patients were asked about side effects. All patients reported crusting after both treatments. After the first

No further side effects were observed.

Patient-reported outcomes

At each study visit, study participants were asked about their satisfaction with the appearance of the two halves of the graft. The results are shown in Figure 2.

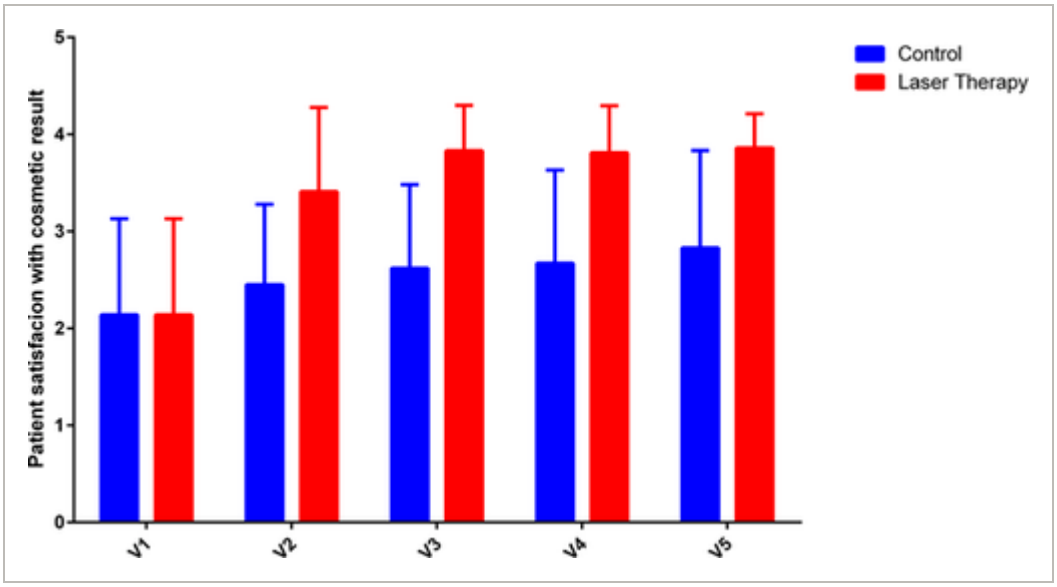

Figure 2

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Satisfaction with skin appearance. Average satisfaction with the appearance of the skin graft before treatment and at the following study visits. Patients were significantly more satisfied with the treated side of the skin graft. Study participants reported that they were equally satisfied with both halves of the skin graft prior to laser therapy. At visit 1, patient satisfaction for both sides was 2.14 ± 0.990 (n = 29), which means somewhat satisfied. Four weeks after the first treatment, patients were satisfied with the appearance of the treated half of the skin graft (3.41 ± 0.867; n = 29), and somewhat satisfied with the control side (2.45 ± 0.827; n = 29). After the 2, 6, and 12 month of second treatment, patients were very satisfied with the treated half of the skin graft (visit 3: 3.83 ± 0.468; visit 4: 3.81 ± 0.483; visit 5: 3.86 ± 0.351; n = 29) and satisfied with the control side (visit 3: 2.62 ± 0.862; visit 4: 2.67 ± 0.961; visit 5: 2.83 ± 1.002; n = 29). *(4 = very satisfied, 3 = satisfied, 2 = somewhat satisfied, and 1 = dissatisfied).

Study participants were equally satisfied with both halves of the skin graft prior to laser therapy. At visit 1, patient satisfaction was 2.14 ± 0.99 (n = 29) for both sides, which means

treatment, patients were very satisfied with the treated half of the skin graft (visit 3: 3.83 ± 0.47; visit 4: 3.81 ± 0.48; $n = 29$) and satisfied with the control side (visit 3: 2.62 ± 0.86; visit 4: 2.67 ± 0.96; $n = 29$) ($P < 0.001$ for both visits). 1 year after the second treatment, patients were very satisfied with the appearance of the treated half of the skin graft (3.86 ± 0.35; $n = 29$) and satisfied with the control side (2.83 ± 1.00; $n = 29$) ($P < 0.001$).

DISCUSSION

The objective of this study was to assess the efficacy of fractional CO_2-laser treatment to improve the cosmetic outcome of skin grafts. Two independent investigators evaluated adaptation of treated and non-treated sides of skin grafts to the surrounding skin on an 11-point scale. We also objectively measured the pigmentation, resizing, and roughness of skin grafts and examined patient satisfaction with the cosmetic result. Two treatments with the fractional CO_2-laser had significantly improved adaptation to the surrounding skin in comparison to untreated controls 8 weeks, 6 and 12 months after the two treatments (Fig. 3). A 1 year after laser treatment, melanin variation and skin roughness were significantly lower at the treated side than at the untreated side. Patient satisfaction with the cosmetic outcome was equal in the two areas prior to laser treatment, as patients were somewhat satisfied with the cosmetic result in both groups. At all other time points, patient satisfaction with the cosmetic result was significantly better after treatment.

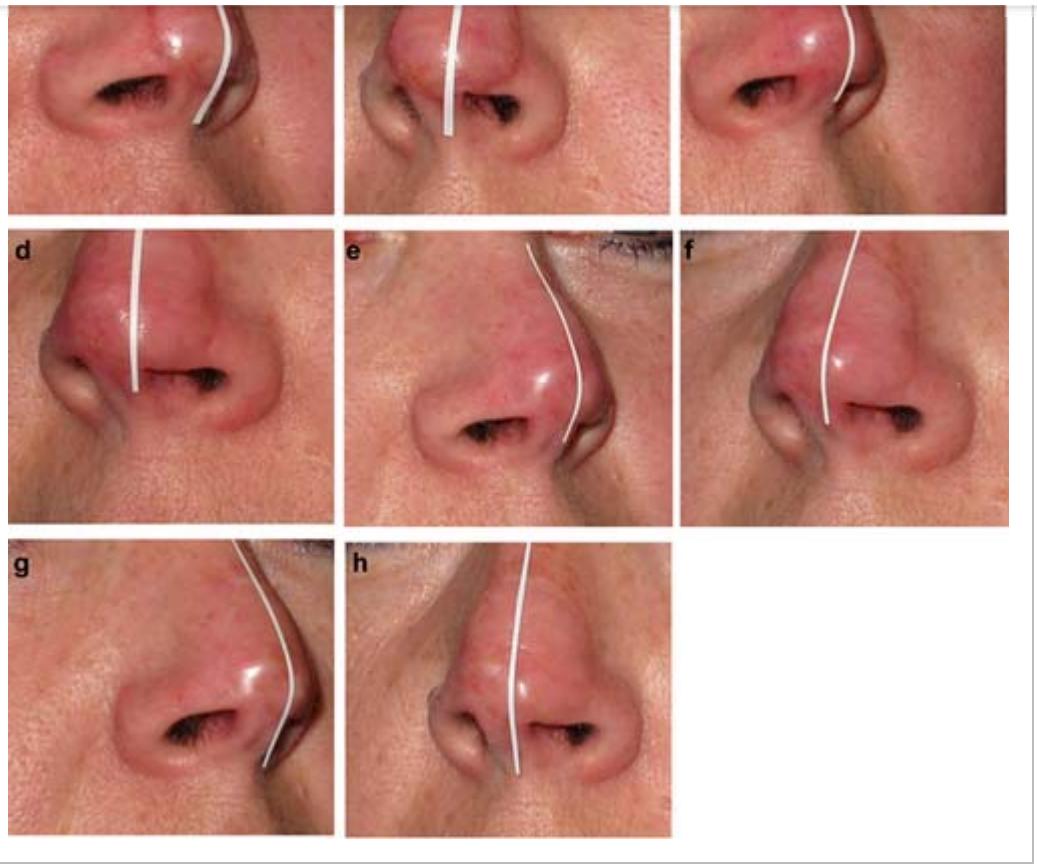

Figure 3

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Skin graft of a 54-year old Caucasian woman before, 8 weeks and 6 and 12 months after fractional ablative skin resurfacing of the right side of the skin graft. A 54-year old Caucasian woman with a skin graft on the nasal bridge before (a,b), 8 weeks (c,d) and 6 (e,f), and 12 months (g,h) after fractional skin resurfacing of the right half of the skin graft. Treatment was conducted on the right half of the nasal bridge (a,c,e,g), whereas the skin graft on the left nasal bridge was not treated. Adaptation to the surrounding skin was equal at both sides before treatment. A 8 weeks (c,d) and 6 (e,f) and 12 months (g,h) after fractional skin resurfacing of the right half of the skin graft, adaptation to the surrounding skin of the treated half of the skin graft was rated significantly better than control. The margins of the skin graft were already not visible 8 weeks after the second treatment.

It was striking that—8 weeks after the second treatment—adaptation to the surrounding skin was already significantly improved and improvement was significantly better than in the control area. The improvement seen 8 weeks after the second laser treatment was even more substantial than that present 6 and 12 months after the second laser treatment.

(SD 26%) in the controls. The decrease in size in the laser group may be explained by the skin-tightening effects of the fractional CO_2-laser. Park et al. 22 showed in an animal model immediate skin shrinkage by 11.5% and a prolonged effect of 9% 4 months after a serial four-time treatment. Skin-tightening effects have also been well documented in clinical trials 7, 23.

Fractional CO_2-laser treatment significantly improved the adaptation of skin grafts to the surrounding skin. Due to better cosmetic outcome evaluated on the basis of objective and subjective assessment criteria, this laser procedure can be offered to patients with skin grafts in the face or to patients with high aesthetic demands. However, patients were also satisfied with the cosmetic result of the non-treated half of the skin graft at the control visits three to five. Thus, some patients requiring a skin graft may refrain from further resurfacing treatments, although patients were just somewhat satisfied with the non-treated half of the skin graft at visit two.

The impact of fractional ablative laser therapy for resurfacing older scars has been shown by Jared et al. 24. In this clinical trial, one single fractional CO_2-laser treatment was compared with diamond fraise dermabrasion for resurfacing a scar in the face. The safety profile and cosmetic efficacy was equivalent in both groups. These results support our findings, although we treated patients twice and refrained from diamond fraise dermabrasion as a control group.

This clinical study has several limitations. Because we could only include two patients with split-skin grafts—of which one was a mesh-graft,—no further statements can be made about split-skin grafts due to the very small sample size. The laser parameters used in this trial were based on clinical experience and laser settings that have been used in the present study as well as in other clinical trials on skin resurfacing 7, 25. Because almost all laser-treated areas showed pinpoint bleeding after treatment, it may be assumed that treatments were conducted with adequate laser parameters as the depth of ablation was not too superficial 8. However, it is not clear, whether an earlier treatment start after surgery, a higher density of microscopic treatment zones or an even higher fluence would have yielded better results. Moreover, additional treatments might have also attained better results.

CONCLUSION

Two treatments with the fractional CO_2-laser substantially improved adaptation to the surrounding skin in skin grafts compared to non-treated control sites. Cosmetic outcome evaluated on the basis of objective assessment criteria such as homogeneous pigmentation and decreased skin roughness as well as subjective assessment criteria was significantly better. Because patient satisfaction was also significantly improved after laser treatment,

postoperative treatment start.

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Citing Literature