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Laser treatments in early wound healing improve scar appearance: a randomized split-wound trial with nonablative fractional laser exposures vs. untreated controls*

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Summary

Background In recent years, various lasers have increasingly been applied during wound healing to minimize scar formation. However, no consensus regarding treatment procedures exists.

Objectives To assess scar formation clinically after three nonablative fractional laser (NAFL) exposures, targeting the inflammation, proliferation and remodelling wound healing phases in patients vs. untreated controls.

Methods A randomized controlled trial was performed using a split-wound design to assess excisional wound halves treated with 1540-nm NAFL vs. no laser treatment. Three NAFL exposures were provided: immediately before surgery, at suture removal and 6 weeks after surgery. NAFL exposures were applied using two handpieces, sequentially distributing energy deeply and more superficially in the skin (40–50 mJ per microbeam). Evaluated at 3 months of follow-up, the primary outcome was blinded, on-site evaluation using the Patient Observer Scar Assessment Scale (POSAS total; range from 6, normal skin to 60, worst imaginable scar). Secondary outcomes comprised blinded evaluation on the Vancouver Scar Scale (VSS) and standardized assessment comparing scar sides, carried out by blinded on-site, photo and patient assessments. This trial was registered with ClinicalTrials.gov (NCT03253484).

Results Thirty of 32 patients completed the trial. At the 3-month follow-up, the NAFL-treated scar halves showed improvement compared with the untreated control halves on POSAS total: NAFL treated, median 11, interquartile range (IQR) 9–12 vs. control, median 12, IQR 10–16; $P = 0{\cdot}001$. The POSAS subitems showed that the NAFL-treated halves were significantly less red and more pliable, and presented with smoother relief than the untreated controls. VSS total correspondingly revealed enhanced appearance in the NAFL-treated halves: median 2, IQR 1–2·5 vs. control, median 2, IQR 1·75–3, $P = 0{\cdot}007$. The standardized assessment comparing appearance of scar halves demonstrated a low degree of correspondence between on-site, photo and patient assessments. NAFL-treated scars were rated as superior to untreated scars by 21 of 29 patients.

Conclusions NAFL-treated scars showed subtle improvement compared with untreated control scars.

What's already known about this topic?

- There are indications that early laser treatment may reduce scar formation during wound healing.

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- No consensus exists regarding the optimal treatment procedure for early laser treatment to reduce scar formation.

What does this study add?

- This is the first trial investigating the clinical effect of three nonablative fractional laser (NAFL) treatments, initiated as early as immediately before surgery and repeated throughout the wound healing phases.
- NAFL-treated scars showed subtle superiority over untreated control scars.
- NAFL may be promising as an integrated part of surgical procedures and postsurgical care to reduce scar formation.

Innumerable surgical procedures are performed daily, with scarring being their inevitable consequence. Postoperative scar tissue has the potential to be symptomatic and mutilating and to restrict movement, all of which may compromise quality of life.[1,2] To address this, a range of procedures such as optimized surgical techniques, compression and wound dressing are used to minimize scar formation.[3,4]

Laser treatment of scars has been used for decades and established methods aim at remodelling mature scar tissue older than 1 year.[5,6] As conventional laser techniques may not completely normalize mature scar tissue, a preventative approach consisting of laser exposure during the wound healing process has emerged. Laser treatment of wounds may induce a shift towards a regenerative process, as seen in the scarless healing during early fetal life, and thus promote reduced scar formation.[7,8] The concept of early laser intervention to reduce scar formation has already been investigated in several clinical studies, but no consensus regarding treatment procedures exists.[9–12]

In the wake of the development of fractional laser technology,[13] nonablative fractional lasers (NAFLs) and ablative fractional lasers (AFLs) have increasingly been used in scar-reducing regimens. The fractions of thermal injury provided by AFL and NAFL devices may induce a beneficial wound healing response consisting of various cytokines, including heat shock proteins, transforming growth factor-β and matrix metalloproteinases. This upregulated cytokine environment is believed to benefit skin healing by improving the distribution and quality of collagen fibres in the dermis.[14–16] NAFL creates columns of coagulated tissue in the skin with no or minor disruption of the epidermis, unlike AFL treatments, which typically disrupt the epidermal barrier.[14]

Compared with a fractional ablative skin response, a nonablative skin response possesses some advantageous properties, including lower likelihood of prolonged erythema, dyspigmentation or secondary infection. NAFL may thus be preferred for wound treatment.[17,18] A previous study showed that a single NAFL treatment applied 1 day prior to, immediately after or 2 weeks after wounding provided significant improvement in scar formation compared with untreated scars.[19] However, repeated NAFL treatments as an integrated part of surgical procedures and postsurgical care have yet to be examined. This randomized controlled trial explored the clinical effect of targeting surgical wounds with NAFL in all three wound healing phases compared with untreated control wounds. Thus, NAFL was applied immediately before surgical wounding, after suture removal and 6 weeks after surgery in an effort to target the wounds during inflammation (0–3 days), proliferation (4–21 days) and remodelling (21 days to 1 year).

Patients and methods

Study design

A randomized, controlled intraindividual split-wound trial was carried out comparing the clinical appearance of surgical scars vs. untreated control scars after three consecutive NAFL exposures: immediately before excision, at suture removal and 6 weeks after excision. Blinded on-site clinical evaluation of scars was performed 3 months after the last NAFL exposure, supported by photo evaluation and patient evaluation. The study was approved by the Danish Research Ethics Committee (H-17012492) and registered at ClinicalTrials.gov (NCT03253484). All study participants provided written informed consent.

Patients

Thirty-two patients undergoing surgical excision were recruited from the Department of Dermatology, Bispebjerg Hospital, Denmark. NAFL treatments and follow-up evaluations were carried out between June 2017 and January 2018. Included patients were ≥ 18 years of age, had Fitzpatrick skin type I–III, were nonsmokers and were referred for excision with suspicion of either benign, premalignant or nonmelanoma skin cancer lesions. Postoperative wounds were estimated to be a minimum of 2·5 cm in size at any anatomical region. Exclusion criteria were a history of keloid scarring, patients with unstable systemic disease, pregnancy, recent sun exposure or infection in the test area.

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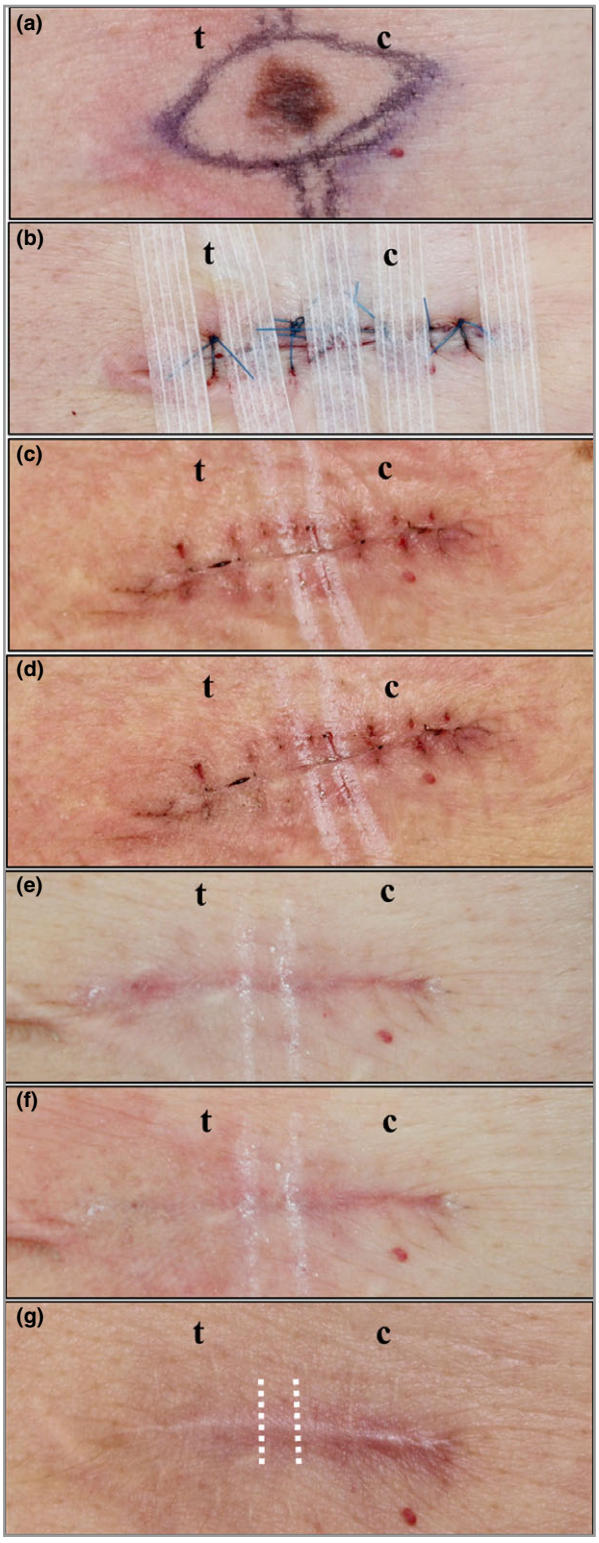

Fig 1. Study procedure shown for study patient #24. (a) First treatment with nonablative fractional laser (NAFL) immediately prior to surgery. Biological responses were erythema and oedema. The length of the elliptical demarcation was ≥ 2·5 cm. A double-lined 'exclusion zone' prevented the bystander effect of NAFL treatment in the control scar halves. (b) After suturing and bandaging. (c) Two weeks after surgery and immediately after suture removal. (d) Second NAFL treatment immediately after suture removal. Biological responses were erythema, oedema and laser grid. (e) Six weeks after surgery. (f) Six weeks after surgery immediately after the third NAF treatment. Biological responses were erythema, oedema and laser grid. (g) At the 3-month follow-up. t, NAFL-treated scar side; c, untreated control scar side.

Surgical procedure

Elliptical demarcation was performed with a surgical marker around the lesions before excision. A central 0·5-cm section of each ≥ 2·5-cm-long wound was excluded from evaluation to prevent the NAFL bystander effect on the untreated control side. During the sterile procedure, after local infiltrative anaesthesia, the elliptically demarcated area including the lesion was removed by excision. Subcutaneous sutures were provided with polyglactin 910 (Vicryl, needle 3/8c – FS-2, 70 cm, V422H 4-0 or PS-2, 45 cm, V497H 3-0 – according to anatomical region) and superficial sutures with polyamide 6 (Ethilon, needle 3/8c – FS-2, 45 cm, EH7790H 5-0 or EH7144H 4-0 – according to anatomical region; all Ethicon, Somerville, NJ, U.S.A.). Sutures and sterile strips were distributed equally on each wound half to standardize the impact on the interventional and noninterventional halves. This ensured that the scars were as comparable as possible for evaluation (Fig. 1). A drawing on a transparent sheet was used as a template to find the treated side, excluded buffer zone and untreated control side of the scars at each study visit. The surgical wounds were dressed with a dry bandage but no topical agents were applied.

Randomization, concealment and blinding

At baseline, the two lesion halves were randomized to NAFL treatments or untreated control. The sequence was concealed using consecutively numbered, closed, nontransparent envelopes prepared by a third party to ensure allocation concealment. The treating dermatologist (K.E.K.) was not blinded and was not involved in the evaluation. Outcome evaluation was performed on site by the same blinded trained physician (C.A.B.), on photographs by two blinded, experienced dermatologists (A.N. and U.P.) and by the patients themselves. The full randomization procedure is described in Appendix S1 (see Supporting Information).

Laser interventions

All laser treatments were performed by the same dermatologist (K.E.K.) using a 1540-nm erbium–glass NAFL (Icon; Cynosure Palomar, Westford, MA, U.S.A.). A combined approach of targeting deep and more superficial skin compartments was achieved using a 15-ms pulse duration with an extra-deep handpiece (XD Microlens) with a spot size of 12 × 12 mm, microbeam density 25 microbeams cm^{-2}, three stacks in two passes of 50 mJ per microbeam; and a superficial extra-fast handpiece (XF Microlens), with a spot size 15 mm in

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diameter, microbeam density 115 microbeams cm^{-2} and fluence of 40 mJ per microbeam. Treatment dosages were chosen according to a previous screening study testing the optimal dosages of 1540-nm NAFL for prevention of scar formation.[19] The first NAFL treatment was performed on top of the elliptical demarcation line, avoiding exposing the lesion itself. The second and third treatments were performed with the cicatrix located centrally on the NAFL probe area. A cooling bag was provided after each NAFL treatment.

Outcome measures

All evaluations were performed at the 3-month follow-up. The primary outcome measure was on-site blinded clinical evaluation using the observer portion of the Patient Observer Scar Assessment Scale (POSAS) to derive a total score for each scar half. The POSAS observer evaluates separate scar components by the following items: vascularity, pigmentation, thickness, surface area, relief, pliability and overall opinion. Each component is assessed on a scale ranging from 1 to 10, where 1 indicates 'normal skin' and 10 represents the 'worst imaginable scar' compared with normal skin at a comparable anatomical site. The calculated sum of the six first items comprises the POSAS total score, ranging from 6 to 60 points (Table 1).[20]

Secondary outcomes comprised the following. Firstly, on-site clinical assessments based on the total Vancouver Scar Scale (VSS). VSS total scores vascularity, pigmentation and height from 0 to 3, and pliability from 0 to 5. A 0 score represents normal skin, while maximum scores indicate the worst possible outcome (scoring 14 on VSS total).

Secondly, a standardized assessment, carried out during on-site and photo evaluation, and evaluation by the patients themselves. The standardized assessment consisted of the following questions: is there a difference between the two scar halves (yes/no)? If 'yes', which side is superior? (Scar half 1 or scar half 2). Clinical photos were obtained under standardized lighting conditions and with the body positioned 40 cm from the camera. A digital camera was used (Canon EOS 60D) with a 60-mm macro objective and flash (Canon Macro Ring Lite MR-14EX; Canon, Lake Success, NY, U.S.A.). Two dermatologists (A.N. and U.P.) evaluated the clinical photos according to the standardized assessment. To avoid intraobserver discrepancy the evaluation procedure was performed twice by each of the two dermatologists and a final result was determined by the following algorithm: if any of the four ratings stated 'no difference' or if there was a mismatch as to which scar half was rated as superior, the final result was determined as 'no difference'.

Thirdly, patient-reported outcomes included POSAS patient (Table 2) (range 1–10; from 1, not at all/normal skin to 10, yes very much/yes very different from normal skin); a visual analogue scale (VAS) (range 0–10 cm; 0 indicating normal skin, 10 maximal scarring) and a questionnaire asking patients if they would recommend the treatment procedure to friends and family. Fourthly, reflectance measurements were recorded (Appendix S1; see Supporting Information).

Table 1 Patient Observer Scar Assessment Scale (POSAS) at the 3-month follow-up

	Treated scar side	Control scar side	P-value
POSAS total (n = 30)	11 (9–12)	12 (10–16)	< 0·001*
Vascularity	2 (1–3)	2·5 (2–4)	0·005*
Pigmentation	1 (1–1)	1 (1–1)	0·13
Thickness	1 (1–1)	1 (1–2)	0·13
Surface relief	2 (2–3)	3 (2–3)	0·023*
Pliability	2 (1–2)	2 (2–3)	0·037*
Surface area	2 (2–3)	2 (2–3)	0·016*
Overall opinion	2 (2–3)	3 (2–4)	0·003*
POSAS total by scar location			
Head and neck (n = 8)	9 (9–10)	9·5 (2–11)	0·53
Thorax (n = 15)	11 (9–14)	14 (12–18)	< 0·001*
Extremities (n = 7)	12 (11–15)	12 (9–16)	0·63
POSAS total by age			
≤ 50 years (n = 9)	12 (11–15)	15 (14–16)	0·008*
> 50 years (n = 21)	10 (9–11)	11 (9–14)	0·015*

Values are the median (interquartile range). *Statistically significant difference, Wilcoxon signed-rank test ($P \leq 0{\cdot}05$).

Statistical analysis

A sample size of 29 patients provided 90% power to detect a clinical minimal relevant difference of 6 (11% improvement) on POSAS total (range 6–60) with an estimated SD of 7 and a two-tailed significance level of 5%. As a pre-emptive measure against dropout, 32 patients were included. Each scar half was analysed in the group to which it was randomized. Two of the 32 patients dropped out of the study, but as each patient was his or her own control this did not break the randomization. Hence, we performed an intention-to-treat analysis on the primary outcome and no data imputation was needed for POSAS or VSS. A nonparametric test of paired data (Wilcoxon signed-rank test) was used because the data were not normally distributed. Spearman (nonparametric) correlation tests were used. The remaining outcomes were reported with descriptive statistics. SPSS for Windows version 22 (IBM, Armonk, NY, U.S.A.) was used.

Results

Thirty-two patients were recruited and 30 completed the study. Two patients dropped out after the first treatment; one passed away due to conditions considered unrelated to study treatment, and one had a surgery-related abscess and did not want to continue study procedures. Table 3 shows the baseline demographics.

Clinical response

Excisional wounding and scar remodelling over the course of time is illustrated in Figure 1, along with the study

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Table 2 Patient Observer Scar Assessment Scale (POSAS) patient items at the 3-month follow-up

	Treated scar side	Control scar side
Has the scar been painful in the past weeks?	1 (1–1); n = 30	1 (1–1); n = 30
Has the scar been itching in the past weeks?	1 (1–2); n = 30	1 (1–2); n = 30
Is the scar colour different from the colour of your normal skin at present?[a]	4 (2–6); n = 29	4 (3–7); n = 29
Is the stiffness of the scar different from your normal skin at present?	2 (1–3·5); n = 26[b]	3 (1–4·25); n = 26[b]
Is the thickness of your scar different from your normal skin at present?	2 (1–3); n = 27[b]	2 (1–5); n = 27[b]
Is the scar more irregular than your normal skin at present?	2 (1–3); n = 29[b]	2 (2–4·5); n = 29[b]
What is your overall opinion of the scar compared with normal skin?[a]	3 (2–4·5); n = 30	3 (2–6·25); n = 30

Values are the median (interquartile range). [a]Fourteen scars were evaluated on photos due to localization at the dorsum of the body. [b]Missing data as some scars were out of reach for patient evaluation.

Table 3 Patient demographics and scar characteristics

Sex	
Female	15
Male	17
Age (years), median (interquartile range)	65·5 (47–78·5)
Localization of scar	
Head	4
Neck	4
Thorax	16
Upper extremities	4
Lower extremities	4
Length of included scars (cm), mean (range)	4·9 (2·5–9)

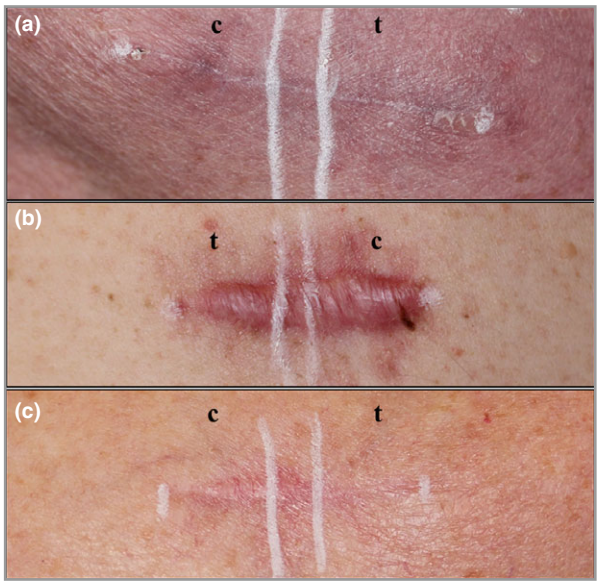

Fig 2. The spectrum of clinical response to nonablative fractional laser (NAFL) treatment at the 3-month follow-up. (a) Study patient #4, a representative patient scoring worse on the NAFL-treated scar according to Patient and Observer Scar Assessment Scale (POSAS) total (1-point difference favouring the control side). (b) Study patient #32, a representative average responder (POSAS total difference 3 points favouring the NAFL-treated scar section). (c) Study patient #7, a representative from the best responders (POSAS total, 11-point difference favouring the NAFL-treated scar section). t, NAFL-treated scar side; c, untreated control scar side.

procedures and immediate skin response to NAFL exposures. Regarding the primary outcome, the NAFL-treated scar halves improved compared with the control halves on POSAS total: NAFL-treated median 11, interquartile range (IQR) 9–12 vs. control median 12, IQR 10–16; $P < 0·001$. Nevertheless, considerable variation in the effect of NAFL treatment was illustrated on POSAS total: improvement on the NAFL-treated scar halves compared with the control halves was shown in 63% of patients, there was no difference in 26% of patients, and in 10% of patients the untreated control scars rated better than the corresponding NAFL-treated scar. In the three patients where the NAFL-treated scar halves received inferior ratings, only a 1-point difference on POSAS total separated the NAFL-treated and untreated control scar halves. Conversely, the three best responders showed improvement on the NAFL-treated scar halves vs. controls with a POSAS total difference ranging from 8 to 11 points (Fig. 2).

With regard to the anatomical regions of the scars, the largest NAFL improvement in median POSAS total was observed for scars located on the thorax, showing a median difference of 3 points ($P \leq 0·001$). Based on POSAS total, patients aged < 50 years and > 50 years responded similarly. Thus, improvement in the NAFL-treated scars vs. the untreated control scars was observed both in patients aged ≤ 50 years ($P = 0·008$) and in those aged > 50 years ($P = 0·015$) (Table 1). No correlation was found between the change in POSAS total at the 3-month follow-up and scar length ($P = 0·83$). On the separate POSAS observer items the NAFL-treated scar halves showed significantly less vascularity and erythema, smoother relief, improved pliability, lower surface area and improved overall opinion compared with controls, whereas no difference was found in pigmentation and thickness (Table 1).

Secondary outcomes, with regard to VSS total, supported a subtle but statistically significant benefit of NAFL compared with control: NAFL-treated, median 2, IQR 1–2·5 vs. controls, median 2, IQR 1·75–3; $P = 0·007$. Furthermore, less erythema/vascularity but no difference in pigmentation was detected on the NAFL-treated scars compared with controls on VSS (Table 4).

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Table 4 Vancouver Scar Scale (VSS) at the 3-month follow-up

	Treated scar side	Control scar side	P-value
VSS total (n = 30)	2 (1–2·25)	2 (1·75–3)	0·007*
Vascularity	1 (0–1)	1 (1–1)	0·031*
Pigmentation	0 (0–0)	0 (0–0)	0·22
Height	0 (0–0)	0 (0–0·25)	0·34
Pliability	1 (0–1)	1 (1–1)	0·25

Values are the median (interquartile range). *Statistically significant difference, Wilcoxon signed-rank test ($P \leq 0{\cdot}05$).

In the standardized assessment comparing the NAFL-treated and corresponding untreated control halves, a 'no difference' rating was given by on-site evaluation in eight patients, by photo evaluation in 20 patients and in one patient evaluation (Table 5). Among the control halves rated better than their corresponding NAFL-treated halves (on-site evaluation n = 7, photo evaluation n = 2, patient evaluation n = 7), complete agreement among all evaluation methods was shown in only one patient. Thus, large inconsistencies were demonstrated between the three evaluation methods.

Patient-reported outcomes

According to the POSAS patient evaluations, patients scored the NAFL-treated scar halves as having normalized colour, less stiffness, less thickness and a less irregular surface compared with the untreated control halves (Table 2). The patients' VAS evaluations showed that the NAFL-treated scar halves rated better (median 3·0 cm, IQR 1·4–5·7) than the untreated control scars (median 4·15 cm, IQR 2·0–5·9). All patients reported that they would recommend the treatment procedure to friends and family.

Adverse events

Three participants had an infection after the surgery, one of whom dropped out of the study. The two other patients were treated sufficiently with oral antibiotics and continued the study procedures. NAFL did not induce any dyschromia.

Discussion

This is the first study to investigate the clinical outcome of three NAFL treatments all influencing early wound healing phases, starting as early as immediately before surgery. We found a beneficial effect of NAFL treatment compared with untreated controls. A randomized, controlled, blinded, split-wound design was used and scars were evaluated on POSAS, VSS, photo evaluation and patient-reported outcomes. Under these standardized conditions, VSS showed that the NAFL-treated halves appeared statistically significantly improved compared with the control scar halves. The standardized assessment comparing the appearance of the scar halves on site, during photo evaluation, and by the patients demonstrated a low degree of correspondence.

The clinical effect of NAFL treatments was subtle but consistent, as reflected in the primary outcome and the VSS. In specific cases no clinical differences were detected, and in three cases the NAFL-treated halves appeared worse than the untreated controls. On the other hand, we found that patients responded to the NAFL treatment by gaining up to 11 points on POSAS total (range 6–60). This variation may be explained by inter- and intraindividual factors such as scar location, type of scar, individual reaction to NAFL-induced cytokine response and patients' age.

The anatomical region with the best response to NAFL was the thorax (POSAS total, median difference 3, $P \leq 0{\cdot}001$). On the thorax a higher median POSAS total score of 14 was detected for the untreated control halves. Thus, the enhanced effect of NAFL may be explained by either a higher effect on the thorax location or NAFL inducing a better effect on severe scarring. Scars in this study scored low on both the treated (median 11, IQR 9–12) and control halves (median 12, IQR 10–16) on POSAS total, indicating that our study population did not have severe scarring in general. Improvement on a mild scar might be difficult to detect, even on POSAS, and the clinical relevance must be questioned even though the changes were statistically significant. With regard to age, patients aged ≤ 50 years and those aged > 50 years both responded, with improved NAFL-treated scars compared with untreated scars, and thus the NAFL scar improvement did not relate to age.

Table 5 Standardized assessment comparing the nonablative fractional laser (NAFL)-treated scar half with the corresponding untreated control scar half

	Is there a difference between the two scar halves?		If 'yes' which half was superior?	
Evaluators	Yes	No	Treated	Control
On-site blinded clinical evaluation by physician (n = 30)	22	8	15	7
Blinded photo evaluation by two dermatologists (n = 30)[a]	10	20	8	2
Patient evaluation (n = 29)	28	1	21	7

[a]The result of the two dermatologists' evaluations was determined by the following algorithm: if any of the four ratings stated 'no difference' or if there was a mismatch as to which scar half was rated as superior, the final result was determined as 'no difference'.

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Various scales have been used in scar evaluation, and VSS is more frequently used than POSAS.[11,12,21–23] However, only a few scar characteristics are examined by VSS and therefore POSAS was added. Not all patients were able to evaluate the stiffness and thickness of their scars on POSAS, as their scars were located on the dorsum of the thorax. Despite the fact that POSAS patient and VAS in many cases are suboptimal evaluation tools, we found them to be the best available methods to capture patients' perceptions of their acquired scars.

Cutaneous infection developed in three of 32 patients (9%) after excision. In the literature reporting on infection in relation to excisions the rate is typically < 5%.[24,25] The higher infection rate in our study may be explained by the fact that the lengths of all three infected scars were longer than the mean scar length (4·9 cm) in this study. Liu *et al.* found correspondingly that excisions with larger defect size were significantly more at risk of secondary infection.[25] Another factor is age, as the patients with infection in our study were all aged > 75 years. No infections were seen after the second or third NAFL treatment, thus the NAFL treatment in itself was not considered to be the reason for infection. A larger patient group is necessary to gain more reliable safety data.

While most patients rated the treated side as being superior to the control side, 25% favoured the control side. This may be due to the short follow-up time of 3 months, as the full potential of the NAFL-induced remodelling process may not have been reached at this stage. Capon *et al.* applied diode laser immediately after skin closure and found no significant difference at 3 months of follow-up; in contrast, at the 12-month follow-up the treated scars appeared significantly improved compared with the controls.[10] Thus a 12-month follow-up may reveal greater benefit of the NAFL treatment. All patients recommended the treatment, possibly due to the longer time spent on each patient in a study situation compared with regular consultations.

Particular strengths of this study are the randomized, allocation-concealed, controlled and blinded split-wound study setup with internal controls, an aspect that is unprecedented in the field of early laser intervention to reduce scar formation.[26] Furthermore, the detailed and validated POSAS as the primary outcome measure enabled detection of differences in scar characteristics such as relief, thickness, pliability and overall scar appearance that would have been overlooked by VSS. To explore the effect of early NAFL treatment further, a standardized assessment was done, as presented in Table 5. The low level of agreement in the standardized assessment results may indicate that on-site, photo and patient evaluations focus on different aspects of the scar appearance. Similarly, Zhang *et al.* concluded, in a recently published review, that subjective and objective scar grading reveal disagreement between patients and clinicians.[27]

The present study further adds that even experienced clinicians disagree when using on-site scar evaluation and photo evaluation, which may be explained by the lack of a three-dimensional effect in two-dimensional photographs, and that pliability is not captured on photographs. Furthermore, the algorithm to provide the final result of the photo evaluation was conservative as the dermatologists had to agree intra- and interpersonally to conclude a difference between the treated and control scar halves. This was mirrored by only eight NAFL-treated scar halves being rated by dermatologists as superior to the corresponding control halves. Additionally, disagreement between objective evaluations and patient evaluation may be explained by the fact that on-site evaluation and photo evaluation were blinded, whereas the patients were not. The results may thus be biased, as reflected by the 21 NAFL-treated scar halves rated superior to the corresponding control scar halves (Table 5). Hence, several confounding factors may account for the low level of agreement between scar assessment on photo, on-site and patient evaluation.

Although this study demonstrated a high standard of methodological quality, it does possess some limitations. We conducted data analysis only on the patients completing the study, which underestimates variability in data. However, using the spilt-wound design, randomization was not affected but simply resulted in a smaller sample size. We deemed it acceptable that data were missing for 6% of patients (two of 32), as this had been accounted for when estimating the sample size. The dropouts were not likely to have influenced the results of the efficacy analysis. Only one blinded evaluator performed the on-site evaluation, and additional evaluators would have strengthened our findings. On the other hand, two independent evaluators were used in the photo evaluation. Furthermore, the patients were not blinded, as a sham laser treatment was not provided on the untreated control wound half. Thus, the patient-reported outcomes may be biased. Lastly, the follow-up time of 3 months is rather short for scar evaluation, as scar tissue undergoes constant remodelling for at least a year after wounding.

We conclude that three NAFL treatments provided in early wound healing may improve scar formation. Although the NAFL-treated wounds did not heal without scarring, the NAFL procedure examined in this study offers a viable contribution to the enigma of scarless healing.

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Supporting Information

Additional Supporting Information may be found in the online version of this article at the publisher's website:

Appendix S1 Randomization procedure and reflectance measurements.

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