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Clinical and Histological Assessment of Combined Fractional CO_2 Laser and Growth Factors Versus Fractional CO_2 Laser Alone in the Treatment of Facial Mature Burn Scars: A Pilot Split-Face Study

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Background and Objectives: To investigate the therapeutic efficacy and safety of growth factors combined with fractional carbon dioxide (CO_2) laser in comparison with fractional CO_2 alone in a sample of patients with facial mature burn scars.

Study Design/Materials and Methods: Fifteen Egyptian patients with bilateral facial burn scars were treated with six sessions of fractional CO_2 laser at 6-week intervals. Following each laser session, a topical growth factors cocktail was applied to one side of the face in a split-face manner. Clinical evaluation by Vancouver Scar Scale (VSS), Patient and Observer Scar Assessment Scale (PSOS), and photography before and 2 months after the last laser session was done. Three millimeter punch biopsies were obtained from each side of the face pre- and 1-month post-treatment to measure the mean area percent of collagen.

Results: Posttreatment, both VSS and PSOS scores decreased on both sides of the face being more significant on the growth factors treated side, showing more scar pliability and shorter downtime ($P = 0.001$). A significant difference in the mean area percent of collagen was also noted on both sides.

Conclusion: Adding topical growth factors to fractional CO_2 laser treatments is effective and safe with better results as regards scar pliability and shorter downtime than fractional CO_2 laser alone. Lasers Surg. Med. © 2020 Wiley Periodicals, Inc.

Key words: burn; fractional carbon dioxide laser (fractional CO_2 laser); growth factors (GF)

INTRODUCTION

Burn scars, especially on the face and the neck are cosmetically unappealing and have a negative impact on the quality of life due to associated disfigurement, pain, and itching [1]. A full set of factors that share the pathogenesis of burn scars is not yet fully established. However, the main defect is an abnormal exaggerated wound-healing process, characterized by an inflammatory phase, a proliferative phase, and a remodeling phase [2–4].

Clinically, the treatment of burn scars is difficult in spite of a wide range of options including surgery, lasers, corticosteroids, subcision, radiation, and interferon, with inconsistent degrees of success [5]. No standard treatment guidelines have been recognized yet, and combined therapies propose superior improvements in scar quality than remote modalities [6].

Fractional CO_2 laser therapy is currently used for treating different types of scars, including burn scars with negligible side effects attaining good results as regards scar contour, color, and texture [7,8]. The introduction of the fractional photothermolysis concept allowed for much deeper penetration than the traditional laser, resurfacing through the generation of micro-columns of coagulated tissue that extend deep into the dermis leaving an intact overlying epidermis [9,10]. The resultant injury initiates a physiological wound-healing process with the release of cytokines as heat shock proteins, matrix metalloproteinases (MMPs), transforming growth factor-β (TGF-β), and myofibroblasts. Those cytokines interactions result in proper scar remodeling [11].

Growth factor (GF) therapy has shown some efficacy in the management of a variety of refractory wounds such as chronic venous ulcers [12], diabetic foot ulcers [13], and pressure ulcers [14], and has provided positive clinical benefits. According to the available data in the literature, GF therapy could be a safe and effective add-on to the classic wound care regiments for partial-thickness burns [15].

We hypothesize that GFs might have a synergistic effect with fractional CO_2 laser in the treatment of burn scars. The fractional laser-induced wounds could provide delivery routes that will enable exogenous GFs to bypass the

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TABLE 1. Comparison between Results of Vancouver Scar Scale (VSS), and Patient and Observer Portions of Patient and Observer Scar Assessment Scale (PSOS) Before and After Treatment in Both Groups

	VSS (pre)	VSS (post)	*P* value	Patient portion of POSAS (pre)	Patient portion of POSAS (post)	*P* value	Observer portion of POSAS (pre)	Observer portion of POSAS (post)	*P* value
Laser-only treated side mean ± SD	7 ± 3.5	3.5 ± 1.5	0.001*	41.1 ± 2.5	23 ± 2.2	0.003*	32.8 ± 1.8	19.2 ± 2.2	0.001*
Growth factors treated side mean ± SD	6.5 ± 1.6	3 ± 1.95	0.003*	40.2 ± 2.4	20 ± 1.9	0.001*	31.8 ± 1.7	15.9 ± 1.7	0.001*

*$P < 0.05$ is statistically significant.

skin barrier and penetrate deep into the dermis enhancing neocollagenesis and might also be associated with shorter downtime.

Therefore, the aim of the current study was to investigate the therapeutic efficacy and safety of topically applied GFs combined with fractional CO_2 compared with fractional CO_2 alone in a sample of patients with facial mature burn scars.

Patients

After randomly screening 53 patients with burn scars, 19 patients fulfilled the inclusion criteria. Four patients skipped some of the follow-up sessions, so they were excluded from the study. Accordingly, this split-face pilot study included 15 patients suffering from burn scars affecting both sides of the face for more than 1 year duration, and who have not received any previous treatment in the past 6 months prior to the study. Patients were with skin phototype II–IV. Exclusion criteria included pregnant and lactating females, patients with history of poor wound healing and keloid formation. All patients were recruited from the dermatology outpatient clinics of the National Research Centre, Giza, Egypt and Kasr Alainy Hospital, Cairo University. All subjects gave an informed consent to participate in this study, and an explanation of the steps of the study was done. The study protocol was approved by the Dermatology Research Ethical Committee (REC), Cairo University.

Methods

At baseline, a thorough history check as well as general and dermatological clinical examination were done on all patients. All patients were photographed for both frontal and profile views using the same digital camera (Sony DSC-W530,Tokyo, Japan, 14 mega pixel resolution) with standardized settings at baseline and 2 months postlaser sessions.

Scar Scoring

Two scores were suggested by the authors to evaluate the patients. At baseline and 2 months after the final treatment, the patient and treating physician completed scar rating scales. Patients completed two scales: The Vancouver Scar Scale (VSS), which measures pigmentation, pliability, vascularity, and height [16] and the patient portion of the Patient and Observer Scar Assessment Scale (PSOS), which asks questions concerning scar conditions such as pain, pruritus, and stiffness. [17]. A blinded investigator completed the Observer portion of the PSOS. Both were calculated at baseline and 2 months after the last treatment session.

Patient Satisfaction Level

Two months posttreatment, all patients were asked to record their opinion regarding the efficacy of the technique. They were asked to score their level of overall satisfaction from 0 to 3 [18].

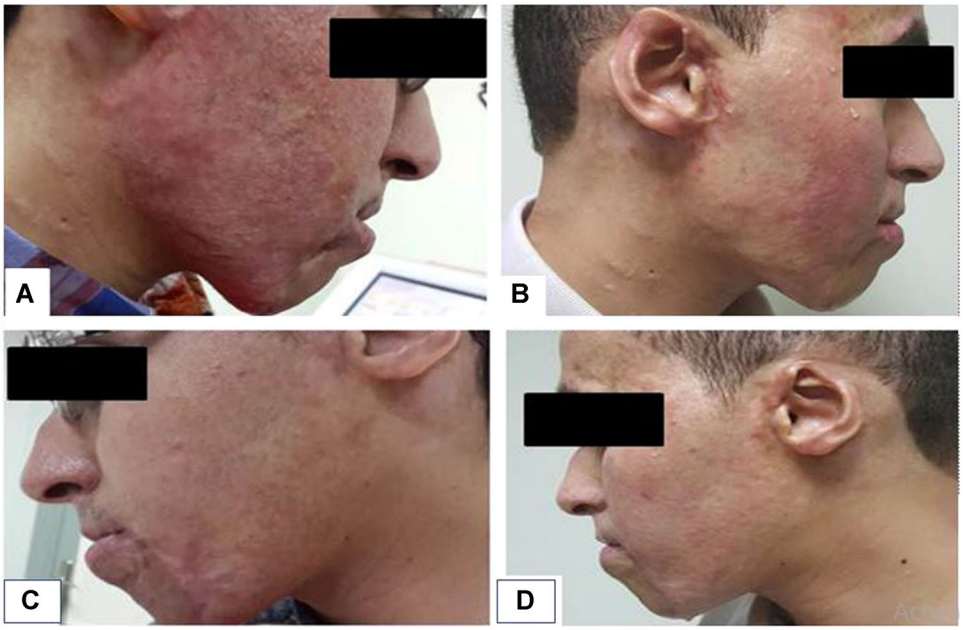

Fig. 1. (**A**) The right side of a 25-year-old male patient before treatment. (**B**) The right side, 2 months after the last fractional CO_2 laser followed by growth factors application. (**C**) The left side of the same patient before treatment. (**D**) The left side, 2 months after the last fractional CO_2 laser treatment.

Treatment Protocols

All patients were subjected to fractional CO_2 laser sessions on both sides of the face. The closed envelope technique for randomization was then used to determine which side of the face would receive the topically applied GFs. Before each session, both sides of the face were disinfected with an antiseptic solution. A topical anesthetic cream (lidocaine 2.5% and prilocaine 2.5%) was applied to the treated area for 30 minutes before the session and then the face was washed and dried before the laser treatment.

Fractional Carbon Dioxide Laser Treatment

Each side of the face was subjected to six treatment sessions using a fractional ablative 10600 nm CO_2 laser (SmartXide DOT®; DEKA, Florence, Italy). Sessions were performed 6 weeks apart. The following parameters were used in a single pass (in all cases): smart stack, dot mode, power: 30 W, dwell time: 800 microseconds, spacing: 400 μm and smart stacking: 2, depth 200 μm, spot size 15 × 15 mm, and density 17%. All patients were instructed to apply emollients twice daily for 1 week and sunscreen after each session. Any possible undesirable side effects following the procedure were recorded as erythema, edema, crusting, infection, and pigmentary changes.

Application of GFs

To one side of the face, topical application of readymade GFs was done following the fractional CO_2 laser treatment (AQ Recovery Serum; Skin Solutions, Mission Viejo, CA, which contains a mix of TGF-β), granulocyte monocyte-colony stimulating factor (GM-CSF), and platelets-derived growth factor (PDGF). Patients were instructed not to wash their faces for at least 6 hours after the session.

Histological Assessment

Three millimeter punch biopsies were obtained from each side of the face to be treated at baseline and 2 months posttreatment. Biopsies were fixed in 10% neutral-buffered formalin, and then embedded in paraffin blocks. Sections were prepared for histochemical staining of collagen fibers using Masson's trichrome stain. The mean area percent of collagen expression was assessed by a certified dermatopathologist blinded to the methods of treatment. This was done by examination of five non-overlapping high power field (×400) using Leica Qwin 500C image analyzer computer system (Ltd, Cambridge, England). The mean area percent is the relation between the areas of selected colors marked by the binary images to the field area, which is 7381.109 μm^2.

Statistical Analysis

Data were analyzed using the statistical program for social science (SPSS) (version 20 for windows; SPSS Inc., Chicago, IL). $P < 0.05$ was considered significant.

RESULTS

This pilot split-face study included 15 patients with bilateral mature facial burns. The study included 8 (53.3%) males and 7 (46.7%) females. Their ages ranged from 8 to 56 years with a mean ± standard deviation (SD) of 38.95 ± 8.85

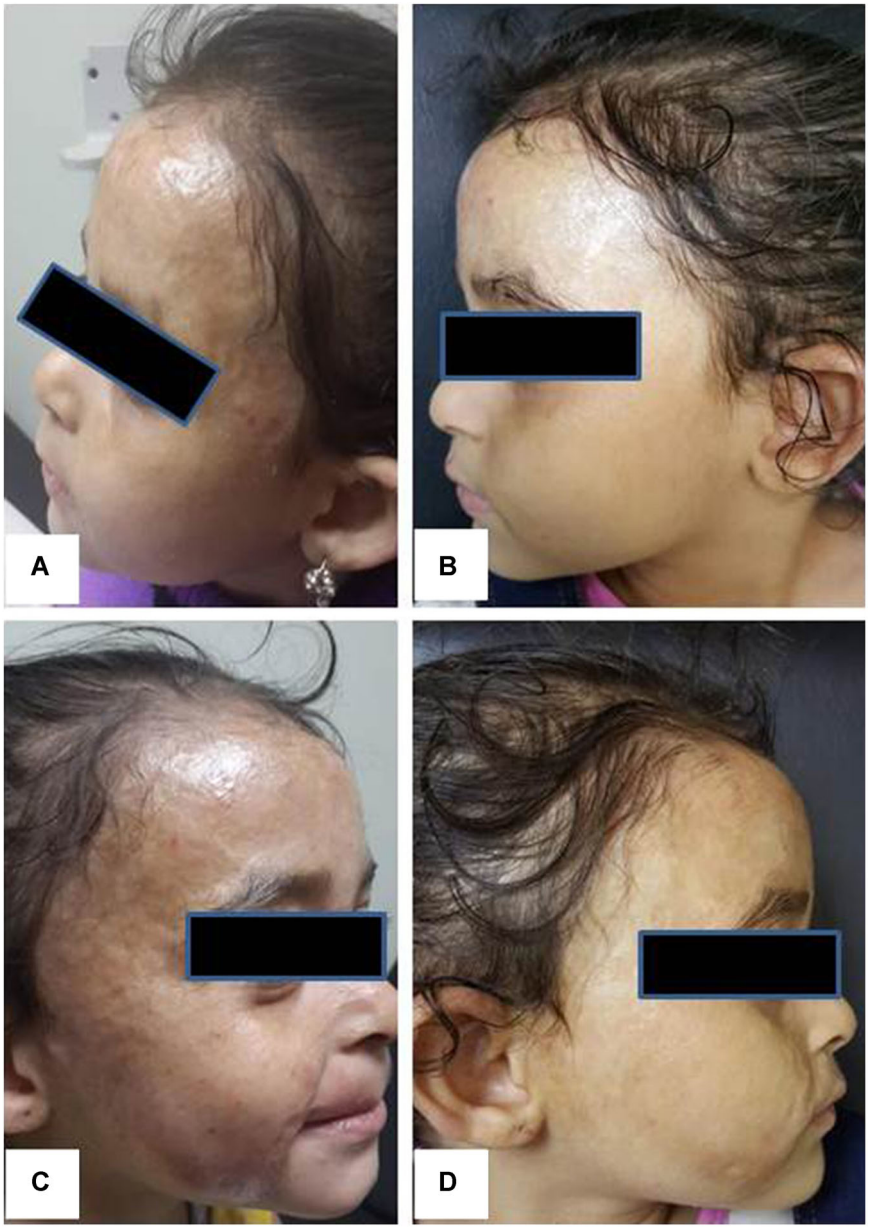

Fig. 2. (**A**) The right side of a 9-year-old female patient before treatment. (**B**) The right side, 2 months after the last fractional CO_2 laser followed by growth factors application. (**C**) The left side of the same patient before treatment, (**D**) The left side, 2 months after the last fractional CO_2 laser treatment.

years. The duration of their burn scars ranged from 1 to 15 years. The Fitzpatrick skin type ranged from III to IV. The cause of burns was due to hot liquids in 8 (53.3%) patients, while in 7 (46.7%) patients the cause was due to direct fire.

Clinical Assessment

Comparison between the fractional CO_2 laser-treated side and fractional CO_2 laser plus GFs-treated side as regards scoring scales. The appearance of mature burn scars noticeably improved after a sequence of six treatments of the fractional CO_2 laser alone and the fractional CO_2 laser plus GFs as regards each of scar vascularity, pigmentation, height, and pliability. Posttherapy, the mean VSS values decreased significantly on both treatment sides with ($P < 0.001$, 0.003, respectively) (Table 1). However, a statistically significant high improvement was observed with the GFs added to fractional CO_2 laser ($P = 0.002$).

On comparing both sides of the face, GFs treated side showed more significant improvement as regards scar pliability ($P = 0.001$), while no statistically significant difference was detected between both sides as regards

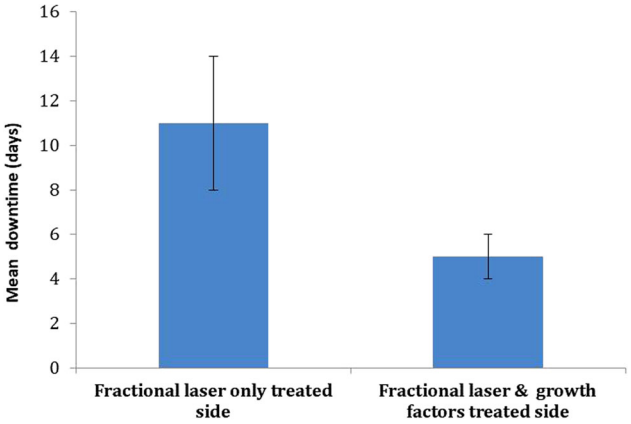

Fig. 3. Comparison between laser-treated side and laser followed by topical growth factors application side as regards the mean downtime.

improvement of scar vascularity ($P = 0.080$), pigmentation ($P = 0.65$), and height ($P = 0.543$) (Figs. 1 and 2).

Patients had statistically major enhancement in scar quality posttreatment as calculated by both patient and observer scar scales. Both treated sides showed significant improvement in both patient portion of POSAS ($P = 0.003$ and 0.001, respectively), and observer portion ($P = 0.0001$) (Table 1) with GFs treated side showing more significant improvement ($P = 0.002$).

The procedure was well tolerated by all patients. No undesired effects were reported after the treatment on both sides other than erythema and edema for few days, but the downtime posttreatment was notably shorter for the GFs treated side (range and mean ± SD: 5–7 and 4 ± 1) than the laser-only treated side (range and mean ± SD: 7–14 and 11 ± 3) ($P = 0.001$) (Fig. 3).

Patient satisfaction. Two months after the treatment, patients reported appreciably higher satisfaction with GFs added to laser treatments (mean ± SD: 2.5 ± 0.2) than the laser treatments alone (mean ± SD: 0.7 ± 0.4) ($P < 0.001$).

Histological Assessment

Following the treatments, the side of the face treated with fractional CO_2 laser alone showed a statistically significant difference as regards improvement of mean area percent of collagen (mean ± SD pretreatment: 12.05 ± 2.38 vs. mean ± SD posttreatment: 13.81 ± 3.02, $P = 0.003$) (Table 2 and Fig. 4).

Similarly, the side of the face treated with fractional CO_2 laser plus GFs showed a statistically significant difference as regards improvement of mean area percent of collagen (mean ± SD pretreatment: 11.84 ± 2.06 vs. mean ± SD posttreatment: 14.37 ± 3.36) with ($P = 0.001$) (Table 2 and Fig. 4).

DISCUSSION

The current study comes in line with the other studies documenting the efficacy of fractional CO_2 laser in the treatment of hypertrophic scars [11,19–21]. Several studies suggested that hypertrophic scars showed significant improvement in elasticity and thickness upon treatment with fractional CO_2 laser [22,23]. It was demonstrated that the depth of penetration of fractional CO_2, significantly affects the objective and subjective pathologic burn scar modulation [24].

Most of the previous studies performed only three sessions and had their follow-up after 6 months. However, in the current study we performed six sessions to the patients with a 6-week interval inbetween, allowing the remodeling phase to take place, which is in concordance with other studies in the literature [6,22].

Moreover, recent studies encourage early use of ablative fractional lasers only 6 weeks after the burn injury [25,26]. Douglas et al. [6] found more significant collagen improvement in the deep dermis in immature scars treated with fractional laser when compared with mature ones.

But unfortunately ablative lasers are still associated with some side effects, especially in facial scars of darker skin types SFP III–IV. The main reported complications include downtime needed for healing ranging from 7 to 14 days, pain and swelling during and after the sessions. Hyperpigmentation or hypopigmentation were more reported in darker skin types in sun-exposed lesions [6].

To avoid these complications multiple posttreatment therapies are prescribed including potent topical steroids, sunscreens, and other healing agents [27]. Some authors suggested combining platelet-rich plasma (PRP) with fractional lasers to accelerate the healing time, minimize the complications, and improve the outcome [28]. Unlike exogenously prepared GF cocktails, where the dose of each GF is calculated accurately, a lot remains unknown concerning PRP as regards: the platelet concentration,

TABLE 2. Comparison between Improvement of the Mean Area % of Collagen Before and After Treatment in Both Groups

	Pretreatment			Posttreatment				
	Mean	SD	SEM	Mean	SD	SEM	Mean difference (95% CI)	*P* value
Laser-only treated side	12.05	2.38	0.61	13.81	3.02	0.78	1.76 (0.72–2.81)	0.003*
Growth factors treated side	11.84	2.06	0.53	14.37	3.36	0.87	2.54 (1.16–3.91)	0.001*

CI, confidence interval; SD, standard deviation; SEM, standard error of the mean.
*$P < 0.05$ is statistically significant.

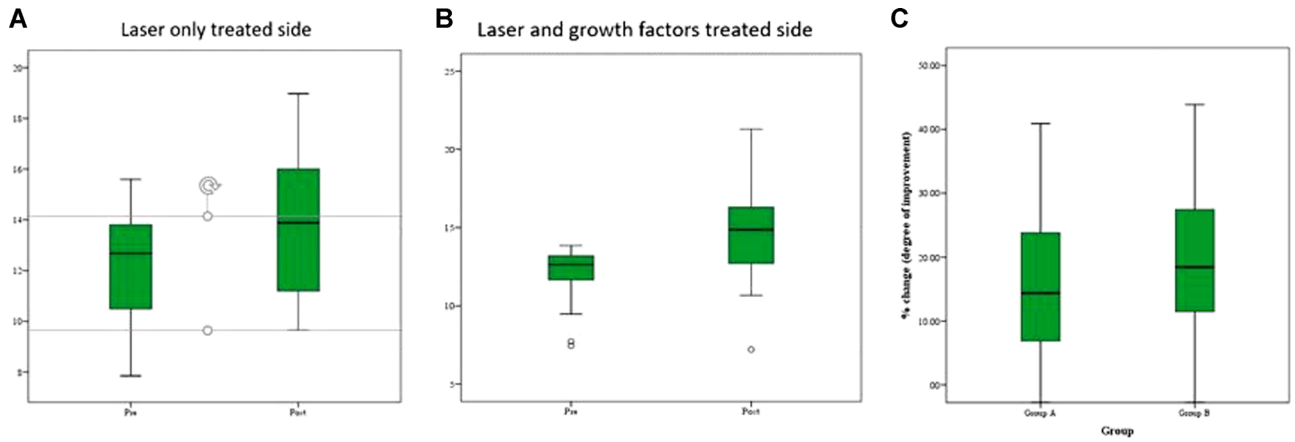

Fig. 4. Improvement of the mean area % of collagen before and after treatment; (**A**) laser-only treated side. (**B**) Laser followed by growth factors treated side. (**C**) Comparison between both groups as regards degree of improvement with group A referring to laser-only treated side and group B referring to laser and topical growth factors treated side.

method of administration, optimal dose, and long-term outcomes. The standardization of PRP to enlarge its clinical use remains a problem as the varying concentrations of platelets, leukocytes, and GFs are perhaps accountable for contradictory study results [29].

In the current study the use of GFs was hypothesized to minimize the complications expected with fractional laser. Moreover, the GFs would have a synergistic effect on the induction of the physiological wound-healing process [30]. This was evident in our results through more significant improvement on the side of GFs and also the significant lower downtime on the side of GFs use.

An earlier study revealed nonsignificant difference in the patients' downtime when GFs including TGF, fibroblast growth factor (FGF), epidermal growth factor (EGF), and vascular endothelial growth factor (VEGF) were topically applied on the face of patients undergoing fractional CO_2 laser [31].

GFs are endogenous signaling molecules that regulate cellular responses for wound-healing process. They are secreted in response to tissue injury. GFs' functions include autocrine, paracrine, and endocrine mechanisms. Binding to their target receptors, results in a cascade of events that activate the cellular machinery to facilitate wound healing [32].

The early stages of wound healing show increased levels of TGF-β and PDGF released mainly from macrophages, and fibroblasts are induced to produce collagen and extracellular matrix. Angiogenesis is initiated by the function of endothelial cells in response to the up regulation of VEGF [33]. Accordingly, the choice of the mixture of GFs in the current study aimed at enforcing the early stage of healing after fractional laser mimicking the naturally produced cytokines by the body.

Later on with remodeling, a variety of extracellular matrix (collagen and elastic fiber) and their corresponding enzyme system (MMPs) act to achieve the purpose of restoring normal histological structure [34].

Zhang et al. [15] reported that add-on therapy with FGF, EGF, and GM-CSF significantly improved scarring, scar lightening effect, and enhanced wound healing in burn scars, thereby reducing average healing time by 5 days as compared with standard treatment alone.

In addition, scar improvement following therapy with FGF and EGF was evident in terms of pigmentation, pliability, height, and vascularity [35]. This was evident in the current study, where there was more significant improvement in scar pliability in the GF treated side.

The main limitations of the current study are the small number of included patients, the short duration of the follow-up period, and the lack of objective tools for patients' evaluation and for confirming actual treatment depth. It might be beneficial to analyze the depth of the scars in future studies. Despite these limitations, we can conclude that GF therapy following fractional CO_2 laser, in treatment of facial mature burn, is effective and safe with better results, especially as regards scar pliability with shorter downtime than fractional CO_2 laser alone.

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