Evaluation of Fractional CO_2 Versus Long Pulsed Nd:YAG Lasers in Treatment of Hypertrophic Scars and Keloids: A Randomized Clinical Trial

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Background: Keloids and hypertrophic scars are challenging to both patients and physicians. They can be aesthetically disfiguring, functionally debilitating, and emotionally distressing. Lasers have introduced new mechanisms to improve scars both on aesthetic and symptomatic levels.

Aim of Work: Comparing the efficacy of fractional CO_2 laser, long-pulsed Nd:YAG laser and their combination in the treatment of hypertrophic scars and keloids on clinical, histopathological, and biochemical basis.

Patients and Methods: Thirty patients with hypertrophic scars and keloids were enrolled in the study. Three scars in each patient were randomly assigned to treatment modalities (i) Fractional CO_2, (ii) Nd:YAG laser, (iii) Combined CO_2 and Nd:YAG lasers. For each treatment area four sessions, 4–6 weeks apart were performed. Clinical evaluation was done before and 1 month following last session using the Vancouver Scar Scale (VSS) and the Patient and Observer Scar Assessment Scale (POSAS). Routine hematoxylin and eosin, Masson's trichrome, and Orcein stains were used to evaluate the appearance and pattern of dermal collagen and elastic fibers. Image analysis was used to quantitatively assess the density of collagen and elastic fibers. Biochemical evaluation of tissue level of transforming growth factor-β I (TGF-β I) and TGF-β III was performed using enzyme-linked immunosorbent assay studies.

Results: Both VSS and POSAS showed significant improvement following treatment with the three used modalities. Collagen fibers showed significant improvement as regards appearance and pattern while it was insignificant as regards density. Elastic fibers density improvement was only significant in fractional CO_2 (treatment area A). Hypertrophic scars showed more significant improvement with fractional CO_2 laser, while in keloids there was no significant difference between the three modalities regarding improvement. Level of TGF-β I showed significant reduction after treatment in all treatment modalities, while TGF-β III levels showed insignificant elevation in all treatment modalities. Side effects were significantly higher in treatment area C (combined treatment).

Conclusion: Long pulsed Nd:YAG laser is effective and safe treatment of hypertrophic scars and keloids. Fractional CO_2 laser yields better improvement in hypertrophic scars, while in keloids both fractional CO_2 and Nd:YAG lasers achieve comparable improvement. Combination in the same session did not add significant additional benefit and the side effects profile was higher.

Limitations: small sample size and short follow-up period**.** Lasers Surg. Med. © 2020 Wiley Periodicals, Inc.

Key words: fractional CO_2 laser; hypertrophic scars; keloids; Nd:YAG laser; RCT

INTRODUCTION

Since their earliest descriptions, keloids and hypertrophic scars are significantly distressing to both patients and clinicians. The consequent cosmetic disfigurement and functional disability negatively affect patients' quality of life [1].

Advances in laser therapy have introduced novel therapeutic options for hypertrophic scars and keloids [2]. Recently, lasers are considered the first-line therapy in the management of traumatic scars and contractures [3].

Fractional ablative lasers promote wound healing resulting in textural remodeling of scars with minimal adverse effects [4]. However, pulsed dye laser (PDL) is the gold standard treatment for erythematous scars [5].

The neodymium-doped yttrium aluminum garnet (Nd:YAG) laser is a multipurpose laser [6]. The 1064-nm wavelength deposits nonselective heat into the dermis. It is absorbed by melanin and hemoglobin and to a lesser extent by water with greater penetration of the lower

Conflict of Interest Disclosures: All authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest and none were reported.

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Accepted 6 April 2020
Published online in Wiley Online Library (wileyonlinelibrary.com).
DOI 10.1002/lsm.23249

dermal layers [7]. Versatility of the Nd:YAG laser has led to its application in the treatment of keloids based on its property of heating both the collagen and vascular elements in the dermis [8].

PATIENTS AND METHODS

This intra-individual randomized controlled clinical trial included 30 Egyptians of both sexes with hypertrophic scars or keloids. Patients were recruited from the outpatient clinic of the Dermatology Department, Cairo University between September 2016 and October 2017. This study was approved by the scientific and ethical research committees.

Patients

Inclusion criteria for this study were as follows: age >18 years and ≥3 hypertrophic scars or keloids. Exclusion criteria included the following: any treatment received over 4 weeks preceding study enrollment, known contraindications to laser therapy, and pregnancy and lactation.

Keloids were distinguished from hypertrophic scars based on extension of pathological scarring beyond the wound margins in the former [1].

Thorough history taking and physical examination were performed in all patients, and all patients provided written informed consent for treatment, biopsy, and photographs that might identify the patient.

Laser Treatment

Three comparable keloids or hypertrophic scars were labeled A, B, and C. The sealed envelope method was used to randomly assign treatment areas for specific laser treatment as follows: Treatment area A received fractional carbon dioxide (CO_2) laser alone, treatment area B received long-pulsed Nd:YAG laser alone, and treatment area C received a combination of fractional CO_2 laser followed by the Nd:YAG laser after half an hour.

Four laser sessions were performed at 4–6-week intervals for each treatment area. The following parameters were used for the ablative fractional 10600-nm CO_2 laser (DEKA smartxide DOT, Calenzano FI, Italy): 20 W of power, 1000 μs dwell time, 800 μm spacing, and stack of 5. Parameters for the long-pulsed Nd:YAG laser (DEKA Synchro FT) included the following: fluence of 40 J/cm^2, pulse duration of 0.3 m/s, and spot size of 5 mm in a focused mode for 3 passes.

All laser treatments were performed under complete aseptic conditions after the application of topical 2% lidocaine under occlusion for 40 min. Antibiotic ointment was prescribed after laser application. No other scar treatments were performed between laser therapy sessions to avoid bias in our results.

Assessment

Clinical assessment. Scar assessment was performed by an investigator who was blinded to the modes of treatment prior to treatment initiation, after each session, and 1 month after the final laser treatment. The Vancouver Scar Scale (VSS) [9] and the Patient and Observer Scar Assessment Scale [10] were used in this study. The Sony Exmor RS 20.7 MP digital camera was used for photographic documentation. Patients were evaluated at each session for adverse effects including pain, edema, pruritus, infection, and hyperpigmentation or hypopigmentation.

Histopathological assessment. Routine hematoxylin-eosin (H&E) stained specimens were evaluated and graded by a certified dermatopathologist who was blinded to the modes of treatment. The appearance and pattern of dermal collagen and dermal elastic tissue (in orcein-stained specimens) were assessed based on the grading system (criteria) reported by Ozog et al. [11].

Image analyzer evaluation (quantitative morphometric study). A certified pathologist blinded to modes of treatment assessed the mean area percentage of elastic and collagen fibers in the dermis in orcein- and Masson's trichrome-stained specimens, respectively. The Leica Qwin 500C image analyzer computer system (Cambridge, England) was used to evaluate five nonoverlapping fields at ×400 magnification across a field area of 7381.109 μm^2 in each patient. The mean area percentage represented the association between the areas of selected colors marked by the binary images and the field area (7381.109 μm^2).

Biochemical evaluation. A solid-phase sandwich enzyme-linked immunosorbent assay (ELISA) technique was used to assess transforming growth factor-β1 (TGF-β1) and TGF-β3 expression in skin biopsy specimens. TGF-β1 levels were measured using the Human TGF-β1 ELISA kit (ID Labs Biotechnology, London, ON, Canada). TGF-β3 levels were measured using the Human TGF-β3 PicoKine™ ELISA kit (MyBioSource Catalog No MBS177188, San Diego, CA, USA).

Statistical methods. Data were coded and entered using the SPSS software, version 15 (SPSS Inc., Chicago, IL). Data were presented using numbers and percentages for qualitative variables, mean and standard deviation and ranges for normally distributed quantitative variables, and median and interquartile ranges for normally distributed quantitative variables.

The χ^2 test was used for intergroup comparison of qualitative variables. The non-parametric Kruskal–Wallis test was used for quantitative variables that were not normally distributed, and the non-parametric Friedman and Wilcoxon signed-rank tests were used for pair-wise comparison to test quantitative variables that were not normally distributed. Correlation analysis was performed to confirm a linear correlation between variables. $P \leq 0.05$ were considered statistically significant.

RESULTS

Patients' Demographic Data

This randomized controlled comparative clinical study included 30 patients with hypertrophic scars or keloids (22 women [73.3%] and 8 men [26.7%]). Patients' ages ranged between 18 and 49 years (mean age 25.97 ± 9.32 years). On the basis of the Fitzpatrick skin type classification, patients

were classified as follows: skin type II (1 patient [3.3%]), skin type III (17 patients [56.7%]), and skin type IV (12 patients [40%]). Causal injuries included the following: 15 patients (50%) reported scalding, 12 patients (40%) reported burns, 2 patients (6.7%) reported a history of cuts at the site of involvement, and 1 patient (3.3%) reported post-acne scars.

Scars were distributed on the upper extremities in 13 patients (43.3%), lower extremities in five patients (16.7%), trunk in nine patients (30%), and on mixed sites (scars affecting upper extremities and trunk) in three patients (10%). Scar duration ranged from 0.5 to 30 years (mean 8.84 ± 7.65 years).

Following the classification of scars, we observed that 10 patients showed keloids (8 [80%] women and 2 [20%] men), and 20 patients showed hypertrophic scars (16 [80%] women and 4 [20%] men).

Clinical Assessment of Keloids

Assessment using the Vancouver scar scale. The post-treatment VSS score was significantly lower in all three treated scar areas, suggesting significant improvement ($P = 0.0001$). Comparison of the treatment modalities applied to the aforementioned treatment areas (A vs. B vs. C) revealed statistically nonsignificant differences between them ($P = 0.682$) (Table 1) (Figs. 1 and 2). Pliability scores showed the most significant improvement ($P = 0.019$, 0.013, and 0.0010) with modalities A, B, and C, respectively.

Assessment using the patient and observer scar assessment scale. A significant reduction in the post-treatment POSAS score was observed following application of the aforementioned treatment modalities ($P = 0.0001$). Comparison of the treatment modalities applied to the aforementioned treatment areas (A vs. B vs. C) revealed a statistically nonsignificant difference in post-treatment PSOAS scores ($P = 0.229$) (Table 1).

Assessment of complications. Hyperpigmentation occurred in two patients (6.7%); in one patient it was observed with the use of all three treatment modalities, whereas in the other, it was observed only with the use of modalities applied to sites A and C. Comparison of the three treatment modalities revealed a statistically nonsignificant difference in post-treatment hyperpigmentation ($P = 0.368$). Hypopigmentation occurred in three patients who received a combination of fractional CO_2 and Nd:YAG lasers (modality applied to site C), and comparison with modalities applied to sites A and B revealed a statistically significant difference in post-treatment hypopigmentation ($P = 0.05$).

All patients reported mild-to-moderate pain during and after laser therapy in treatment area B; however, in treatment areas A and C, severe pain was reported by 10 patients (33.3%) and mild-to-moderate pain by 20 patients (66.7%). Notably, no patient withdrew from the study owing to pain.

All patients reported erythema, edema, and discharge in treatment areas A and C after laser sessions; these complaints were more common after ablative CO_2 laser application. No patient developed any infection.

Correlations with demographic data. Correlations of scar improvement with scar duration, scar site, and patients' age were all nonsignificant with all treatment modalities except for scar duration, which was significantly correlated with the VSS score following application of the aforementioned modality to site B.

Histopathological, Morphometric, and Biochemical Assessment

Assessment of collagen fibers. After treatment, H&E grading score of collagen fibers showed significant improvement in the appearance and pattern of dermal collagen with the use of all treatment modalities ($P = 0.002$, 0.003, and 0.002 for modalities applied to sites A, B, and C, respectively). The mean area percentage of collagen fibers (Masson's trichrome stain) measured by the image analyzer showed a slight decrease with the use of all treatment modalities; however, the change was statistically nonsignificant ($P = 0.776$, 0.427, and 0.46 with the use of modalities applied at sites A, B, and C, respectively). Comparison of the percentage change of the H&E grading score and the percentage change of the mean area of collagen fibers showed a statistically nonsignificant difference with the use of all three modalities (Table 1).

Assessment of elastin fibers. Statistically, significant post-treatment improvement was observed in the arrangement of elastin fibers assessed by the orcein stain grading system (score) with the use of all treatment modalities (those applied to sites A, B, and C, $P = 0002$, 0.021, and 0.021, respectively) (Table 1).

Comparison between the percentage change in the orcein stain grading score and the percentage change in the post-treatment mean area percentage of elastin fibers showed a statistically significant difference with the use of all three modalities; improvement with the use of the fractional CO_2 laser alone (modality applied to site A) was higher ($P = 0.005$ and 0.038 for percentage change in the orcein stain grading score and mean area percentage of elastin fibers, respectively) (Table 1) (Fig. 3).

Assessment of TGF-β I and TGF-β III levels. Post-treatment TGF-β I levels showed statistically significant reduction with the use of all treatment modalities ($P = 0.001$). Although post-treatment TGF-β III levels were elevated with the use of all treatment modalities, this elevation was statistically nonsignificant ($P = 0.256$, 0.460, and 0.691 with the use of modalities applied to sites A, B, and C, respectively). The percentage change in post-treatment TGF-β I and TGF-β III levels following application of the three treatment modalities was statistically nonsignificant (Table 1).

Comparison of treatment response between hypertrophic scars versus keloids. With regard to hypertrophic scars, a significant improvement was observed in the post-treatment VSS and POSAS scores

TABLE 1. Results of the randomized clinical trial.

	Treatment modalities									
	A Fractional laser alone $n = 30$			B Nd:YAG alone $n = 30$			C Combined: Factional & Nd YAG $n = 30$			P value
Assessment score	Range	Mean ± SD	P value	Range	Mean ± SD	P value	Range	Mean ± SD	P value	A vs. B vs. C
VSS					41.9146 ± 20.5785					
Percent change	16.67–100	47.3393 ± 19.9598	0.0001*	16.67–100		0.0001*	16.67–100	45.6332 ± 21.3426	0.0001*	0.682
Total POSAS	30.43–66.2	46.4997 ± 9.21984	0.0001*	5.71–64.4	41.1983 ± 14.07904	0.0001*	19.15–63.4	44.9245 ± 10.13493	0.0001*	0.229
H&E collagen score	0–60	26.5556 ± 17.944			25.2222 ± 17.614		0–60	30.8889 ± 18.991		0.280
			0.002*	0–50		0.003*			0.002*	
Masson Trichrome Mean area percent	(−63.44)–45.12	−7.1946 ± 33.133	0.776	(−72.46)–42.49	−2.1057 ± 34.667	0.427	(−57.28)–43.23	−0.8769 ± 32.713	0.460	0.627
Elastic tissue score	0–75	28.8889 ± 23.525	0.002*	−33.33–50	12.8889 ± 20.339	0.021*	−33.33–50	50 13.6667 ± 21.036	0.021*	0.005*
Orcein		−123.3162 ± 200.227			31.1382 ± 115.335	0.955	(−195.92)–71.13	−33.9206 ± 87.761	0.650	0.038*
Mean area percent	−544.23–97.27		0.053*	(−319.91)–85.57						
TGF-β I	24.40–78.37	42.3382 ± 17.04787	0.001*				22.14–75.69		0.001*	0.627
ELISA				17.38–82.28	41.0361 ± 17.545-71	0.001*		47.4840 ± 15.622		
TGF-β III				−2784.81–87.02				−330.4232 ± 842.478	0.691	0.549
ELISA	−2580.40–(−88.62)	−273.5543 ± 707.568	0.256		−335.7775 ± 880.609	0.427	−2569.65–(−85.58)			

ELISA, enzyme-linked immunosorbent assay; POSAS, Patient and Observer Scar Assessment Scale; SD: standard deviation; TGF: transforming growth factor; VSS, Vancouver Scar Scale.
*$P < 0.05$.

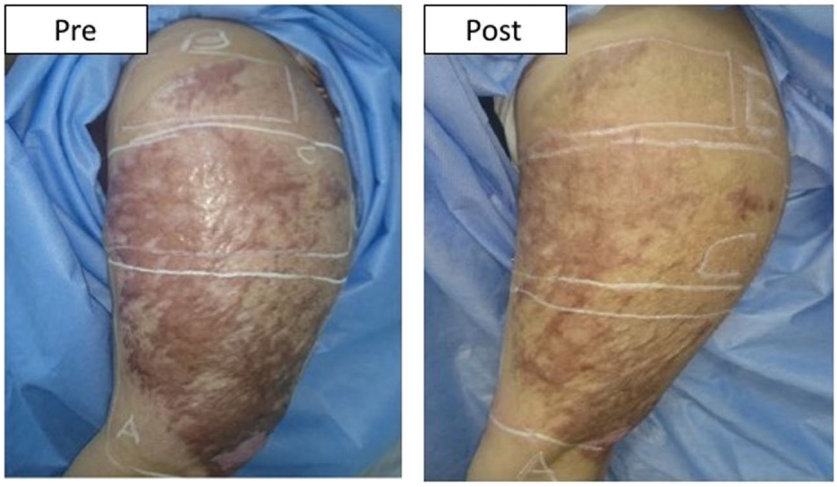

Fig. 1. Demonstration of clinical response (case 5). Lesions labeled A, B, and C. Pre, before treatment. Post, after treatment. All three lesions show comparable improvement in the redness and height of lesions.

in all three treatment areas ($P = 0.004$ and 0.001, respectively) with the highest improvement observed in treatment area A (application of fractional CO_2 laser).

With regard to keloids, no significant improvement was observed in the post-treatment VSS and POSAS scores in all three treatment areas ($P = 0.648$ and 0.323, respectively).

Comparison of each treatment modality between the hypertrophic scar and keloid group showed that improvement in the post-treatment VSS scores was significantly greater in the hypertrophic scar group than in the keloid group ($P = 0.006$, 0.000, and 0,002) for treatment areas A, B, and C, respectively. Similarly, a significant difference was observed in post-treatment POSAS scores ($P = 0.001$, 0.000, and 0.001) for treatment areas A, B, and C, respectively.

Correlation analysis. Statistical analysis showed no significant correlation between histopathological and biochemical scores and the degree of improvement in clinical scores.

DISCUSSION

The current study investigated and compared the efficacy of fractional ablative 10600-nm CO_2 and long-pulsed 1064-nm Nd:YAG lasers alone and in combination to treat hypertrophic scars and keloids based on clinical, histopathological, and biochemical parameters.

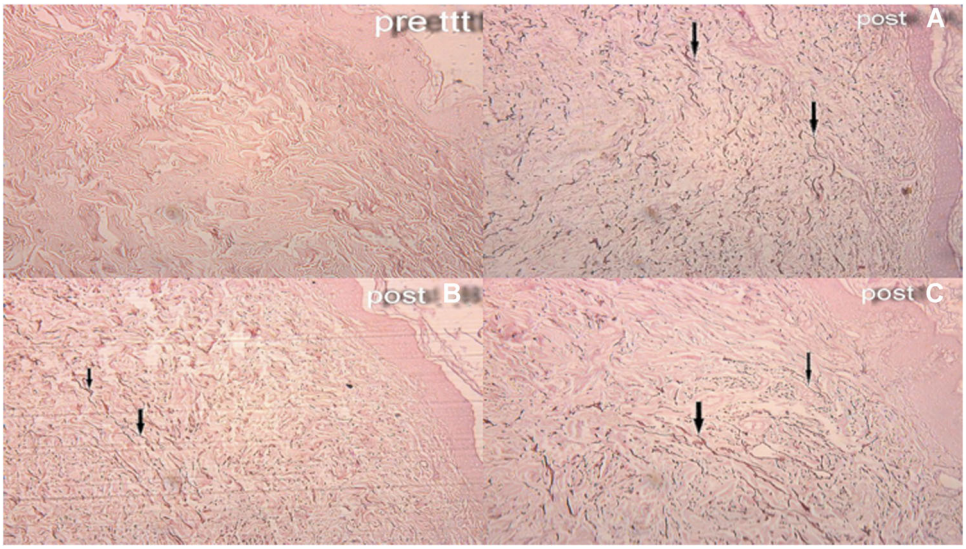

Fig. 2. Photomicrographs representing results of orcein staining for elastic fibers. Following treatment, significant increase in density of elastic fibers (black arrows) was detected by image analyzer, most marked in modality A. (Orcein stain ×10).

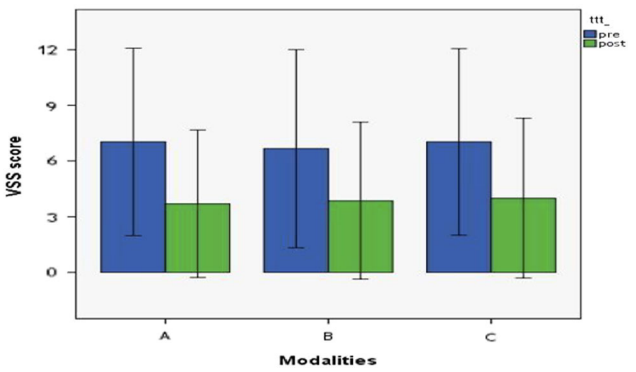

Fig. 3. Total Vancouver Scar Scale (VSS) before and after treatment in modalities A, B, and C.

The study included 30 patients with hypertrophic scars or keloids. Three treatment areas were randomly assigned to receive laser therapy using different modalities as follows: area A received fractional CO_2 laser, area B received long-pulsed Nd:YAG laser, and area C received combined therapy with fractional CO_2 laser followed by Nd:YAG laser after half an hour. Four laser sessions were performed for each area at 4–8-week intervals.

The VSS and POSAS scores were calculated before treatment initiation and 1 month after the last treatment session to evaluate clinical response. We obtained 3 mm punch biopsies before and after treatment, and specimens were stained with H&E, Masson's trichrome, and orcein stains. Additionally, TGF-β I and TGF-β III levels were measured before and 1 month after the last treatment session for biochemical assessment.

The current study proved the efficacy of long-pulsed Nd:YAG laser in the treatment of hypertrophic scars and keloids. Our results concur with those of several previous studies that prove the efficacy of the fractional CO_2 [12–14] and Nd:YAG laser individually [8,15,16] for scar treatment. To our knowledge, the current study is the first to compare these lasers for the treatment of hypertrophic scars and keloids.

The mechanism of action of the long-pulsed Nd:YAG laser on hypertrophic scars and keloids is as follows: compared with PDL, at the vascular level, this laser targets the deeper vessels in the dermis; therefore, it inhibits scar neovascularization and induces hypoxia that prevents abnormal collagen deposition [15]. Additionally, laser-induced deep tissue heating promotes the production of matrix metalloproteinases (MMPs) accompanied by degradation of abnormal collagen and initiation of a physiological wound healing process with formation of new collagen [8].

The significant improvement observed in patients in our study was attributable to these actions of the aforementioned laser, which is in agreement with the findings reported by Akiashi et al. [8], Koike et al. [15], and Al Mohamedy et al. [16]. Notably, in this study, the pliability component of the VSS score showed maximum improvement, which concurs with the findings reported by Al Mohamedy et al. [16].

The parameters evaluated in the current study were selected from those reported by the study performed by Koike et al. [15] that successfully investigated the role of long-pulsed Nd:YAG laser in the management of hypertrophic scars and keloids. Those parameters would achieve proper action on deep vessels and neocollagenesis with minimal collateral damage and no scarring [15].

Evaluation of Masson's trichrome-stained scar specimens after Nd:YAG treatment showed lesser sclerotic, finer, and more fibrillar collagen fibers. Akaishi et al. [8] reported similar structural changes in collagen fibers after Nd:YAG laser treatment.

Improvement in keloids was comparable between patients who received the Nd:YAG and fractional laser. Additionally, the Nd:YAG laser was better tolerated by most patients. However, the fractional CO_2 laser showed better results in those with hypertrophic scars. Similar findings were reported by El-Zawahry et al. [13], who suggested that compared with keloids, hypertrophic scars showed greater improvement following treatment with fractional CO_2 laser. Moreover, Waibel et al. [17] suggest earlier intervention of acute burn injuries with ablative fractional laser in the first 3 months post-injury.

Fractional lasers act through various mechanisms, including scar tissue ablation, physiological wound healing via the release of heat shock proteins, and concomitant activation of MMPs, TGF-β3, and myofibroblasts, all resulting in effective scar remodeling [12,18].

An interesting finding in the current study is the significant increase in the mean area of elastic fibers identified by image analysis associated with the use of exclusive fractional laser therapy. This finding concurs with that reported by Shin et al. [19] and Jiang et al. [20]. Improvement in elastic fibers was reflected as greater improvement in relief with fractional CO_2 than Nd:YAG laser.

Notably, vascularity was improved better with Nd:YAG laser than with fractional laser, suggesting that the choice of laser depends on the individual scar characteristics. Fractional laser serves as the optimal modality for firm scars, and the Nd:YAG laser is useful for erythematous fleshy scars.

In the current study, the combined use of fractional CO_2 and Nd:YAG lasers resulted in significant improvement in both clinical and histopathological scores. This finding concurs with the findings reported by Annabathula et al. [21], who attempted the application of combined lasers for the treatment of keloids. The decision to initiate treatment with the CO_2 laser was based on the results of this aforementioned study, which highlights that the microscopic treatment zones induced by fractional lasers enable better penetration of the Nd:YAG laser used subsequently [21].

However, the adverse effect profile associated with the combined use of both lasers was higher; three patients developed hypopigmentation, which could be attributed to excessive thermal injury to the epidermis with melanocyte destruction following the combined use of these lasers. This complication can be avoided by alternating the use of both lasers across separately spaced sessions

rather than combined use during a single session or by lowering the treatment parameters for each laser.

With regard to changes in TGF-β I and TGF-β III levels, we observed a statistically significant decrease in TGF-β I levels in all treatment areas, which concurs with the findings reported by Makboul et al. [14] who described a significant decrease in TGF-β I expression after fractional CO_2 laser therapy. The slight elevation in TGF-β III levels was statistically nonsignificant. However, reports in the literature have proved an association between elevated TGF-β III levels and scarless healing [22].

Assessment of the correlation between demographic data and the percentage of improvement observed in patients revealed that the duration of keloids is negatively correlated with the degree of improvement, which highlights the importance of early treatment of scars as recommended by Niwa et al. [23] who suggested that younger scars (scar duration <1 year) showed a better response. Notably, patient age and scar site were not correlated with the degree of clinical improvement, which concurs with the findings reported by Haedersdal et al. [5] and Azzam et al. [12].

In conclusion, Nd:YAG lasers can serve as a potential therapeutic option for hypertrophic scars and keloids. Fractional CO_2 results in greater improvement only in hypertrophic scars. Combination therapy is a useful alternative to minimize adverse effects.

LIMITATIONS OF THE STUDY

Limitations of the current study included a small sample size, short duration of follow-up after the last session of laser therapy, and lack of control areas to compare with those that received laser therapy. Moreover, objective measurement of scars was not performed in this study, and our results were based exclusively on subjective clinical scores.

ACKNOWLEDGMENT

The authors would like to acknowledge Dr. Dalia Ibrahim (Professor of community medicine, Cairo University) for her valuable help in the statistical analysis of this work.

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