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ORIGINAL ARTICLE

Efficacy and safety of Nd:YAG laser alone compared with combined Nd:YAG laser with intralesional steroid or botulinum toxin A in the treatment of hypertrophic scars

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Abstract

The aim of this study is to evaluate the efficacy and safety of Nd:YAG laser alone or in combination with intralesional injection of botulinum toxin type A or intralesional injection of steroid in treatment of hypertrophic scars. This study included 45 patients with hypertrophic scars who were randomly divided into three equal groups. All participants received 4 sessions of Nd:YAG laser at 4-week intervals. Immediately after the laser treatment, patients in group II were assigned to intralesional triamcinolone acetonide, and those in group III were assigned to intralesional botulinum toxin type A. All patients were followed up monthly for 3 months after the last session for any recurrence, or side effects. Clinical evaluation of the cases was done by Vancouver Scar Scale. Hypertrophic scars in the three groups showed a significant improvement ($p < 0.001$) compared with before treatment in all variables (except for pigmentation) and also a significant improvement in pruritus, pain, and patient relief. The highest percentage of improvements was seen in patients treated with Nd:YAG laser combined with intralesional steroid in all variables according to Vancouver Scar Scale. The degree of improvement was negatively correlated with the patients' age. The three treatment modalities were effective, safe with minimal side effects. Nd:YAG laser followed by intralesional injection of Triamcinolone acetonide had the highest percentage of Vancouver Scar Scale reduction. Combination therapy of Nd:YAG laser with intralesional injection of either Triamcinolone acetonide or Botox revealed better results than using Nd:YAG as a single therapeutic modality for HTS.

Keywords Hypertrophic scars · Nd:YAG laser · Botulinum toxin A · Triamcinolone acetonide

Introduction

Hypertrophic scars (HTSs) are a long-lasting exaggerated fibrous reaction with minimal chances of spontaneous resolution and with a high risk of recurrence after excision. Therapeutic approaches are many, yet, with variable success rates, where the highest rates favored combined over monotherapy [1].

The mechanism of laser treatment is based on heat generation in tissues which triggers inflammatory reactions which in turn upregulate matrix metalloproteinase (MMP) production. The later increases vascular permeability and stimulates decomposition of collagen fiber fascicle. Stimulation of MMP production like collagenase is the main mechanism of action of pulsed dye laser (PDL) and Nd:YAG laser; yet, it is more evident with the latter [2].

Corticosteroids, especially intralesional injections, are the mainstay therapeutic agent for HTSs as they inhibit collagen synthesis, alter glucosaminoglycan synthesis, and minimize the production of both inflammatory mediators and fibroblasts during wound healing [3].

Botulinum toxin type A (BoNT-A) is an exotoxin of the anaerobic spore forming bacterium (Clostridium botulinum). It has been used to treat hyperactive muscles of facial expression as it induces muscle paralysis via inhibition of the exocytosis of acetylcholine which indirectly blocks neuromuscular transmission [4].

Botulinum toxin type A can minimize facial scarring by reducing the muscle tension that acts on the healing wound. It may produce changes in the muscle spindles that could lead to altered sensory input and changes in the cell cycle distribution of fibroblasts derived from the hypertrophic scar [5].

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The aim of this study was to evaluate the efficacy and safety of Nd:YAG laser alone or in combination with intralesional injection of botulinum toxin type A or intralesional injection of steroid in treatment of HTSs.

Patients and methods

This is a randomized, parallel groups, comparative single-blinded prospective study, which enrolled 45 patients with HTS. This study was approved by the Research Ethical Committee of Benha University according to Helsinki declaration principles. Patients were selected from the outpatient clinic of Dermatology, Andrology and Venereology department between January 2018 and July 2019. A signed informed written consent was obtained from each patient or their legal guardian before starting the study.

Patients of both sexes presenting with HTS resulting from burns, surgical injuries, or traumatic injuries, with no previous clinical intervention, were included in this study; a hypertrophic scar was defined as a scar caused by any of the previous causes and does not extended beyond the confines of the original wound. Patients with a known allergy, underlying neuromuscular disorder or history of malignancy, were excluded. Pregnant and breast-feeding females were also excluded from the study as well as any case who had received botulinum toxin injection or isotretinoin within 6 months prior to the study (Fig. 1).

Study design

Patients with HTS were randomly allocated to three groups: Group I (Nd:YAG laser), group II (Nd:YAG laser + intralesional Triamcinolone acetonide{TAC}), and group III (Nd:YAG laser + intralesional BoNT-A). Each group received 4 sessions of Nd:YAG laser at 4-week intervals. Immediately after the Nd:YAG session, patients in group II were assigned to intralesional TAC; 20–40 mg/mL administered in a dose of 2 U (0.050 ml) by an insulin syringe (25- to 27-gauge needle) and those in group III were assigned to intralesional BoNT-A (Botox Allergan ®, Irvine, CA, USA. About 100 U vacuum-dried powder in a single-use vial for reconstitution diluted in 2 mL of sterile, preservative-free 0.9% saline to constitute a solution at a concentration of 5 U/0.1 mL. Botox was injected into the body of the scar with the help of an insulin syringe (25- to 27-gauge needle) until slight blanching was visible. The dose was adjusted to 2.5 U/cm^3 of the lesion, not exceeding 100 units per session.

Topical anesthetic cream (EMLA cream) that was applied under occlusion 60 min before the laser session and wiped off by a wet gauze just before 1064-nm-long pulsed Nd:YAG laser (Synchro HP, Italy) was used over the entire scar in a contact mode. According to scar character and site, the following parameters were used; spot size of 7 mm, fluence of 75 J/cm2, pulse duration of 20 ms, and frequency of 0.3 Hz s. The copper-cooling tip of the hand piece was used to cool the skin before and after treatment. Each session consisted of 3 passes.

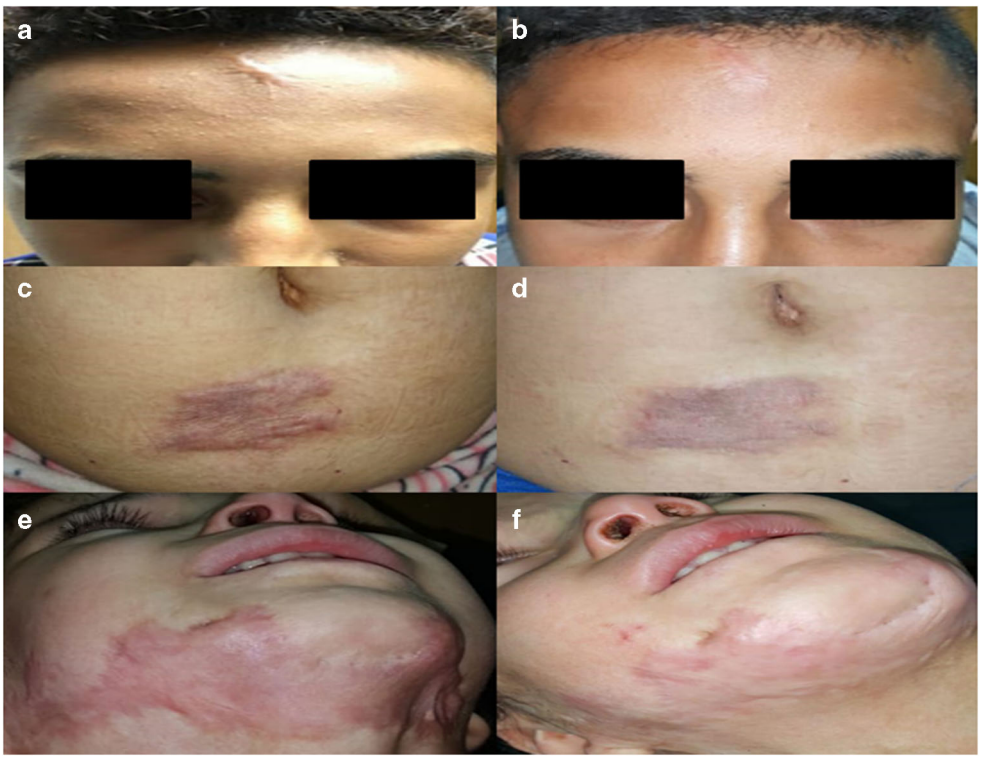

Fig. 1 **a** Hypertrophic scar before treatment. **b** After treatment with Nd:YAG laser. **c** hypertrophic scar before treatment. **d** After treatment with Nd:YAG laser combined with intralesional steroid. **e** Hypertrophic scar before treatment. **f** After treatment with Nd:YAG laser combined with intralesional BoNT-A

Baseline and clinical assessment

All patients were subjected to personal history taking including personal data as age and gender. Scar duration and medical history were also recorded.

Baseline scar assessment was made by Vancouver Scar Scale (VSS) [6], which assesses four variables including vascularity, height/thickness, pliability, and pigmentation. A total score ranged from 0 to 13, whereby a score of 0 reflected normal skin. Photographs were obtained at baseline, after each session and 1 month after the last session.

Patient Scar Assessment Scale (part of Patient and Observer Scar Assessment Scale (POSAS)) was also used for assessment of pain, pruritus, and patient relief using numeric scales from 0 to 10 for each of them. Lower scores represent those with minimal symptoms, and higher scores represented the vice versa [7].

Statistical analysis

Data collected, revised, coded, and entered into the Statistical Package for Social Science (IBM SPSS) version 20. Quantitative data were analyzed using mean and standard deviation, while frequency and percentage were used with qualitative data. Student *t* test was used for independent samples, chi-square test for comparing categorical data, Pearson's correlation coefficient for spotting associations of two continuous variables, and Spearman's correlation coefficient for measuring the strength of any detected association. Fisher's exact test (*F* test) was used to know the different proportions for one variable among other variables values. *P* values less than 0.05 was considered statistically significant.

Results

A total of 45 patients (20 (44.4%) males and 25(55.6%) females) joined this study. Their age ranged from 9 to 56 years (with a mean of 17.2 ± 12.7 years) with no significant difference in age, sex, and smoking between the three studies groups ($P = 0.18$, 0.3, and 0.67, respectively).

Hypertrophic scars were mainly caused by burns (45%), trauma (33%), and surgery (22%). The majority of the HTSs were in the upper limb (38%), and chest (27%), followed by face (11%), back and lower limb (8.5%), neck (4.5%), and abdomen (2.5%). The most prevalent symptoms were disfigurement (95%) followed by pruritus (88%), pain (84%), and limitation of movement (48%).

There was insignificant difference ($p > 0.05$) between the three studied groups regarding baseline scar characteristics according to duration of the scar, maximum diameter, VSS, and symptoms (Table 1).

According to VSS, HTS in the three studied groups showed a significant improvement ($p < 0.001$) compared with before treatment in all variables except for pigmentation (in the three studied groups) and vascularity (only in group I). Moreover, there was a significant improvement ($p < 0.001$) in pruritus, pain, and patient relief compared with pretreatment in all studied groups. The highest percentage of improvements was seen in patients of group II in all variables according to VSS. Pruritis and patient relief also showed the highest percentage of improvement among those in group II, while pain was dramatically reduced in those in group III compared with the other groups (Table 2).

The degree of improvement of HTS characteristics and symptoms showed a significant negative correlation to patients' age ($r = -0.1$, $p = 0.01$), while an insignificant relation ($p > 0.05$) was detected with other sociodemographic data (gender and smoking), as well as to baseline scar characteristics (scar duration and length).

Table 1 Comparison between the three studied groups regarding scar characteristics

		Group I	Group II	Group III	P
Duration (Ms) (mean ± SD)		12.8 ± 8.05	12.8 ± 6.6	12.7 ± 7.04	0.98
Max. diameter (cm) (mean ± SD)		3.45 ± 2.85	3.5 ± 1.39	4.57 ± 3.1	0.11
Baseline VSS (mean ± SD)	Vascularity	1.2 ± 0.78	2.1 ± 0.73	1.6 ± 0.5	0.44
	Pliability	2.5 ± 0.52	2.7 ± 0.67	2.4 ± 0.5	0.67
	Pigmentation	1 ± 0.66	0.8 ± 0.6	0.8 ± 0.9	0.47
	Height	1.7 ± 0.48	2.4 ± 0.59	2.1 ± 0.5	0.55
	Total score	6.5 ± 1.6	8 ± 1.56	6.9 ± 1.2	0.75
Associated symptoms (mean ± SD)	Pain	5.6 ± 1.45	4.6 ± 2.99	4.66 ± 2.5	0.22
	Pruritus	6.3 ± 1.98	4.88 ± 2.85	4.8 ± 2.54	0.07

Group I (Nd:YAG laser); group II (Nd:YAG + intralesional TAC); group III (Nd:YAG + intralesional botox); $p > 0.05$ = insignificant

Table 2 Percentage of improvement among the three studied groups according to VSS, associated symptoms, and patients' satisfaction

	Group I (Nd:YAG)				Group II (Nd:YAG + IL. steroid)				Group III (Nd:YAG + IL. botox)			
	V_1 Mean ± SD	V_2 Mean ± SD	P	% of improvement	V_1 Mean ± SD	V_2 Mean ± SD	P	% of improvement	V_1 Mean ± SD	V_2 Mean ± SD	P	% of improvement
Vascularity	1.2 ± 0.8	1.1 ± 0.3	0.67	8.3%	2.1 ± 0.7	0.9 ± 0.6	0.001*	57%	1.6 ± 0.5	0.9 ± 0.1	0.001*	43%
Pliability	2.5 ± 0.5	1.6 ± 0.5	0.001*	36%	2.7 ± 0.7	1.2 ± 0.4	0.001*	55%	2.4 ± 0.5	1.4 ± 0.5	0.001*	41%
Pigmentation	1 ± 0.66	0.9 ± 0.56	0.34	10%	0.8 ± 0.6	0.66 ± 0.5	0.16	17.5%	0.8 ± 0.9	0.7 ± 0.88	0.16	15%
Height	1.7 ± 0.5	1.2 ± 0.7	0.001*	29%	2.4 ± 0.6	1.3 ± 0.7	0.001*	46%	2.1 ± 0.5	1.4 ± 0.6	0.001*	33%
Total score	6.5 ± 1.6	4.3 ± 0.9	0.001*	34%	8 ± 1.6	4.2 ± 1.3	0.001*	48%	6.9 ± 1.2	4.3 ± 0.9	0.001*	38%
Pain	5.6 ± 1.5	2.6 ± 0.9	0.007*	53%	4.6 ± 2.99	1.9 ± 1.3	0.005*	58%	4.66 ± 2.5	1.7 ± 1.0	0.006*	63%
Pruritus	6.3 ± 1.98	3.3 ± 2	0.011*	47%	4.88 ± 2.9	1.8 ± 1.3	0.006*	63%	4.8 ± 2.5	2 ± 1.1	0.006*	58%
Relief	5.06 ± 0.9	1.9 ± 0.9	0.001*	31.6%	7.2 ± 1.1	0.8 ± 0.9	0.001*	64%	7.1 ± 0.9	1.3 ± 0.6	0.001*	58%

V_1 = baseline visit; V_2 = after the last session; group I (Nd:YAG laser); group II (Nd:YAG + intralesional TAC); group III (Nd:YAG + intralesional botox); * = significant difference

Regarding side effects, Nd:YAG laser therapy was well tolerated without any adverse effects. On the other hand, there was a slight tolerable pain during intralesional injection of steroid and Botox.

Discussion

Numerous methods have been described for the treatment of HTS, but to date, no gold standard has not been established.

In this study, we explored for the first time the efficacy of combining Nd:YAG laser with intralesional injections of either TAC or Botox and compared their potential synergetic effect with Nd:YAG alone for HTS treatment.

According to VSS, HTS in the three studied groups showed a significant improvement compared with pretreatment in all variables except for pigmentation (in the three studied groups) and vascularity (only in group I). Other studies [8–10] confirmed our results regarding the significant effect of Nd:YAG laser as a single treatment modality for HTSs. This efficacy was attributed by many authors [8–11] to Nd:YAG laser deeper penetration due to its low absorption by hemoglobin, reduction of collagen production, and suppression of neovascularization. On the other hand, Al-Mohamady et al. [9] reported a significant and nonsignificant improvement of vascularity and pigmentation respectively after 6 sessions; this difference could be attributed to different number of sessions between the two studies. In addition, Akaishi et al. [2] in their study stated that Nd:YAG is weakly absorbed by melanin and water.

The percentage of improvement in the current study according to total score of VSS was 34% in group I, whereas the average percentage of the VSS was 65.4% in Al-Mohamady et al. [9] study. This difference is due to many factors, as their patients' age ranged from 5 to 35 years old, while we had a wider age range and according to the current study, patients' age showed a significant negative correlation to VSS score. Moreover, the previous study had a shorter scar duration than ours (scar duration showed a negative correlation to VSS score in the current study) and their patients had more sessions than ours.

Intralesional injection of steroid is a well-recognized method in treating HTS. The mode of action of TAC has been shown to include inhibiting expression of VEGF and TGF-β1, act on fibroblasts (inhibit its proliferation, growth, accelerate its degeneration, and induce apoptosis), and act on collagen density (reduces its synthesis and accelerate its degeneration) [12]. Koike et al. [8] along with ours showed a significant improvement in pain, pruritis, satisfaction domain, and in all VSS parameters (except for pigmentation) when they used Nd:YAG laser after intralesional injection. Another study [13] also stated that combining Nd:YAG and steroid decreases the total treatment time of HTS. Moreover, Song et al. [12] clarified that reduction of inflammatory mediators by TAC might be the reason for its significant reduction of pain and pruritis of scars. They also stated that treating early stage scars (≤ 6 months after injury) gives better alleviation according to VSS scores.

Wang et al. [14] in their systemic review and meta-analysis demonstrate that after identification of 9 randomized controlled trials, they confirmed that VSS score was significantly lowered by intralesional BoNT-A (cases group) when compared with control. Plentiful studies [15–18] stated that BoNT-A has many actions involving regulation of cell cycle, apoptosis, reducing TGF-β1expression in fibroblast of HTS, and inhibiting the formation of collagen fibers and fibroblast proliferation. Other studies [19, 20] compared the efficacy of intralesional steroid versus BoNT-A in HTS treatment with opposing results. Çalıskan et al. [19] showed that TAC had a superior effect in decreasing hypertrophic indexes compared with BoNT-A, while Lu et al. [20] demonstrated that intralesional injection of BoNT-A can achieve comparable results to TAC. This discrepancy can be attributed to methodological differences.

To the best of our knowledge, this is the first study which treated HTS by using Nd:YAG laser followed by intralesional injection of BoNT-A. This combination showed a significant reduction of VSS total score as well as pain, pruritis, and patient relief domains when compared with before treatment.

Patients' relief and pruritis showed the highest percentage of improvement in those treated with intralesional TAC (group II) followed by those treated with intralesional Botox (group III). Other studies [(12, 21)] elucidated that patients treated with intralesional TAC were mainly satisfied because their scar pigmentation, pruritis, and vascular distribution were improved.

Knowing that pruritis, pain, and cosmetic disfigurement are usually the reason for patients to seek dermatologic consultation and according to the results of this study, patients in group II had the best improvement in all study variables followed by those in group III. On the other hand, those in group I had the least improvement when compared with the other two groups.

Similar to Haedersdal [22]. and Azzam et al. [23], there was significant negative correlation between the improvement in VSS parameters and patients′ age. This can be explained by that the tensile strength of wounds and accumulation of wound healing factors is affected with age.

Regarding side effects, Nd:YAG laser therapy was well tolerated without any adverse effects. On the other hand, there was a slight tolerable pain during intralesional injection of steroid and Botox.

Conclusion

Combination therapy of Nd:YAG laser with intralesional injection of either TAC or Botox revealed better results than using Nd:YAG as a single therapeutic modality for HTS,

where the former had the highest percentage of VSS reduction score along with marked reduction of pruritis and the highest percentage of patient relief. Pigmentation exhibited no significant improvement in the three studied groups. Combining Nd:YAG laser with intralesional injection of Botox is effective in treating hypertrophic scars and is worth further investigation with different doses and sessions.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval This study was conducted after being approved by the Department of Dermatology and Cosmetology and the research ethics committee.

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