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Combined Fractional Erbuim-YAG Laser with BotulinumToxin-A Versus Botulinum Toxin-A Alone for the Treatment of Hypertrophic Scars and Keloids

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ABSTRACT

Background:
The treatment of hypertrophic scars (HTS) and keloids remains a challenge. Not alltreatment modalities have been adequately tested.

Objectives:
We aimed to compare the efficacy between combined fractional Er:YAG with intra-lesional botulinum toxin (Botox) and intra-lesional Botox as a monotherapy for the treatment of HTS and keloids.

Patients and methods:
Thirty patients with HTS and keloids were treated by intra-lesional injection of Botulinum Toxin Type –A (Botox) as a monotherapy and Botox combined with ablative fractional Er:YAG laser. Each lesion was divided into two parts. The allocation of treatment method was randomly selected. One part was treated with Botox intra-lesionally 5 IU/cm2. The other part was subjected to combined intra-lesional Botox and ablative fractional Er:YAG laser (2,940 nm) sessions (4 sessions every 4 weeks). Evaluation of the treatment outcomes was done by the Vancouver Scar Scale (VSS), clinical imaging, and immuno-histochemical studies.

Results:
There was a significant decline in VSS after treatment with the combined regimen compared to the sites treated with botox injection only (P<0.001). Additionally, there was a highly significant difference between the combined treated sides and the Botox monotherapy sides in both the epidermal thickness (P=0.001) and area% hypodermis (P=0.001).

Conclusion:
Treatment of HTS and keloids with the combined approach of Er:YAG and Botox ismore effective than Botox alone.

Keywords: Combined Fractional Erbuim-YAG Laser with Botulinum, Toxin-A Versus Botulinum Toxin-A Alone, Treatment of Hypertrophic Scars and Keloids

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INTRODUCTION

Hypertrophic scars and keloids are a common problem of cosmetic concern, particularly in the head and neck regions; these lesions are conspicuous and difficult for patients to conceal[1]. Wound healing cascade consists of inflammation, proliferation, and a remodeling phase; however, in pathologic scar formation, a prolonged inflammatory phase and some molecular alterations may account for excessive scarring[2]**.** These pathologic scarring is characterized by excess collagen deposition which can be attributed to the stronger proliferating activity of keloid fibroblasts[3]. Moreover, Kelsh et al[4] and Andrew et al[5] found that keloid-derived fibroblasts show a rate of fibronectin biosynthesis that is as much as four times as high as that of fibroblasts from normal scars and normal dermis. Treatment modalities for keloids and hypertrophic scars are many and varied. They include surgical excision; occlusive dressings; topical and intra- lesional corticosteroids; interferon; cryotherapy; radiation; pressure therapy; retinoic acid and silicone gel sheeting[6]**.** Also, non-ablative fractional lasers showedearly promise in the treatment of hypertrophic scars. Their mechanism may include focal dermal heating in microscopic thermal zones (MTZ), which eventually results in normalization of collagenesis and collagenolysis. However, there are few reports on the use of ablative fractional lasers (AFLs), such as CO2 or Erbium:yttrium aluminum garnet (Er:YAG) fractional lasers, for the treatment of hypertrophic scars[7]**.** It was supposed that tissue penetration leads to remodeling and production of new collagen. When compared to CO2, Er:YAG produces columns with a narrower rim of thermal coagulation due to its higher affinity for absorption by water which leads to more ablation than coagulation. Moreover, Tawfik et al[8] showed that the Er:YAG laser was effective when used for ablation of the subcutaneous layers to enhance skin absorption in laser assisted drug delivery.Botulinum toxin type-A has been shown to havea triple action on wound tension, collagen, and fibroblasts[9]**.**Intra-lesional botulinum toxin-A has been suggested to inhibit fibroblast proliferation and reduce connective tissue growth factor protein[10]**.** Additionally, it paralyzes local muscles and reduces skin tension, thereby decreasing scar tension and subsequent inflammation in wound edges[11]**.**

To the best of our knowledge, management of hypertrophic scars and keloids has been treated using fractional CO2 combined with pulsed dye lasers. Few studies have been done to evaluate the efficacy of fractional Er:YAG in this context. Also, botulinum toxin injection appeared to be a successful emerging modality for the treatment of these lesions. As a result, we aimed to compare the efficacy between combined fractional Erbium with intra-lesional botulinum toxin and intra- lesional botulinum toxin as a monotherapy for the treatment of hypertrophic scars and keloids.

Patients and Methods

Thirty patients with hypertrophic scars and keloids were included in this comparative study. The study was conducted according to the Declaration of Helsinki principles and was approved by the ethical committee of

National laser Institutional review board, Cairo University, Egypt. Signed informed consent was obtained from each patient before enrollment in the study. A legal guardian provided written informed consent for any participant under the age of 18 years, including written informed consent for images to be published. Patients were instructed to avoid using any other modalities of treatment during the course of the study. Patients were excluded from the study if: they had been taking an oral retinoid 6 months prior to treatment, had participated in a prior trial to treat the scar within the previous 12 months, were pregnant and breast feeding, had an active infection, had lesions suspected to be malignant, or had a history of photodermatoses or skin cancer.

Treatment protocol

Each scar was divided into two parts. The allocation of treatment method was randomly selected using a coin flip as a method of randomization. The whole lesion was subjected to monthly injections of 5 IU/cm2 Botulinum Toxin Type -A (Neuronox, 100 U; Medytox, Kak-rl, Ochang-myeon, Cheongwon-gun, Chungcheongbuk-do, Korea), for 4 months. While only one half of the lesion was subjected to ablative fractional Erbium YAG laser (2,940 nm) (SkinPlus Erbium YAG laser, Fotona Medical Lasers, Ljubljana, Slovenia) sessions monthly, for 4 months. Laser sessions started two weeks after the Botulinum Toxin Type-A injection.

Fractional laser parameters were handpiece PSO1, spot size 7 mm, pixel size 450 μ, and density of 75 pixels. We use a short pulse mode 300 μs with a fluence of 5 J/cm2. Two passes were applied in two perpendicular directions, one horizontal and the other vertical.

Evaluation method

Assessment of clinical improvement was measured regarding overall appearance, vascularity, hyperpigmentation, hypopigmentation, height, and pliability using (VSS). Vancouver scar scale (VSS) [12] assesses four variables: vascularity, height/thickness, pliability, and pigmentation. Also, standardized photographs (Sony Cyber-shot DSC-W320 14.1 mega pixel camera) were taken at baseline, at every session, and 6 months after the end of the treatment. While for objective evaluation, three mm punch biopsy from each of the treated lesions, before treatment and 4 weeks after last treatment session, were taken and subjected to histological and immuno-histochemical assessment for fibronectin. All slides were examined using an image analysis system which included a Leica Qwin 500 IW (Leica microsystems imaging solutions Ltd, Cambridge, UK, 2002), photomicroscope was taken with Leica DFC295 camera. Ten non-overlapping fields were randomly selected from the slides stained with H&E and Fibronectin. H&E stain was used to compare the epidermal thickness. Scale bar microscopic measurement was used to measure the epidermal thickness in micro-meter (μm) before and after treatment, while Fibronectin stain was used to compare the Area percentages of fibroblast before and after treatment.

Statistical analysis

The collected data were revised, coded, tabulated and introduced to a PC using Statistical package for Social Science **((IBM Corp. Released 2011. IBM SPSS Statistics for Windows, Version 20.0. Armonk, NY: IBM Corp).** Data were tested for normality with shapiro-wilk test and expressed as mean (standard deviation) for parametric numerical data or median (interquartile range) for non-parametric numerical data. Paired t- test was used to assess the statistical significance of the difference between means of matched pairs**.** Wilcoxon signed rank test was used to assess the statistical significance of the difference between non-parametric matched pairs. Probability (*P*-value) P>0.05 was considered non- significant (NS), P< 0.05was considered as significant (S). P<0.01 was considered as a highly significant (HS).

RESULTS

Herein, we performed a randomized, intra-patient, comparative study. Thirty patients with HTS & keloids were enrolled in this study: (63.3%) HTS and (36.7%) keloids. The mean age of the study cases was 20.27±8.86 years, ranging between 7 and 47 years. All Thirty patients had either skin type III or IV. Their mean lesion duration was 2.36 ±2.62 years with a median of 1 year. Hypertrophic scars were present among 63.3% of the cases. Cut wounds were the most common cause (50%). Face and arm were the most common affected sites (26.7%) for each site. 56.7% of the cases received no previous treatment. (as shown in table 1:dermographic data of patient)Clinical examination revealed that: new scar lesion was erythematous and harder than old lesions which were skin-colored and more pliable. Using VSS, the vascularity, pliability, pigmentation, and height were assessed and compared in both treatment modalities. There was a highly significant decrease in the mean height and pliability of the parts treated with combined botulinum toxin A and laser compared to the parts treated with botulinum toxin A as a monotherapy (*P*<0.001). Similarly, there was a significant decline in VSS after treatment with the combined regimen compared to the sites treated with botox injection only (*P*<0.001). Moreover, there was a highly significant difference between the mean VSS before treatment and after treatment with Botox only (9.33 vs 5.17) (*P*<0.001); similarly, on the combined treated sides, there was a highly significant difference between the mean VSS before treatment and after treatment (9.33 vs 3.6) (*P*<0.001). However, no significant difference was found between the two treatment regimens as regard vascularity (P=0.317) and pigmentation scale (P=0.157) after treatment (Table 2). Regarding the total percentage of improvement, no (<25%), mild (>25%), moderate (>50%) and excellent (>75%) improvement in VSS, the combined treatment showed moderate to excellent improvement in 70% (21 patients) of scars treated, whereas the botulinum toxin-A as a monotherapy revealed mild improvement in 56.7% (17 patients) and moderate improvement in 40% (12 patients). Excellent improvement was elicited in the pliability of nine (30%) lesions which were treated with the combined approach. Eleven (36.7) lesions showed moderate decrease in height when treated by botulinum toxin A only, whereas twenty (66.7%) lesions showed moderate improvement in height when treated by combined approach, 63.3% (19 patients) showed moderate improvement in the vascularity using botulinum toxin A alone while 56.7 (17 patients) showed moderate and 10% (3 patient) showed excellent improvement using the combined therapy. Regarding the histopathological assessment after treatment (epidermal thickness, area % dermis and area% hypodermis), there was a highly significant difference between the combined. treated sides and the botox monotherapy sides in both the epidermal thickness (P=0.001) and area% hypodermis (P=0.001). On the other hand, there was no statistical difference after treatment of both sides regarding the area %dermis (P=0.2) (Table 3).

DISCUSSION

Although scar formation is a part of the normal healing process, treatment of hypertrophic scars and keloids

represent a challenge; not only for its functionalimpairment but also for its cosmetic concerns that can impair social interactions and quality of life[13]. Physical approach for the treatment of these lesions includes laser and light therapy, autologous transfer of adipose tissue, and surgery[14]. Our certainty of the mechanism of scarring is still incomplete. Moreover, each treatment modality has its own limitations; therefore, multiple comparative studies are required to determine the efficacy of each in the treatment and prevention of hypertrophic scars and keloids.This study showed that treatment of HTS & keloids using combined ablative fractional Erbium YAG laser, and interlesional botulinum toxin A was more effective than the use of interlesional botulinum toxin as a monotherapy. Botulinum toxin intra-lesional injection as a monotherapy was initially used by Zhibo and Miaobo[15] in an uncontrolled study, where 3 out of 12 patients showed excellent cosmetic outcomes. In a randomized double-blinded study conducted by Shaarawy et al[16], 24 patients with keloids were divided into 2 groups. The first group received intra-lesional BoNT-A, while the second group recieved intra-lesional steroids. At the 7-month follow-up, both groups improved, but the improvement was more evident in the BoNT-A group. Of note, three patients of those who received intra-lesional steroid injection had skin atrophy and telangiectasia. Therefore, the efficacy and safety of intra-lesional BoNT-A was more evident compared to intra-lesional corticosteroids. Several studies have proven the efficacy of ablative fractional Erbium YAG laser as a successful method in treatment of HTS through remodeling and production of new collagen[17]. Madni and Phelan [18] revealed that burn patients who were treated with the 2,940 nm ablative fractional Erbium YAG laser were highly satisfied with the improvement of their burn scars. Despite the great momentum of studies that proved the efficacy of ablative fractional Erbium YAG laser as a successful method in treatment of HTS, there is a lack of research exploring the efficacy of the combined approach of the Erbium YAG laser and botulinum toxin A in the treatment of keloids & HTS.In the present study, intra-lesional injection of botulinum toxin A in HTS & keloids significantlyimproved the vascularity, pliability and height, and total score of VSS. Our results are in agreement with those of a prospective, single arm study of Elhefnawy[19] who reported an excellent outcome in six out of 20 keloid cases who received BTX-A once a month for 3 months (injected dose: 2.5 IU/cm3, not exceeding 100 IU/session) and a good outcome in the remaining 14 cases. Similarly, Xiao et al[10], reported acceptable results, 6 months after treating hypertrophic scars, of 19 cases with intralesional botulinum toxin injections (2.5 U/cm3 per lesion at 1-month intervals) for 3 months. Eventually, Bi et al[20] conducted a systematic review and meta-analysis, in which they showed that injection of intra-lesionalbotulinum toxin type A was more effective in the treatment of hypertrophic scar and keloids than injection.

of intra-lesional corticosteroids or placebo.The additionof fractional Erbium YAG laser combined with intra- lesional botulinum toxin A in HTS & keloids significantly reduced the VSS; as a result of, improvement in vascularity, pigmentation, pliability, and height. It also revealed significant better results than intralesionalbotulinum toxin as a monotherapy. As far as we know,the current study is the first to combine Fractional erbium YAG laser with intra-lesional botulinum toxintype A for treatment of HTS and keloids. Sabry et al[21] subjected 20 cases suffering from HTSs and keloids to a monthly dose of one of the following treatment regimens for four successive months; (botlulinum toxin type A alone or CO2 laser followed by topical botlulinum toxin type A application) and reported that the VSSsignificantly reduced one month following the last treatment session in all cases ($P < .05$). Compared to the CO2 laser, the Er:YAG laser's wavelength of 2,940 nm is absorbed by water approximately 15 times more effectively. This leads to decreased energy requirementfor tissue ablation. On the contrary, the added energy necessary for CO2 tissue ablation results in a thicker surrounding zone of coagulation tissue. A recent histopathological study[22] revealed that the different wavelengths of lasers produce different wounds. Themain difference in the pattern of injury between the CO2 and Er:YAG laser is the coagulation zone. The coagulation zone is an inherent physics property based on the laser wavelength. Since the CO2 lasers have absorption coefficients significantly lower than the Er:YAG, the CO2 needs more energy to ablate epidermal and dermaltissues. The additional energy generates heat that increases collateral thermal damage resulting in a coagulation zone around the ablation zone. Therefore, fractional ablative Er:YAG laser wounds have little to nocoagulation zones.In our study, the highly significant improvement in the pliability and height of the scars recorded using the VSS mirrored the highly significantimprovement in the dermal thickness of the scars measured using histo-pathological examination. This is in agreement with an experimental study by Zhibo et al, where 8 rabbits with hypertrophic scars on both their ears, received intralesional BoNT-A injections on their right ears only once a month for a period of 3 months. After 6 months, the hypertrophic scars injected with BoNT-A and those of the control side where subjected to H&E staining and observed under a microscope. There were thinner collagen fibers on the scars injected with BoNT-A compared to the control side [23]. Another effect of BoNT-A on hypertrophic scars and keloids was that onthe cell cycle distribution of fibroblasts. Fibroblasts hyperproliferation is considered as one of the factors thatresult in hypertrophic scars and keloids. BoNT-A maydirectly modulate the activity of fibroblast by altering apoptotic, migratory, and fibrotic pathways on pathological scars and thus improve their appearance[3]. To the best of our knowledge, this is the first study to combine fractional Erbium YAG laser with botulinum toxin type A with clinical and histopathological assessment before and after treatment using imageanalysis of epidermal thickness of the scars and areapercentages of fibronectin biosynthesis that is as much as four times as high as that of fibroblasts from normal scars and normal dermis. Limitations of our study are the lack of objective non- invasive assessment of clinical improvement of scars, that would have given a better evaluation, also the small sample size but was not feasible due to the high cost of the study.

CONCLUSION

Botulinum toxin A is an emerging promising therapy for HTS and keloids. Additionally, fractional Erbium YAG laser has been found to be an effective and safe device when combined with botox. The combined tested approach is a novel modality of treatment with minimal side effects and promising efficacy.

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None

CONFLICT OF INTEREST

The authors have no conflict of interest to declare.

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Tables:

Table 1: Description of personal and medical dataamong study cases

		Mean	±SD	Minimum	Maximum	Median	IQR*	
Age		20.27	8.86	7.00	47.00			
Duration of scar (Yrs.)		2.36	2.62	0.20	8.00	1.00	0.5	4.0
Type of scar	Hypertrophic scar	19	63.3%					
	Keloid	11	36.7%					
Cause	Cut wound	15	50.0%					
	Burn	8	26.7%					
	Post surgical	3	10.0%					
	Post acne	2	6.7%					
	Post injection	1	3.3%					
	Crush injury	1	3.3%					
Site	Face	8	26.7%					
	Arm	8	26.7%					
	Shoulder	4	13.3%					
	Leg	2	6.7%					
	Chest	2	6.7%					
	Back	2	6.7%					
	Abdomen	2	6.7%					
	Neck	1	3.3%					
	Foot	1	3.3%					
Pervious treatments	No	17	56.7%					
	ILS	6	20.0%					
	Topical silicone gel +ILS	3	10.0%					
	Topical silicone	3	10.0%					
	Fractional co2 laser	1	3.3%					

*Inter quartile range.

Table 2: Comparison between the two treatmentregimens as regard clinical features after treatment (Vancouver, vascularity, pigmentation, pliability andheight)

	Group										p	Sig
	Botox					Botox and laser						
	Mean	±SD	Median	IQR*		Mean	±SD	Median	IQR**			
Vancouver scale after TTT	5.17	1.64	5.0	4.0	6.0	3.60	1.65	3.0	2.0	5.0	0.0001*	HS
Vascularity after TTT	1.10	0.71	1.0	1.0	1.0	1.03	.61	1.0	1.0	1.0	0.317*	NS
Pigmentation after TTT	0.33	0.71	0.0	0.0	0.0	0.20	0.55	0.0	0.0	0.0	0.157*	NS
Pliability after TTT	2.07	.87	2.0	1.0	3.0	1.47	.97	1.0	1.0	2.0	0.0001*	HS
Height after TTT	1.70	.60	2.0	1.0	2.0	1.00	.59	1.0	1.0	1.0	0.0001*	HS

Table 3: Comparison between the two treatmentregimens as regard histopathological features after **treatment (epidermal thickness, area % dermis andarea% hypodermis)**

	Botox					Botox and laser					P	Sig
	Mean	±SD	Median	IQR		Mean	±SD	Median	IQR			
ET after TTT	158.08	15.79	149.8	148.6	169.8	92.23	13.12	94.0	86.5	103.8	0.001*	HS
Area% after TTT dermis	1.91	1.11	1.7	1.1	2.3	1.35	0.43	1.2	1.2	1.5	0.201**	NS
Area after TTT hypodermis	7.66	0.75	7.9	7.4	8.2	2.65	0.70	2.4	2.3	2.9	0.001**	HS

Figure legends:

Figure 1: A 25- year-old female patient presented with keloid on the left shoulder of 9-month duration. The upper part was treated with combined approach, while the lower part with Botox monotherapy. **A:** Before treatment, **B:** After treatment.
Figure 2: A 23-year-old female patient presented withHypertrophic scar of 6-month duration. The right part was treated with combined approach, while the left part with Botox monotherapy. **A&C:** Before treatment, **B&D:**
After treatment.

Figure 3:
A: showing epidermal thickness before treatment.
B: showing epidermal thickness after treatment withbotox only.
C: showing after treatment with combined approach.
D&E: showing fibronectin area % before treatment in thedermis and hypodermis.
F&G: showing decrease fibronectin area % aftertreatment with botox only in the dermis and hypodermis.
H&I: showing significant decrease in fibronectin area % after treatment with combined approach in the dermis and hypodermis.