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ORIGINAL ARTICLE

Combination Treatment of Intra/Perilesional Botulinum Toxin-A Injection and Ablative Fractional Laser for Better Clinical Outcomes of Hypertrophic Fibrotic Thyroidectomy Scars Following Fractional Ablative Laser Resurfacing

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Background: Recent reports have shown that intralesional botulinum toxin type-A (BTX-A) works on scar cosmesis. **Objective:** To evaluate the clinical efficacy of combination treatment of laser and BTX-A injection and compare the effects of conventional intralesional injection and intra- and perilesional BTX-A injection on fibrotic thyroidectomy scars. **Methods:** Patients with fibrotic thyroidectomy scars showing insufficient responses to previous ablative fractional laser (AFL) treatment were enrolled. Combination treatment with AFL and BTX-A injection was performed. Patients who received intra/perilesional BTX-A injections were classified into group A. Group B was patients in whom the injection was performed only intralesionally. The improvement was assessed based on the Vancouver Scar Scale (VSS). **Results:** A total of 24 patients was included. Statistically significant improvement in pliability and total VSS score after the combination treatment were observed in overall patient group. Subgroup analysis demonstrated that pliability, height, and total VSS improved significantly in group A. In group B, only pliability significantly improved. **Conclusion:** BTX-A injection combined with AFL can provide better relief for the previously treated fibrotic thyroidectomy scars. Injection of BTX-A not only into the scar itself, but also into perilesional muscles that can exert tension on the scar site may provide additional benefit in flattening scar height. **(Ann Dermatol 33(2) 170~177, 2021)**

-Keywords-
Botulinum toxins, type A, Scar, Thyroidectomy

INTRODUCTION

A scar results from proliferation of fibrous tissue, which replaces normal collagen after a wound or ulceration heals[1,2]. Inflammation, neural factors, cytokines, and tension are well known factors associated with the formation of abnormal scarring, which can be of great concern to patients. Tension that acts on the wound edges during the healing process is a key factor in determining final scar cosmesis[3]. From this point of view, botulinum toxin type-A (BTX-A) intralesional injections for treating abnormal scarring have gained attention since 2000. BTX-A cause temporary paralysis of the wound muscles, resulting in immobilization and reduction of perpendicular tension on the scar site[4,5]. Previous randomized controlled or prospective studies have proven that BTX-A intralesional injections induce

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better results in the treatment of early postoperative scars including hypertrophic scars and keloids[4-10].

There are various modalities for scar treatment including surgical revision, intralesional steroid injection, topical therapies, antimitotic agents, and laser treatment[1,2,11]. Scars, especially those located on exposed areas such as the neck after thyroidectomy, could be major cosmetic concerns. Treatment with pulsed dye laser and non-ablative fractional lasers (AFLs) in the early period after surgery has proven to be effective in mitigating hypertrophic changes in these scars[12,13]. Although minimization of hypertrophic changes with subjective discomfort symptoms such as itching and pain is the major concern in scar treatment, scars with fibrosis in the course of maturation can be another issue for patients. In this study, "fibrotic thyroidectomy scars" are defined as a type of hypertrophic scar raised from the skin surface but exhibit few or no symptoms with little or no erythema. The management of such scars sometimes remains a challenge to dermatologists if they occur in highly movable area with severe tension.

The aim of this study is to evaluate the clinical efficacy of combination treatment of laser and BTX-A injection on fibrotic thyroidectomy scars and to compare the clinical outcomes between intra/perilesional BTX-A injection and conventional intralesional injection.

MATERIALS AND METHODS

Study design and patients

This study was performed by reviewing electronic medical records and clinical photographs and was approved by the Samsung Medical Center Institutional Review Board (IRB no. 2013-06-071).

Between January 2016 and June 2017, patients with fibrotic thyroidectomy scars were enrolled in the study. All patients have been treated for their scars in 2 to 3 weeks after total thyroidectomy using pulsed dye laser (V-beam perfecta; Candela, Wayland, MA, USA) and fractional non-ablative laser (Fraxel dual; Solta Medical®, Hayward, CA, USA) in order to reduce or prevent hypertrophic changes. At 3-month follow-up after these early active laser treatments (average number of treatments was 4.42), patients with scars in which erythematous hypertrophic changes improved but fibrosis remained, were selected. For these scars, we applied an AFL first and after 2 to 4 months, combination treatment of AFL and BTX-A injection were performed afterwards. A total of 31 patients were screened, but 7 who did not complete at least 2 months of follow-up after the combination treatment were excluded from the analysis. A total of 24 patients met the inclusion criteria for the analysis.

Study procedures

AFL only treatment was performed using a fractional 2,950 nm Er:YAG laser (Joule; Sciton, Palo Alto, CA, USA) with one or two passes with parameters of 150 to 200 μm depth, 22% density, and coagulation level 1, with another one or two passes on the scars and perilesional areas of the scars with the parameters of 100 to 150 μm depth, 22% density, and coagulation off mode. For combination treatment of laser and BTX-A injection, AFL with the same parameters was applied first on the fibrotic thyroidectomy scar. The patients were recommended to apply an icepack or refrigerated hydrogel on the laser site to soothe and reduce post-laser edema for 10 to 20 minutes. BTX-A (Neuronox; Medytox Inc., Ochang, Korea; one unit of Botox is comparable to one unit of Neuronox), which was diluted to 4 U/0.1 ml, was injected with a 31-gauge, 8-mm insulin syringe. Patients were divided into two groups according to injection method. Intralesional injection of BTX-A was performed into the body of the scar with 4U of BTX-A at a distance of 1 cm apart on the scar line (conventional injection into the scar itself: Total of 24 to 32 U/person). Perilesional injection was performed into the lower part of the sternocleidomastoid (SCM) muscle where the thyroidectomy scar crossed (two spots on each SCM muscle at a distance of 1 cm apart: A total of 16 U/person). The injection was done until the half of the needle was inserted. Patients who received both intra and perilesional injections were classified into group A. Group B was patients in whom the injection was performed only intralesionally (Fig. 1). All treatments of lasers and injections were performed by a single dermatologist (J.H. Lee). Standardized digital photographs were produced under the same light and camera settings (D300S; Nikon, Tokyo, Japan) at every visit.

Clinical outcome assessment

Postsurgical scars can be assessed using various rating scales like the Vancouver Scar Scale (VSS), the Patient and Observer Scar Assessment Scale (POSAS), the Manchester Scar Scale (MSS), and the Stony Brook Scar Evaluation Scale (SBSES). Although the VSS and POSAS were originally designed to rate burn scars, they were also validated for postsurgical scars. These scales are best used to determine change within an individual rather than between individuals[14]. Two blinded assessors graded the degree of improvement using photographs based on the VSS, which consists of pigmentation (0, normal color; 1, hypopigmentation; 2, hyperpigmentation), vascularity (0, normal; 1, pink; 2, red; 3, purple), pliability (0, normal; 1, supple; 2, yielding; 3, firm; 4, banding; 5, contracture), and height (0,

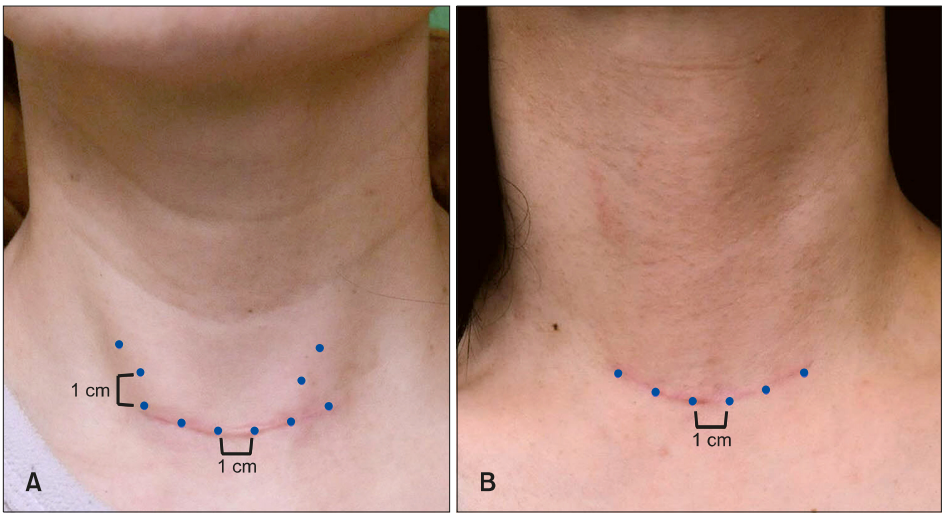

Fig. 1. Botulinum toxin type-A injection method in groups A and B. (A) Patients who received both intra- and perilesional injections were grouped into group A. (B) Patients who received intralesional injection only were grouped into group B. We received the patient's consent form about publishing all photographic materials.

Table 1. Baseline patient demographics (total number of patients = 24)

Variable	Total	Group A	Group B	*p*-value
Mean age (yr)	41.04 (26～58)	42.1 (27～58)	40.28 (26～57)	0.6649
Sex				0.6146
Male	4	1	3	
Female	20	9	11	
Male:female	1:5	1:9	3:11	
Mean BMI (kg/m^2)	21.97 (2.82)	21.02 (3.17)	22.70 (2.39)	0.1615

Values are presented as mean (range), number only, or mean (standard deviation). Group A: patients who received both intra and perilesional botulinum toxin type-A (BTX-A) injections, Group B: patients who received only intralesional BTX-A injection, BMI: body mass index.

normal; 1, < 2 mm; 2, ≥ 2 mm and < 5 mm; 3, ≥ 5 mm). The primary outcome of this study was to weigh the additional clinical benefits of BTX-A injections when it is combined with AFL treatment for fibrotic thyroidectomy scars. The differences between the efficacy of intra/perilesional injection of BTX-A and that of conventional intralesional injection are assessed as the secondary outcome.

Statistical analysis

Data were analyzed by statistical analysis executed using SAS ver. 9.4 (SAS Institute, Cary, NC, USA). The change of the VSS before and after procedures was analyzed using the Wilcoxon signed rank test and paired t-test. Wilcoxon rank sum test and Fisher's exact test were used to analyze the differences in age, body mass index (BMI), and sex between groups A and B.

RESULTS

A total of 24 patients with classified fibrotic thyroidectomy scars was analyzed. The demographics of the included patients are shown in the Table 1. There were no significant differences in age, BMI, and sex between groups A and B.

Laser treatment alone versus combination treatment with laser and BTX-A injection

The difference between before and after combination treatment of laser and BTX-A (V2 and V3) was analyzed. The mean vascularity score before and after combination treatment of laser and BTX-A injection was 1.13 and 0.83, respectively. The mean pigmentation score changed from 0.46 to 0.38, and the mean pliability score improved from 3.13 to 1.79. The mean value of height and total VSS improved from 1.54 to 1.13 and 6.25 to 4.13, respectively. The mean value of vascularity ($p = 0.0391$), pliability ($p < 0.0001$), height ($p < 0.0107$), and total VSS score ($p < 0.0001$) except for pigmentation exhibited statistically significant improvement after the combination treatment (Table 2).
When comparing the difference between the laser treatment alone and combination treatment of laser and BTX-A injection (V2-V1 and V3-V2), additional BTX-A injection with laser treatment resulted in greater significant improvement in pliability ($p < 0.0001$) and total VSS ($p = 0.0056$) compared to laser treatment alone in the overall patient

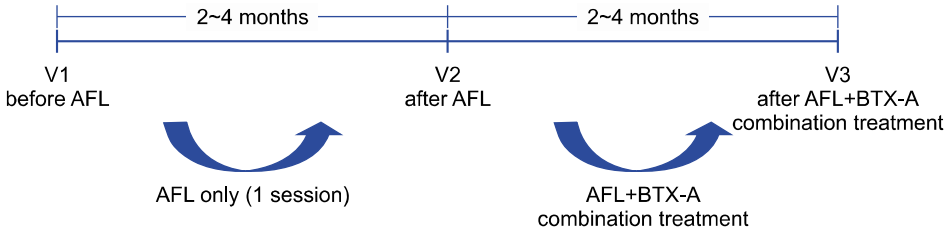

Fig. 2. Point in time comparison. Before combination treatment with AFL and BTX-A injection, all enrolled patients were treated with AFL alone. Two to four months after AFL alone treatment, combination treatment with AFL and BTX-A injection was done. AFL was performed with the same parameter in AFL alone treatment and combination treatment. AFL: ablative fractional laser treatment, BTX-A: botulinum toxin type-A, V1: visit 1, V2: visit 2, V3: visit 3.

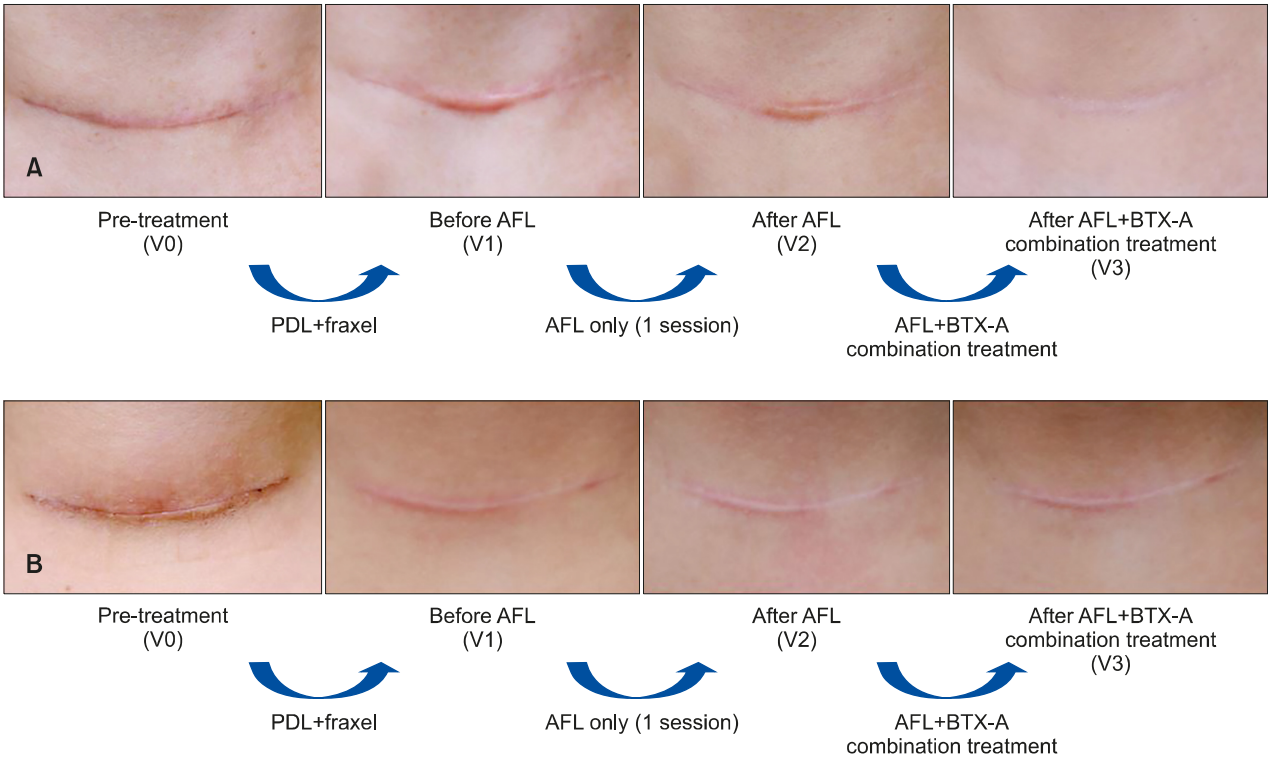

Fig. 3. Comparison of the efficacy of laser treatment alone and combination treatment of laser and BTX-A injection. (A) Group A: patients who received both intra- and perilesional BTX-A injections; (B) Group B: patients who received intralesional BTX-A injection only. V0 means two to three weeks after the total thyroidectomy before any laser treatment. Patients underwent treatment sessions of pulsed dye laser and fractional non-ablative lasers to prevent hypertrophic scars. At least 3 months after mean 4.42 treatment sessions, patients presented with fibrotic thyroidectomy scars were led into AFL treatment. Combination treatment of AFL and BTX-A injection were conducted afterwards. AFL: ablative fractional laser treatment, BTX-A: botulinum toxin type-A, PDL: pulsed dye laser, V0: initial visit of the patient before pulsed dye laser, V1: visit 1, V2: visit 2, V3: visit 3.

group (Fig. 2, 3) (Table 3).

Conventional intralesional injection versus intra- and perilesional BTX-A injections in combination treatment

When comparing the VSS score between V2 and V3 in each group, pliability ($p=0.0078$), height ($p=0.0156$), and total VSS score ($p=0.0015$) statistically significantly improved in group A, while group B exhibited significant differences in pliability ($p=0.0010$) and total VSS score ($p=0.0001$) (Table 2).

The difference between AFL laser treatment alone and combination treatment of AFL and BTX-A injection (V2-V1 and V3-V2) was analyzed separately in groups A and B. Pliability ($p=0.0051$), height ($p=0.0313$), and total VSS ($p=0.002$) were improved significantly in group A, while only pliability ($p=0.0004$) was significantly improved in group B (Fig. 2, 3) (Table 3).

Table 2. Difference between before and after botulinum toxin type-A (BTX-A) injection (V2 vs. V3)

Variable	Group A (n=10)				Group B (n=14)				Total (n=24)			
	V2	V3	V3-V2	*p*-value	V2	V3	V3-V2	*p*-value	V2	V3	V3-V2	*p*-value
Vascularity	1.2	1	−0.2	0.6250	1.07	0.71	−0.36	0.0625	1.13	0.83	−0.29	0.0391*
Pigmentation	0.6	0.6	0	-	0.36	0.21	−0.14	0.5000	0.46	0.38	−0.08	0.5000
Pliability	3.7	2.7	−1	0.0078*	2.71	1.14	−1.57	0.0010*	3.13	1.79	−1.33	<0.0001*
Height	2.5	1.7	−0.8	0.0156*	0.86	0.71	−0.14	0.6250	1.54	1.13	−0.42	0.0107*
Total VSS	8	6	−2	0.0015*	5	2.79	−2.21	0.0001*	6.25	4.13	−2.13	<0.0001*

Values are presented as mean. Group A: patients who received both intra and perilesional BTX-A injections, Group B: patients who received only intralesional BTX-A injection, VSS: Vancouver Scar Scale. *Statistically significant improvement ($p<0.05$).

Table 3. Difference between laser treatment alone and combination treatment (V2-V1 vs. V3-V2)

Variable	Group A (n=10)				Group B (n=14)				Total (n=24)			
	V2-V1	V3-V2	(V3-V2)-(V2-V1)	*p*-value	V2-V1	V3-V2	(V3-V2)-(V2-V1)	*p*-value	V2-V1	V3-V2	(V3-V2)-(V2-V1)	*p*-value
Vascularity	0.3	0.2	−0.1	1.000	0.57	0.36	−0.21	0.5898	0.46	0.29	−0.17	0.3810
Pigmentation	0.2	0	−0.2	0.7500	0.29	0.14	−0.15	0.5313	0.25	0.08	−0.17	0.3047
Pliability	−0.2	1	1.2	0.0051*	0.21	1.57	1.36	0.0004*	0.04	1.33	1.29	<0.0001*
Height	−0.1	0.8	0.9	0.0313*	0.86	0.14	−0.71	0.0039	0.46	0.42	−0.04	0.9896
Total VSS	0.2	2	1.8	0.0020*	1.93	2.21	0.29	0.4063	1.21	2.13	0.92	0.0056*

Group A: patients who received both intra and perilesional botulinum toxin type-A (BTX-A) injections, Group B: patients who received only intralesional BTX-A injection, VSS: Vancouver Scar Scale. *Statistically significant improvement ($p<0.05$).

DISCUSSION

Treatment of thyroidectomy scars with lasers in the early period after surgery has been widely conducted in recent years[15,16]. It was proved to prevent hypertrophic changes successfully in many literatures[12,13]. However, scar fibrosis is sometimes left after the active early treatment, which can be a cosmetic issue to patients. A decrease in height of these scars is the most crucial outcome in scar cosmesis. Raised scars that look like fibrotic bands are commonly treated with AFL, which can blunt the incision line and decrease the volume of scar fibrosis successfully[13]. AFL works by producing a controlled pattern of ablation and thermal injury that induce collagen fiber contraction, robust collagen and extracellular matrix production via cytokine modulation and collagen remodeling[17]. When these fibrotic scars occur on highly movable areas or tension sites such as the neck and perioral area[7,18], the treatment for reducing scar height becomes difficult sometimes. In this study, we defined a raised scar after open thyroidectomy with no or little erythema and without uncomfortable symptoms as a "fibrotic thyroidectomy scar." Mean pigmentation and vascularity scores before laser only and combination treatment indicate that all enrolled scars did not have erythema or hyperpigmentation, and they were fibrotic white scars. This is a type of hypertrophic scar in the maturation period in which erythema or subjective symptoms have improved, with scar cosmesis being the most concerning issue to patients. Patients with fibrotic thyroidectomy scars often present with high tension on their neck scar site with prominence of surrounding SCM muscles. For these scars, conventional lasers and intralesional corticosteroid injections often fail to produce desirable outcomes.

Recently, injecting BTX-A into early postoperative scars and even pathologic scars like hypertrophic scars and keloids has been increasingly performed. With the concept that muscle pull is the central stimulus to scar formation, BTX-A injections have been performed to lessen the tensile force that causes cell proliferation and collagen deposition[19,20]. The mechanism in which BTX-A exhibits its anti-scarring property is not clearly identified, but it is generally thought to be the result of chemo-immobilization that reduces muscular tension on scars[4-6]. BTX-A not only eases tension, but also induces apoptosis, inhibits proliferation of fibroblasts, and has a direct inhibitory effect on the expression of transforming growth factor–ß1 at the molecular level[8,19,21]. In one study using the rabbit hypertrophic scar model, there was a dose-dependent decrease in fibroblast proliferation when treated with BTX-A compared with saline and triamcinolone acetonide, as measured by Ki-67 with immunohistochemistry[21].

In most clinical studies, BTX-A injection for early postoperative scar treatment was used as a monotherapy, with a single injection of BTX-A improving the fate of scars[4-9]. Only one recently published randomized, prospective, placebo-controlled study by Phillips et al.[22] reported that BTX-A injection to early thyroidectomy scars did not demonstrate significant improvement in scar outcomes compared to the control side. This study was very similar to the previous one published by Kim et al.[8] in which the authors claimed positive effects of BTX-A in early postoperative scars. Differences in ethnicity of patients, follow-up period, scar analysis rubric, amount of BTX-A injection, and injection timing (right after the suture[22] versus 10 days after thyroidectomy[8]) between the two studies make them difficult to compare side by side. However, Phillips et al.[22] implicated less scarring in patients with severe scar history.

For hypertrophic scars and keloids, three injections with 2.5 U/cm^2 (not exceeding 100 U/person) every month for 3 months were performed in prior studies and suggested favorable outcomes[10,11,23]. Shaarawy et al.[24] reported in their randomized double blinded study the efficacy and safety of intralesional BTX-A injection were more evident in comparison to those of intralesional corticosteroids, the gold standard treatment modality for keloids. A great deal of prior literature indicates the presumptive conclusion that BTX-A injection can be a suitable potential therapy for various scars especially on the head and neck area.

Based on previous reports above, we tried to evaluate the effects of combination treatment of AFL and BTX-A injection on fibrotic thyroidectomy scars which underwent AFL only treatment before. AFL induce subclinical wounds on the scar site, which drives the scar into the inflammatory phase. Therefore, AFL combined with BTX-A injections for fibrotic thyroidectomy scars was assumed to yield suitable results. For the better combination, timing of BTX-A injection was considered. Prior reports showed that the timing of injection varied from immediately after suturing[7,9] to 3 to 10 days after surgery[4-6,8]. We determined that injection of BTX-A right after AFL application was most beneficial for patient convenience and because BTX-A exerts its effect in days and lasts for 2 to 6 months. For the dose of injection, less than 50 U/person/at a time on the neck was chosen for safety purposes[8,22].

In the present study, there was statistically significant improvement in pliability and total VSS score after combination treatment compared with prior AFL only treatment in the overall patient group. BTX-A injection in addition to AFL treatment appears to provide better outcomes.

BTX-A injection for scars was performed intralesionally in a conventional way based on the theory of tension release on wound edges. However, almost all fibrotic thyroidectomy scars pass by SCM muscles perpendicularly, and the tension of the SCM muscle itself on the adjacent fibrotic thyroidectomy scar may play a role in wielding tension on the scar site. Therefore, intra/perilesional BTX-A injection was performed for these patients (group A), and we attempted to evaluate the effects of added perilesional BTX-A injection. Total VSS score as well as pliability and height improved considerably in group A with intra/perilesional injection and AFL treatment, while in group B, there was no significant change in total VSS score with a noticeable decrease of pliability. The subgroup analysis showed that addition of BTX-A injection into the prominent muscles around the scars can produce better outcomes.

There are limitations to our study. Since this study was retrospectively designed, there was no control to compare directly with the actual effect of BTX-A injection in the combination treatment. To overcome this, we selected patients very strictly who met the enrollment criteria: patients with total thyroidectomy who were previously treated with pulsed dye laser and fractional non-ablative lasers in an early period after the surgery, but fibrosis remained afterwards. Regular follow ups were another criteria for patients' enrollment. For a better comparison, AFL treatment in both sessions (AFL alone and combination treatment) was performed using the same parameters. All procedures were done by one expert dermatologist. Therefore, the comparison in differences between before and after AFL alone treatment and before and after combination treatment implicates the possible beneficial role of BTX-A injection. Second, the injected dose of BTX-A in group A was definitely 16 u more than in group B because of additional injections into two spots of the lower part of the right and left SCM muscles 1 cm apart. The optimal dosage of BTX-A in scar treatment was not agreed upon. However, the concept to minimize tension on the wound and scars provides an appropriate explanation for additional injections into the adjacent large muscles. The AFL alone treatment and combination treatment with BTX-A injection were performed in a successive way. Therefore, it is difficult to determine whether these improvements were due to actual BTX-A effects or natural processes resulting from scar maturation. However, treatments were performed at 2- to 4-month intervals, which is not enough time for full scar maturation. Even though scar maturation occurs, improvement of scar height in these fibrotic scars is rarely achieved without treatment.

BTX-A injection for scar treatment has been studied previously as a monotherapy; to the best of our knowledge, combination treatment of AFL and BTX-A injection in a concurrent session has yet to be reported. BTX-A is not on-

ly effective in treating all aspects of scars, but can also be used selectively for severe fibrotic scars caused by prominent muscles and high tension. It does not mean that we advocate this combination treatment for fresh thyroidectomy scars. Rather, the data indicate that hypertrophic, non-erythematous fibrotic scars in areas of tension may benefit form a combination of AFL plus BTX A for the scar and surrounding muscle.

In conclusion, combination of AFL and BTX-A injection can be a promising therapeutic modality for mature fibrotic thyroidectomy scars, and this study pointed out that perilesional BTX-A injection is a useful treatment for high tension or hypertrophic scars. Better scar cosmesis could be achieved using BTX-A injection for neighboring muscles to create greater tension on the scar in addition to conventional injection into the scar body itself.

CONFLICTS OF INTEREST

The authors have nothing to disclose.

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DATA SHARING STATEMENT

Research data are not shared.

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