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Botulinum toxin type A (BTX-A) to improve the treatment of keloid and hypertrophic scars: A double-blinded randomized clinical trial

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ABSTRACT

Background: Keloid and hypertrophic scars are the results of abnormal skin cells proliferation that usually cause major physical, psychological and cosmetic problems. However, there is no effective method for eliminating this scars yet. Recent reports suggested that BTX-A improves wound healing. However, there is no comprehensive study to assess the efficacy of BTX-A injection for treatment of keloid and hypertrophic scars.
Aim: This study aims to investigate whether BTX-A injection improves the keloid and hypertrophic scars treatment or not.
Methods: Ten patients with keloid or hypertrophic scar lesions were enrolled in this study and randomized into two groups (injected by BTX-A or placebo). Injections were applied at one-month intervals for a total of three months. All the patients were followed up for at least six months. Scars were assessed by mVSS (modified Vancouver Scar Scale) and an independently blinded evaluator with standardized photographs.
Results: The study was completed with ten patients at the six months follow up visits in the treatment group. BTX-A reduced (not significantly, $p>0.09$) mVSS including pliability, vascularity, pigmentation, and height, but did not affect the pruritis and pain.
Conclusion: It can be concluded in this study that BTX-A can reduce some parameters of mVSS and may be a suitable compound for the treatment of keloid and scar tissue.

Keywords: Botulinum toxin type A, keloid, hypertrophic scars.
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INTRODUCTION

Patients with abnormal scars are often disappointed especially with keloid and hypertrophic scars.[1] Patients suffering keloid and hypertrophic scars often experience major physical deformities, restricted joint range of motion, pain, pruritis, and psychological problems. Many pathogenic reasons are suggested as the cause of this disease such as mast cells, TGF-β1 expression in skin cells, alteration in fibroblast proliferation, and tensile strength in lesion edge.[2,3]

Because the etiology of keloid and hypertrophic scars formation has not been fully delineated, treatment of this lesion remains problematic as yet.[4]

Different treatments are currently available, such as steroid injection, surgical methods, radiotherapy, pressure therapy, and silicon sheets.[5] But, none of these methods can provide excellent therapeutic results, so alternative methods are needed. Recent literature has suggested BTX-A injections as an efficient therapy for keloid and hypertrophic scars.[6] However, its clinical effectiveness has not been completely established. BTX-A is a neurotoxin derived from bacteria called *Clostridium botulinum*. It has been used for a long time to remove skin wrinkles by inducing chemo-denervation of muscles. BTX-A exerts its effect through blocking of exocytosis of acetyl-choline and blocking of neuromuscular transmission, and as a result is muscle flaccidity.[1,7] Some scholars reported that BTX-A could influence the cell cycle of fibroblasts in keloid and hypertrophic scars because it can decrease proliferation and enhance apoptosis of fibroblasts.[8-10] TGF-β1 has an important role at the beginning of skin scars. Recent investigations suggested that BTX-A could reduce the expression of TGF-β1 in fibroblast that derived from keloid and hypertrophic scars.[11-13]

Furthermore, some literature demonstrated that BTX-A reduced the tensile stress in ulcer margins by relaxing muscles and consequently helps in better healing of the wounds and decreasing excessive scar formation.[14,15]

Based on these in-vitro findings of the effect of BTX-A on keloid and hypertrophic scars, we were trying to demonstrate the effect BTX-A intralesional injection to alleviate or cure keloid and hypertrophic scars in a double-blinded randomized clinical trial. So, we studied 30 patients with keloid or hypertrophic scars and divided them into two groups of case and control that received drug

or placebo respectively, and followed them for six months after injections.

MATERIALS AND METHODS

This study was a double-blinded randomized control trial, and the rating level of evidence is II according to American Society of Plastic Surgeons.[16]

All the patients enrolled in this study are 15-60 years old, referred to Skin Department of Imam Reza Hospital in Tehran (Iran) from November 2016 to November 2017, and suffered from skin scars. Primary history obtained from 50 patients. All the steps of the study supervised and validated by the ethics committee of AJA University of Medical Science. Patients that had only one lesion and their lesions had persisted for at least one year are included in the study. Patients received other therapy for their lesions were excluded. Pregnant and lactating women and patients planning a pregnancy in the coming year were excluded. Patients with the history of skin diseases such as psoriasis, and neuromuscular diseases such as myasthenia gravis, and patients with the history of sensitivity to BTX-A were excluded from the study. Eventually, 14 patients began the study, and all of them were assigned to one of the groups ("toxin" or "control" group). The toxin group was injected with intralesional BTX-A (Dysport® - Ipsen – Paris), and the control group was injected with serum saline 0.9% as placebo. All the patients were injected once monthly for a total of 3 months with the dose of 4 U per cubic centimeter of the lesion. All the injections were applied to the lesions until blanching of the lesion was visible. All the patients were injected by a skin specialist that did not know the toxin and control group. All the patients were followed up for six months for one visit every month. In each visit, close-up photographs were taken at a 1:1 ratio with Nikon Digital Camera (Nikon®, SLR, D3200), without flash, 20 Megapixels resolution. All the lesions in each disease were assessed by a blinded skin specialist using mVSS that evaluate the scars based on pigmentation, pliability, height, vascularity, pain, and pruritis (Table 1). All the photographs were evaluated by another blinded skin specialist.

Statistical analysis performed by GraphPad Prism V7.03 software and paired t-test analysis were conducted. *P* values of <0.05 were considered significant.

RESULTS

According to inclusion and exclusion criteria that mentioned before, 20 patients entered in this study from November 2016 to November 2017. Six patients were not eligible based on specialist opinion because of their scars properties.

Consequently, 14 patients began the survey and underwent randomization. Seven patients administered randomly to toxin group and seven to the control group. In each group, two patients were lost to the follow up because of personal reasons. So finally ten patients finished the study and then followed up for six months. Demographic features of all the patients including age, sex, type of the scar, the cause of the lesion, lesion location, and

Table 1 **Modified Vancouver Scar Scale (mVSS)**

Modified Vancouver Scar Scale (mVSS)									
Pigmentation:		**Pliability:**		**Height**		**Pain**		**Pruritis**	
Normal	0	Normal	0	Flat	0	Non	0	Non	0
Hypopigmented	1	Supple - flexible with minimal resistance	1	<2mm	1	Occasional	1	Occasional	1
Mixed	2	Yielding - giving way to pressure	2	2-5 mm	2	Requiring medication	2	Requiring medication	2
Hyperpigmented	3	Firm - inflexible, not easily moved, resistant to manual pressure	3	>5mm	3				
		Banding - rope-like tissue that blanches with the extension of the scar	4						
		Contracture - permanent shortening of the scar, producing deformity or distortion	5						

Table 2 Distribution of scar characteristics in the two study groups

Patients	Sex	Age	Type of scar	Cause of lesion	Scar's location	Fitzpatrick's skin type	Group
1	F	16	Hypertrophic scar	Laceration	Foot	3	Toxin
2	M	33	Keloid	Spontaneously	Chest	2	Control
3	M	60	Hypertrophic scar	Surgery location	Chest	3	Toxin
4	F	20	Keloid	Spontaneously	Shoulder	3	Toxin
5	M	50	Hypertrophic scar	Surgery location	Chest	3	Toxin
6	M	55	Hypertrophic scar	Surgery location	Chest	3	Control
7	M	50	Hypertrophic scar	Surgery location	Chest	3	Control
8	F	55	Keloid	Spontaneously	Breast	2	Control
9	M	40	Keloid	Spontaneously	Chest	3	Control
10	F	55	Keloid	Spontaneously	Chest	2	Toxin

Table 3 Scar characteristics based on mVSS in the two study groups

	Pigmentation		Pliability		Vascularity		Height		Pain		Pruritis		mVSS	
Patients	Before	After	Before	After	Before	After	Before	After	Before	After	Before	After	Before	After
1	3	2	3	2	3	2	2	1	0	0	0	0	11	7
2	3	3	3	3	3	3	2	3	1	1	1	2	13	15
3	3	2	3	3	1	1	2	1	0	0	0	0	9	7
4	2	2	2	2	0	0	3	3	0	0	1	1	7	7
5	3	3	3	3	2	2	2	1	2	2	2	2	14	13
6	3	3	3	3	1	1	2	2	0	0	0	0	9	9
7	3	3	3	3	2	2	2	2	2	2	2	2	14	14
8	3	3	3	3	1	1	3	3	1	1	1	1	12	12
9	2	2	2	2	2	2	1	1	2	2	2	2	11	11
10	3	3	3	3	1	1	3	3	1	1	1	1	12	12

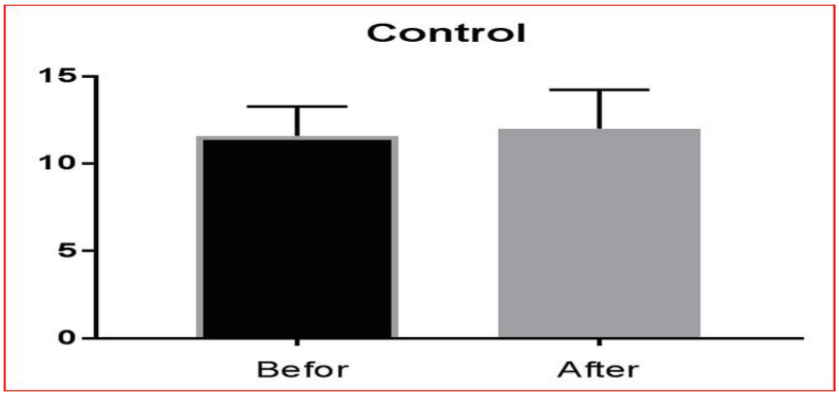

Figure 1 Control group

skins photo type according to Fitzpatrick scale are listed in Table 2.

The results indicated that BTX-A reduced (not significantly, p>0.09) the mVSS including pliability, vascularity, pigmentation, and height, but did not affect the pruritis and pain. In the control group, saline 0.9% injections did not have any effect on the improvement of patients' scars (Table 3). In one of the patients, saline 0.9% injections worsen the scar, which may have been due to the tissue damage, inflammation, and stimulation of the collagen production.

DISCUSSION

Hypertrophic scar and keloids are the results of the hyperproliferative growth of dermal collagen. They always cause functional and cosmetic difficulties, psychological problems, pain, itching, and other suffering symptoms for the patients.[17] This complications significantly reduce the quality of life of the patients and affects their functional performance. Because the etiology of keloid and hypertrophic scar formation is not completely recognized, management and treatment of this lesions remain problematic as yet. Different treatments for this lesions are available, such as surgical methods, steroid injection, radiation therapy, laser therapy, and silicon covers, but none of them could provide

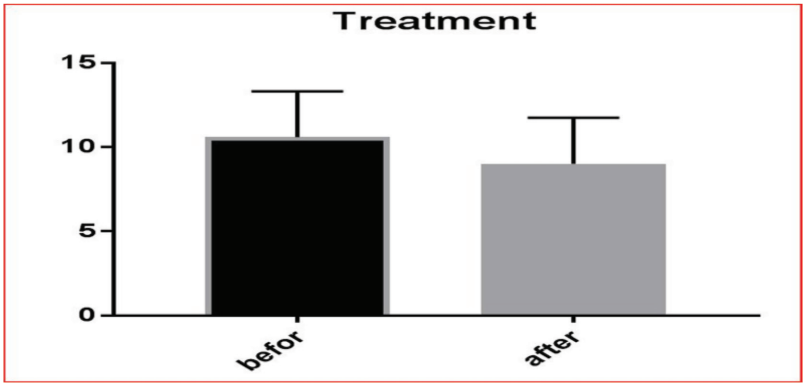

Figure 2 Toxin group

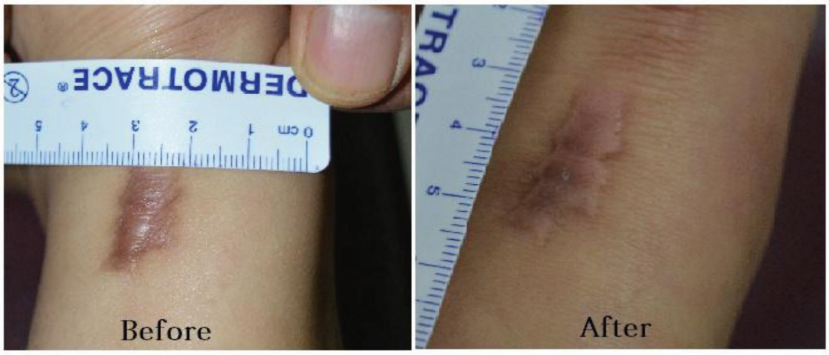

Figure 3

perfect results in patients. Moreover, patients are always not satisfied with these methods,[18] so it is necessary to introduce new therapeutical methods that can satisfy patients.

In recent years, BTX-A has become so popular in various therapeutic indications such as hyperfunctional facial lines, blepharospasm, and reducing facial wrinkles.[19-21] Numerous studies suggested different ways in which BTX-A can influence treatment of keloid and hypertrophic scar. BTX-A can reduce scar formation by paralysis of muscles involved in edges of the ulcers.[22] Secondly, BTX-A can affect fibroblast cycle and reduce their proliferation, and as a result, decrease the synthesis of extracellular matrix in fibroblasts.[1] Recent in-vitro studies also suggest that BTX-A could affect keloid and hypertrophic scar by inhibiting the expression of the TGF-β1 protein in those lesions.[23]

CONCLUSION

It can be concluded in this study that BTX-A can reduce some parameters of mVSS of keloid and scar tissue. Pliability, vascularity, pigmentation, and height were reduced although not significantly, but the pruritis and pain did not. The authors of the present paper believe that BTX-A may be a suitable compound for the treatment of keloid and scar tissue. More research is needed to evaluate the effect of BTX-A on scar treatment.

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