Evaluation of Botulonium Toxin Type A in the Management of Keloid Scar

Rusul Abbas Shaheed, Zakaria Y.Arajy***

ABSTRACT:

BACKGROUND:

One of the common and alarming problems to the patients is keloid formation that may occur after skin injury. Keloid had many cosmetic psychological and functional outcome, Multiple treatment have been present but still the treatment of keloid scar is dilemma due to lack of effective and excellent method .

AIM OF STUDY:

To evaluate the use of intralesional BTX-A for treatment of keloid scar.

PATIENTS AND METHODS:

Between October 2018 to January 2020, 20 patients presented to us with history of keloid in different parts of their body, those patients received intralesional BTX-A injection and they were followed up for one year and evaluated by scar score system.

RESULTS:

Our result showed that 10 patients had good response according to scar score, 7 patients had fair, 1 excellent and 2 patient had no improvement.no local and systemic side effect was seen.

CONCLUSION:

The use of BTX-A for treatment of keloids has shown to be effective in control and treatment of keloid and can be a part of treatment modalities

KEYWORDS: Hypertrophic scar , keloid scar , BTX-A

INTRODUCTION:

Keloid scar is regarded as one of the unique problems to human; it had both functional and aesthetic impact. The underlying pathogenesis of keloid scar formation is still not well understood. Many genetic and environmental factors have been impacted in the pathogenesis of keloid scar. [1,2,3]

Keloid scar can occur in all races, but it is particularly common in dark-skinned race. Keloid scar could be occured many years following initial injury and could be occurred spontaneously. Keloid scar usually occurs during period of physical growth with peak between 10-30 years. The most common causes appear to be non-specific trauma, tattoos, infections and vaccination. The strongest predisposing factor being earlobe piercing. [4,5,6]

There are many treatment modulators for keloid scar including surgical precision, steroid, radiation, antineoplastic agents, interferon, laser and cryotherapy. Each of above-mentioned treatment modulator had its own advantages and disadvantages. One of the recently used treatments for keloid is intralesional Botox injection, which was first used by Zhibo Xiao et al. [7] in this study intralesional BTX-A injection is used for treatment of keloid scar with assessment of its efficacy and safety.

PATIENTS AND METHODS:

Between October 2018 to Jaunary2020, twenty patients (11 females and 9 males) presented to us with history of keloid, their age were ranging between (6-63Years) with duration was ranging between (2-12 years). The dimensions varied between (0.5cm up to 12cm).Those patients were subjected to medical treatment of their keloid using intralesion BTX- A patient's data are shown in table 1 below.

*AL -Kadhmiya Teaching Hospital, Baghdad, Iraq

** The Iraqi Board for Medical Specialization.

Table 1: Patients data.

Pt.No	Gender	Age (years)	Site	Cause	Dimensionsof the scar	Duration of keloid scar
1	Female	30year	Ear lobes	Ear piercing	Rt(2cm*1cm*5mm) Lt (2.5cm*2cm*6mm)	8years
2	Female	10year	Left earlobe	Ear piercing	1cm*.5mm *5mm	4years
3	Male	37year	Sternum	Previous skin infection	4cm*1cm*3mm	7years
4	Female	30year	suprapubic	Previous operation	12cm*.5mm *4mm	4 years
5	Female	18year	Left ear lobe	Ear piercing	1.5 cm*1cm*5mm	5years
6	Male	30year	Sternum	Unknown	4.5 cm*1cm*2mm	12 years
7	Female	13year	Rt ear lobe	Ear piercing	1cm*1cm*2mm	4 years
8	Female	20year	Lt earlobe	Ear piercing	0.5cm*1cm*4mm	3 years
9	Female	29year	Earlobes	Ear piercing	Rt(0.5cm*1cm*5mm) Lt(0.5cm*0.5cm*3mm)	4 years
10	Female	16year	Rt hand	Trauma	2.5 cm*1cm*3mm	2years
11	Male	35year	Neck	Previous operation	5 cm*1cm*5mm	3 years
12	Female	28year	Rt ear lobe	Ear piercing	1 cm*1cm*4mm	2 years
13	Female	14 year	Earlobes	Ear piercing	Rt(5.5cm*3cm*8mm) Lt(5cm*3cm*9mm)	5 years
14	Female	63year	Lt earlobe	Trauma	2cm*1.5cm*4mm	2 years
15	Male	10year	Rt inguinal region	Previous operation	3cm*1.5cm*8mm	3 years
16	Male	6year	Face	Burn	5cm*3cm*6mm	3 years
17	Male	38year	Rt forearm Sternum	Trauma unknown	1cm*3cm *4mm 8cm*2cm*5mm	2years 10 years
18	Male	40year	Sternum	Trauma	5.5cm*2cm*2mm	3years
19	Male	30year	Neck	Unknown	7 cm*4cm*6mm	6 years
20	Male	60year	Sternum	Unknown	5 cm*1.5cm*2mm	10years

All patients included in this study had previously failed and ineffective treatment. The previous treatment modalities were intralesional steroid, silicon sheath, and surgical excision. We excluded from this study patients who are known allergic to BTX-A, planning to pregnancy or pregnant woman, lactation woman, patient with myasthenia grains or patient with chronic renal failure, and patients showing any abnormalities in the liver function tests or blood cell counts. Also we excluded those patients who had functional restriction due to keloid contracture. Patients are instructed not to use other treatment modalities for their keloid during course of therapy. Preoperative assessment of keloid was done including site of keloid, size, color, pliability and hardness, and if it associated with itching or pain sensation, all of our patients had symptoms itching and tenderness with pain of their keloid. Informed consent and photographs were taken from all our patients before injection of BTX A. Our results were assessed at the end of therapeutic course which was done at one year from time of patient presentation.

Assessment of our results depends on the following criteria:

1. Scar scoring for redress, hardness and elevation parameter and as following:
   - Redness: non redness (0) rose color (1), red color (2), intense red (3).
   - Elevation (mm): None (0), 1-4 mm (1), 4-8 mm (2),>8mm (3).
   - Hardness: soft(0), slight hard (1), hard(2), very hard (3) for those patient who had zero score they were regarded to had excellent improvement, those with score 1 regarded to have good improvement, score 2 had fair improvement, and lastly those patient who had score 3 had no improvement
2. Disappearance of itching and pain and direct question to patients about improvement and satisfaction

Procedure

In out-patient, the procedure is done under local anesthesia using topical EMLA cream that applied to keloid after cleaning of the scar and surrounding skin by using povidone iodine. We used BTX-A, 50 units diluted with 2ml of 0.9%

normal saline. Syringe of 1ml with 25 gauge needle is used for injection of keloid scar. We injected in first session 2.5 unit of BTX-A for every cm^2. Then after 3 months, 5 units of BTX-A are injected for every cm^2 then the dose increased to 7.5 unit / cm^2 after 3 months, till we reached to 10 unit/ cm^2 after 3 months. The injection is done in fan-like distribution into the keloid until slight blanching was clinically visible. After finishing of every injection simple dressing is applied to the injected site which was removed in the next day. Our evaluation of the results was done at 3 months after the last injection.

RESULTS:

Intralesional BTX-A injection was used in 20 patients who were presented to us with single keloid in different parts of their bodies.

No reported systemic or local site effect related to injection of BTX-A in all of our patients. Only slight bruising and minimal pain occur at the site of injection which is resolved spontaneously.

According to scar score parameter, our results have shown that 10 patients had good improvement(Fig,No.4&5), one patient had excellent improvement(Fig.No.3), 7 patients had fair improvement(Fig.No.6) ,while only 2 patients had no improvement (Fig.No.7). As shown in table(2)

Table 2: Patients result.

Pt. No.	Preinjection score	Postinjection score	% of reduction	Improvement
1	Rt 8 Lf 7	Rt3 Lf 5	Rt62.5% Lf 28.5%	Redness\Rt+\Lf+- ElevationRt+\Lf+- HardnessRt++\Lf+
2	2	0	100%	Redness++ Elevation++ Hardness++
3	8	4	50%	Redness+ Elevation+ Hardness++
4	9	7	22.2%	Redness- Elevation- Hardness+-
5	7	3	57.1 %	Redness+ Elevation+ Hardness++
6	6	4	33.3%	Redness+- Elevation+- Hardness+
7	8	4	50 %	Redness+ Elevation+ Hardness++
8	8	3	62.5%	Redness+ Elevation+ Hardness++
9	6	3	50%	Redness+ Elevation+ Hardness++
10	8	5	37.5%	Redness+- Elevation+- Hardness+
11	9	4	55.5 %	Redness+- Elevation+- Hardness+
12	7	5	28.57%	Redness+- Elevation- Hardness+
13	Rt8 Lf 9	Rt5 Lf 6	Rt37.5 % Lf33.3%	RednessRt+-\Lf+- ElevationRt-\Lf- HardnessRt++\Lf+
14	8	3	62.5 %	Redness+ Elevation+- Hardness++

15	9	7	22.22%	Redness- Elevation- Hardness+--
16	9	5	44.4%	Redness+- Elevation- Hardness+
17	Rt forearm 8 Chest 7	Rt forearm 5 Chest 4	Rt forearm 37.5% Chest 42.85%	Redness+\- Elevation_\+ Hardness+\+
18	8	3	62.5%	Redness+ Elevation+ Hardness++
19	9	8	11.11%	Redness- Elevation-- Hardness+-
20	7	3	57.14%	Redness+- Elevation- Hardness++

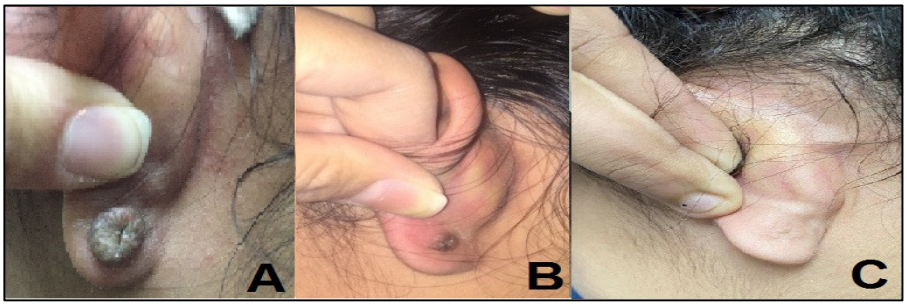

Figure 1: Left ear lobe (A) at presentation (B) after 6 months (C) after 1 year.

DISCUSSION:

One of early reports of using of BTX-A for facial scar was introduced by Sherris et al. [8]. Where they used BTX-A for facial skin wounds to minimize scar formation. By using BTX-A in lacerated facial wound, it will denervate muscle pulling, thus eliminate tension on the wound and subsequent scar hypertrophy during wound healing process. This method of facial muscle chemical immobilization can be used to prevent or minimize scar formation both for elective or traumatic wound. Recently using intralesional BTX–A had been used for established keloid scar with good and effective results as shown by many prospective study [9]

One of the important roles in formation of fibroprolifertive scar is the abnormal fibroblast proliferation and one most potent growth factor which plays role in wound healing is transforming growth factor β1(TGF-β1); by blocking TGF-β1 this may minimize fibroproliferative response. Experimental study which was done by Zhibo Xiao et al. showed that using of BTX-A would inhibit the fibroblast which is derived from hypertrophic scar with reduction of expression of TGF-β1.

These findings may explain partly the molecular action mechanism of BTX-A when used for treatment of hypertrophic scar [10]

In general TGF-β1 regulates both cellular growth and differentiation together with excessive collagen deposition. Thus, reduction of TGF-β1 secretion plays critical role in reduction of fibroproliferative process. Furthermore, experimental studies which were done also by Zhibo Xiao et al. showed that BTX-A when used on fibroblast derived from hypertrophic scar, reduces the expression of connective tissue growth factor (CTGF). CTGF regulates cellular adhesion and growth. [11,9,10].

Using BTX-A reduced proliferation in keloid derived fibroblast in 2 of 3 studies and reduced cellular proliferation in hypertrophic derived fibroblast in two reviewed studies. BTX-A had no effect on fibroblast proliferation from non-scared skin. However, there is a great variation in BTX-A efficacy on keloid derived fibroblast and hypertrophic derived fibroblast. Matrix metalloproteinase (MMP) are important enzymes which play role in collagen degradation in remolding phase of wound healing.

In one study, it showed that expression of MMP-1 is increased in fibroblast derived from keloid scar in response to using of BTX-A. Another proposal effect of BTX-A in treatment of keloid scar is though due to its anti-inflammatory effect by reducing the inflammatory mediators such as substance P and glutamate. Also, BTX-A reduces muscle tension during scarring process which may had role in formation of keloid scar [12].

On the basis of above-mentioned finding, BTX-A can be regarded as novel treatment for fibroproliferative scar. In this study, BTX-A was used in management of keloid scar in 20 patients who had keloid scar in different parts on their bodies.

All of them had previously ineffective treatment like silicon sheet, intralesional steroid and surgery. Our treatment regimen was by giving 2.5 unit of BTX-A for every cm^2 of keloid scar which was increased gradually every 3 months till we reached to 10 unit/cm^2 maximum BTX-A was 100 units per session. Our assessment of results was done after one year from starting our treatment. We depend on many parameters for assessing our results including scar scoring system (redness, elevation, hardness) disappearance of itching and pain, and visual analogue scale for patients' satisfaction.

We had 10 patients showed good improvement in their keloid scar regarding redness, elevation and hardness, one patient had excellent improvement with complete disappearance of keloid with normal color of skin and no recurrence, 7 patients had fair improvement and only 2 of our patients had no improvement or response to intralesional BTX-A. The most noticeable effect was decreasing in size and softness of the scar which was observed after 6 months from the beginning of the first dose. All of our patients had symptomatic itching and pain associated with their keloid and all of them even in that patient who had no response to treatment, had significant decrease in the pain and itching after intralesional BTX-A injection. According to the Lee et al., 86% of patients with keloid experience itching, and 46% had pain.

It is believed that the analgesic effect of BTX-A is due to its effect on vesicle-mediated substance that leading to pain, because BTX-A of affected these vesicle transport as its effect on vesicle-mediated release of acetylcholine Relief of pain was primary concern in many of our patients and they were so grateful to this pain improvement after intralesional BTX-A injection[13]

In all of our cases, we found that the gradual increment of dose of BTX-A was acceptable for all of our patients and achieved response without any local or systemic side effect. There is no standard regimen for BTX-A dose and duration. Zhibo Xiao et al. gave 2.5 units of BTX-A/cm^3 every month for total 3 months provided that the dose does not exceed 100 units per patient in one injection. Zhibo Xiao et al. used BTX-A for hypertrophic scar. Batifol et al. started by 50 units for right ear keloid and 20 units for left ear keloid and increased it gradually every three months [13,14].

Those patients who had improvement after BTX-A injection, it was related to the injections rather than the duration. Because the history of the keloid in our patients was ranging 2-12 years, during this period our patients showed no sign of spontaneous resolution of their keloid or response to other modalities of treatment like steroid injection or surgery. Our patients' response to intralesional BTX-A is obvious and effective .Several studies have documented that keloid does not regress spontaneously with time and it continues to grow, and although some keloid response to treatment, many of keloid scar are resistant to treatment and have rate of recurrence[14,15].

Other studies showed that spontaneous resolution of keloid may occur early in the course of the disease and those keloid that does not resolve, take many years to resolve with treatment or become resistant to the treatment. Intralesional BTX-A injection of keloid was used in twelve patients by Xia Zhibo and Zhang Miaobo. The keloid scars in those patients were of different size and duration. Patients who were involved in this study were informed to stop any other treatment modalities at least 3 months before treatment with using of intralesional BTX-A. The total dose was ranging between 70-140 units per session with time interval between each session was 3 months for maximum of 9 months duration. Their results showed that 3 patients out of 12 had excellent response (76-100% improvement), 5 patients had good improvement (51-75% improvement), and fair response in 4 patients (26-50% improvement). None of patient whom was included in this study had failure to therapy [15].

Batifol et al. used intralesional BTX-A injection for retro-auricular keloid post-otoplasty who had been previously treated with corticosteroid with no response, this patient received injection every 3 months for 3 years starting with 50 units on right ear keloid and 20 units on left ear keloid.[12] Their result in this patient was satisfactory.

Later on, they used BTX-A injection for keloid in 16 patients with good and very good results. In 12 patients, they used in addition to BTX-A injection surgical excision [12].

REFERENCES:

1. Ahuja RB, Chatterjee P. Comparative efficacy of intralesional verapamil hydrochloride and triamcinolone acetonide in hypertrophic scars and keloids. Burn,2014; 40:58-8.
2. Smith OJ, MCgrouther DA. The natural history and spontaneous resolution of keloid scars, Journal of plastic, Reconstructure and Asthestic surgery, 2014;67:87-92.
3. George Broguton , Rod J. Roohrich. Wound and scars selected reading in plastic surgery, 2005;10:1-56.
4. Micheal L. Bentz Bruce S. Bauer, Ranald M. Zaker. Principles and practice of pediatric plastic surgery 2nd edition, Thieme,2016;104.
5. Jill Sorch, Jan Rice. Reconstructure plastic surgical nursing; Clinical management and wound care, 1st ed. Blackwell Publishing, 2005:177.
6. Maria Z. Simionom, Marita Eisenmann-Klein. Plastic and reconstructure surgery,1st ed. Springer,2010:8.
7. Xia Zhibo, Zhang Miaoboo. Intralestional botulinum toxin type A injection as a new measure for keloid plastic and reconstructure surgery, 2009;124:275e-279e.
8. Parid A. Sherris, Holgar G. Gassuer. Botulmnue toxin to minimize facial scaring. Facial plastic surgery, 2002;18:35-39.
9. Gerd G. Gauglitz. Management of keloid and hypertrophic scars: current and emerging options. Clinical, cosmetic and investigational dermatology, 2013;6:103-14.
10. Zhibo Xia,Fengmin Zhang, Weibin Lin, Miaobo Zhang, Ying Lin, effect of botulinum toxin type A or transforming growth factors β1 in fibroblast derived from hypertrophic scar: a preliminary report. AethPlastSurg, 2010;34:424-27.
11. Zhibo Xiao, Miaobo Zhang, Ying Lin, LihhonyRen.Botuliunm Toxin type A inhibits connective tissue growth factor expression in fibroblasts derived from hypertrophic scar. Aesthplastsurg, 2011;35:802-7.
12. Dominigue Batifol et al. Treatment of keloid scar by botulinum toxin. Journal of ear, nose and throat disorder, 2017;2:1024.
13. Uyesugi B, Lippincott B, Daves. Treatment of painful keloid with botulinum toxin type A. AmJphys Med Rehabil, 2010; 89:153-55.
14. Zhibo Xiao, Fengmin Zhang, Ziwei Cui. Treatment of hypertrophic scar with intralesionalbotulinum toxin type A injection: A preliminary report. Aesthplastsurg, 2009; 33:409-12.
15. Xia Zhibo, Zhang Miaobo.Intralesionalbotulinum toxin type A injection as a new treatment measure for keloid. Plastic and reconstructive surgery, 2009;124:253e-79e.