Efficacy of Intralesional Injection of Botulinum Toxin in Treatment of Keloids

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Authors’ contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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ABSTRACT

Background: Keloid is generally accepted to be the result of prolonged and aberrant wound healing. Botulinum toxin injections are considered an efficient therapy for keloids. The current study evaluated the efficacy and safety of intralesional injection of botulinum toxin in treatment of keloids.

Methods: This prospective interventional study was carried out on 20 patients presented with keloids. Patients were treated by intradermal injection at the periphery of lesions by botulinum toxin as 100 IU diluted by 2 ml normal saline (5 IU/cm3). Vancouver Scar Scale (VSS) and Verbal Rating Scale (VRS) were used for the assessment of the therapeutic efficacy.

Results: There was a statistically significant improvement in all VSS and VRS parameters. Vast majority, 18 (90%) patients, were satisfied and 2 (10%) patient was not satisfied. There was non-significant correlation between the age of patients, duration of keloid nor size of keloid in relation to degree of improvement of VSS after treatment. There was positive significant correlation between VSS before treatment and degree of improvement of VSS after treatment.

Conclusions: Intralesional injection of botulinum toxin was effective and safe therapeutic techniques in inhibiting keloids regarding the statistically significant improvement on comparing between before treatment and after the end of follow up period.

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Keywords: Botulinum toxin; keloids; lesion; intradermal; therapeutic option.

1. INTRODUCTION

Keloid is generally accepted to be the result of prolonged and aberrant wound healing that involves excessive fibroblast participation, accelerated angiogenesis, and collagen accumulation found mainly in the reticular dermis [1,2]. The pathogenesis of keloid scarring has remained poorly understood to date [3].

There are multiple treatment options for keloid like surgical therapy, laser therapy, low dose radiation, silicone sheeting, topical retinoids, and intralesional injections of steroid, 5-fluorouracil (5FU) and bleomycin [4].

Botulinum toxin injections are considered an innovative and efficient therapy for keloids [5]. As it prevents contraction of muscles and skin near the keloid tissue, which decreases tensile force during the course of traumatic cicatrization [6,7]. It also suppresses the secretomotor function and trophic effect of the cell and influences cellular apoptosis and cellular proliferation which maintains the balance of cellular dynamics [8].

The current clinical study evaluated the efficacy and safety of intralesional injection of botulinum toxin in treatment of keloids.

2. PATIENTS AND METHODS

This prospective interventional study was carried out on 20 patients presented with recent keloids who were diagnosed clinically and confirmed histopathologically and did not receive any previous medical or surgical treatment. Participants were selected from the outpatient clinic of Dermatology and Venereology Department, Tanta University Hospitals.

Patients with any systemic or other dermatological diseases, pregnant and lactating women and children less than 12 years were excluded from this study.

Prior to injection, a topical anesthetic cream (lidocaine 5%) was applied to the keloid for 15 minutes, and then washed by saline followed by antiseptic solution. Patients were treated by intradermal injection at the periphery of keloids by botulinum toxin as 100 IU diluted by 2 ml normal saline (5 IU/cm²), with the degree of injection 45°. Each patient received 3 treatment sessions at four weeks intervals and monthly followed up for three months with assessment of adverse effects and patient’s satisfaction.

Assessment of the therapeutic efficacy was based on clinical assessment before and after treatment according to Vancouver Scar Scale (VSS) and Verbal Rating Scale (VRS) before each treatment session and 3 months after last treatment session. The clinical degree of improvement was graded as following: (0-25 % improvement) = no change, (25-50 % improvement) = mild improvement, (50- 75 % improvement) = moderate improvement, (75-100 % improvement) = excellent improvement.

All patients were subjected to: history taking, clinical and dermatological examination (Vancouver Scar Scale, [9] to evaluate the vascularity, pigmentation, pliability and height and Verbal Rating scale to evaluate pain and itching) [10].

2.1 Statistical Analysis

The data was analyzed using Microsoft Excel 2010 and SPSS ver. 24.0. Continuously normally distributed variables were represented as mean ±SD. with 95% confidence interval and compared by paired T test, and using the frequencies and percentage for categorical variables; a p value < 0.05 was considered statistically significant.

3. RESULTS

There were 12 (60%) males and 8 (40%) females participants. Their age ranged from 18 to 64 years with a mean of 27.3±6.3. Duration of keloids ranged from 3 to 6 months with a mean of 4.4±3.2. According to the topographical location, there were 4 (20%) patients with keloids on the head and neck, 8 (40%) patients on the trunk, and 6 (30%) patients on the extremities. Regarding the family history of keloids, there was positive family history in 4 (20%) patients.

Regarding the clinical parameters (according to Vancouver Score) of the studied patients, before and after treatment, there was a statistically significant improvement of keloids pigmentation after the end of treatment sessions in comparison to before treatment (p value=0.001). There was statistically significant improvement of vascularity of keloids after end of treatment in comparison to before treatment (p value=0.001). There was a statistically significant improvement
of pliability of keloids after end of treatment in comparison to before treatment (p value=0.001) (Figs. 1 - 2). There was statistically significant reduction of keloids height after end of treatment in comparison to before treatment (p value=0.001). There was with a significant improvement in VSS of studied patients after treatment (p value= 0.001) (Table 1).

Regarding the clinical degree of improvement according VSS after treatment, 16 (80%) patients showed excellent improvement and 4 (20%) patients showed mild improvement (Table 1).

Regarding VRS of the studied patients before and after treatment, there was a statistically significant improvement of pain after treatment in comparison with baseline (p value= 0.001). Also there was a statistically significant improvement of itching after treatment (p value= 0.001) (Table 2).

Table 1. Comparison between VSS before and after treatment

<table>
<thead>
<tr>
<th></th>
<th>Before treatment</th>
<th>After treatment</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pigmentation</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal</td>
<td>3 (30.0%)</td>
<td>10 (10%)</td>
<td>0.001</td>
</tr>
<tr>
<td>Hypopigmentation</td>
<td>0 (0.0%)</td>
<td>0 (0.0%)</td>
<td></td>
</tr>
<tr>
<td>Hyperpigmentation</td>
<td>7 (70.0%)</td>
<td>0 (0.0%)</td>
<td></td>
</tr>
<tr>
<td>Vascularity</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal</td>
<td>0 (0.0%)</td>
<td>8 (80.0%)</td>
<td>0.001</td>
</tr>
<tr>
<td>Pink</td>
<td>2 (20.0%)</td>
<td>2 (20.0%)</td>
<td></td>
</tr>
<tr>
<td>Purple</td>
<td>0 (0.0%)</td>
<td>0 (0.0%)</td>
<td></td>
</tr>
<tr>
<td>Red</td>
<td>7 (70.0%)</td>
<td>0 (0.0%)</td>
<td></td>
</tr>
<tr>
<td>Pliability</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal</td>
<td>0 (0.0%)</td>
<td>8 (80.0%)</td>
<td>0.001</td>
</tr>
<tr>
<td>Supple</td>
<td>2 (20.0%)</td>
<td>2 (20.0%)</td>
<td></td>
</tr>
<tr>
<td>Firm</td>
<td>8 (80.0%)</td>
<td>0 (0.0%)</td>
<td></td>
</tr>
<tr>
<td>Height</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>0 (0.0%)</td>
<td>2 (20.0%)</td>
<td>0.001</td>
</tr>
<tr>
<td>1</td>
<td>0 (0.0%)</td>
<td>6 (60.0%)</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>3 (30.0%)</td>
<td>2 (20.0%)</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>7 (70.0%)</td>
<td>0 (0.0%)</td>
<td></td>
</tr>
<tr>
<td>Vancouver scale</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Range</td>
<td>5 - 13</td>
<td>0 - 7</td>
<td>0.001</td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>10.9±0.5</td>
<td>1.8±0.4</td>
<td></td>
</tr>
</tbody>
</table>

Fig. 1. (A): Before treatment; a post traumatic keloid on the right ankle (VSS=11). (B): After treatment with BTX-A injection, it showed excellent improvement (VSS =1)
Table 2. Comparison between VRS before and after treatment

<table>
<thead>
<tr>
<th></th>
<th>Before treatment</th>
<th>After treatment</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pain in keloid</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>1(10.0%)</td>
<td>9(90.0%)</td>
<td>0.001</td>
</tr>
<tr>
<td>Mild</td>
<td>2(20.0%)</td>
<td>1(10.0%)</td>
<td></td>
</tr>
<tr>
<td>Moderate</td>
<td>4(40.0%)</td>
<td>0(0.0%)</td>
<td></td>
</tr>
<tr>
<td>Severe</td>
<td>3(30.0%)</td>
<td>0(0.0%)</td>
<td></td>
</tr>
<tr>
<td>Itching in keloid</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>1(10.0%)</td>
<td>9(90.0%)</td>
<td>0.001</td>
</tr>
<tr>
<td>Mild</td>
<td>2(20.0%)</td>
<td>1(10.0%)</td>
<td></td>
</tr>
<tr>
<td>Moderate</td>
<td>4(40.0%)</td>
<td>0(0.0%)</td>
<td></td>
</tr>
<tr>
<td>Severe</td>
<td>3(30.0%)</td>
<td>0(0.0%)</td>
<td></td>
</tr>
</tbody>
</table>

Fig. 2. (A): Before treatment; a post traumatic keloid on the trunk (VSS=10). (B): After treatment with after treatment with BTX-A injection, it showed moderate improvement (VSS =2)

According to the satisfaction of patients after treatment, 18 (90%) patients were satisfied and 2 (10%) patient was not satisfied.

4. DISCUSSION

Keloids are benign fibroproliferative tumors that may lead to cosmetic disfigurement, functional impairment and/or pain thus affecting the patient’s quality of life [11]. Keloid development is characterized by uncontrolled proliferation of fibrogenic cells with excessive production and deposition of extracellular matrix mainly collagen and glycosaminoglycan [12].

The present study revealed that, most of patients (83.3%) were adults and only 16.6% of them were young adults. In agreement with our results, Sun et al. [13] and Goyal et al. [14] reported that keloids most likely occur in the second and third decades of life and tend to decrease in older age groups, which is supported by the following phenomena: (a) younger people may have a higher frequency of trauma and their skin is more elastic than the skin of elderly people. [15] (b) they have higher level of sexual hormone than older people (Keloid growth may also be stimulated by various hormones, as indicated by some studies in which results have suggested a higher incidence of keloid formation during puberty and pregnancy, with a decrease in size after menopause, that related to localized hyper androgen metabolism which may play a causal or at least contributory role in the pathogenesis of keloids, or elevated androgen receptor levels exist in clinical active keloid tissue) [16,17].

The results of the current study showed significant clinical improvement according to VSS (vascularity, pliability and height) after treatment with botulinum toxin injection. Also, no recurrence was reported after the end of follow up period in all patients.
Botulinum toxin type A is a neurotoxin that causes paralysis of the injected muscles and reduces skin tension. Botulinum toxin prevents contraction of muscles and skin near the keloid tissue, which decreases tensile force during the course of traumatic cicatrization [6,7]. It also suppresses the secretomotor function and trophic effect of the cell and influences cellular apoptosis and cellular proliferation, which maintains the balance of cellular dynamics [8].

Zhibo and Miaobo, [18] documented that BTX-A may be an effective and safe treatment for keloids of all sizes and any duration. All patients included in their study were responsive to treatment and there were no serious adverse side effects. Peripheral regression of lesions was noted, in addition to flattening in all cases, and there was no evidence of recurrence up to 1 year after treatment.

Also, Robinson et al. [19] used BTX-A in treatment of 12 patients with Keloid scars. The patients had received between 20 and 100 IU of BTX-A injected /session, depending on the size and the location of the keloid scar. On average, it took 11 months of repeated injections to completely flatten the keloid scar. Visible reduction in size, color, consistency, symptoms and further progression was recorded using the VSS.

In consistent with our result, Bi et al. [20] showed that injection of botulinum toxin was more effective in the treatment of keloid than injection of steroid.

Botulinum toxin causes temporary paralysis on the wound muscles, causing immobilization and therefore reducing the perpendicular tension. BTX-A allows near-complete elimination of dynamic muscle tension on the wound during the healing process [21].

Shaarawy et al. [22] and El Morsy et al. [23] reported that all subscales of the VSS showed improvement after treatment comparative to that before treatment.

Recently, Gamil et al. [24] in 2019 reported that the combination of botulinum toxin and steroids seems to offer the balanced benefit of faster and more efficacious response with lesser adverse effects when compared to individual orally taken drugs.

A study done by Haubner et al. [25] demonstrated that, neither cell proliferation, growth nor cytokines were affected by BTX-A incubation. In the same opposing line, another study done by Gauglitz et al. [26] demonstrated that BTX-A did not result in regression of keloid tissue and that cell proliferation and metabolism of keloid fibroblasts were not affected by BTX-A treatment. However, this study was carried out on only four patients.

In addition, anti-melanogenic effects of BTX-A on melanocytes, BTX-A can suppress ultraviolet B–induced melanogenesis through both direct and indirect mechanisms, BTX-A decreased dendricity of melanocyte and melanin content in the cells. In addition, subcutaneous injection of BTX-A had a preventative effect on skin pigmentation [27].

In association with our findings, Shaarawy et al. [22] showed that, all keloid patients treated with steroid and botulinum toxin mentioned a significant reduction of their subjective complaints (pain & itching) starting 2 months after the treatment.

However, in the study of El Morsy et al. [23] all patient's complaint (itching, burning, tenderness and pain) had improved in both groups (BTX-A and steroid) after treatment with no significant difference between the two groups.

Botulinum toxin inhibits the release of acetylcholine. It inhibits an intracellular endopeptidase required for adherence of the vesicle to the presynaptic membrane. In this manner, botulinum toxin prevents vesicle-mediated release of acetylcholine into the synaptic cleft [28].

In agreement with our results, Shaarawy et al. [22] reported complete absence of side effects in their studied keloid patients receiving BTX-A whereas skin atrophy and telangiectasia were evident in three patients (25%) of those receiving the steroids.

In the current study, according to the satisfaction of patients after treatment in the three studied groups: (90%) of patients were satisfied. In agreement with our result, Shaarawy et al. [22] showed that, 6 (50%) of patients in group A (steroid) were highly satisfied, 5 (42%) of them were satisfied, and only 1 (8%) was unsatisfied with their results. While in group B (botulinum toxin), 9 (75%) of patients were highly satisfied,
and 3 (25%) of them were satisfied with their results.

Also, Neinaa et al. [29], showed significant reduction of VSS after treatment with botulinum toxin and platelet rich plasma (PRP) more than those treated by intrallesional steroids.

5. CONCLUSIONS

It could be concluded that intrallesional injection of botulinum toxin was effective and safe therapeutic technique in inhibiting keloids regarding the statistically significant improvement on comparing between before treatment and after the end of follow up period.

DISCLAIMER

The products used for this research are commonly and predominantly use products in our area of research and country. There is absolutely no conflict of interest between the authors and producers of the products because we do not intend to use these products as an avenue for any litigation but for the advancement of knowledge. Also, the research was not funded by the producing company rather it was funded by personal efforts of the authors.

CONSENT

As per international standard or university standard, patient’s written consent has been collected and preserved by the author(s).

ETHICAL APPROVAL

The protocol and all corresponding documents were declared for Ethical and Research approval by Tanta University Institutional Review Board (IRB), 32429/06/18.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

REFERENCES

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