Evaluation Of Intralesional Injection Of Botulinum Toxin Type A, Methotrexate, And Verapamil In Treatment Of Keloids: A Preliminary Study

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Evaluation Of Intraleisional Injection Of Botulinum Toxin Type A, Methotrexate, And Verapamil In Treatment Of Keloids: A Preliminary Study

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ABSTRACT

Background: Keloids are due to overgrowth of dermal collagen following trauma to the skin that usually cause major physical, psychological and cosmetic problems. Intraleisional injection treatments show promising results and many agents have been used as single treatments or in combination to get the best result.

Aim of the study: To evaluate the clinical outcome of the three injectable drugs (botulinum toxin type A, methotrexate, and verapamil) in treatment of keloids.

Patients and Methods: This is a prospective comparative non-randomized clinical study including 20 patients with 30 keloid lesions divided into 3 groups A, B and C including 10 lesions each. Group A received intraleional injection of Botulinum toxin Type A (BTX-A) 2 U/cm², Group B was treated with Methotrexate (MTX) 1 mg/cm² and group C with Verapamil 0.125 mg/cm².

Results: The percentage of improvement of VSS was better in group A than group C which was statistically significant (p1=0.01). Also, group B was better than group C in the percentage of improvement of VSS which was statistically significant (p2<0.01), while, there was no statistically significant difference in the percentage of improvement between group A and group B (p3=0.233).

Conclusion: This study supports the efficacy of the 3 mentioned drugs in treatment of keloids with better results obtained from intraleional injection of Botulinum Toxin A and Methotrexate than Verapamil.

Keywords: Keloid; Botulinum Toxin; Methotrexate; Verapamil

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Authorship: All authors have a substantial contribution to the article.

INTRODUCTION

Keloids are fibro-proliferative dermal conditions that can lead to pruritus, discomfort, and disfigurement. Keloids spread wider than the range of the original injury and have a persistent and long development against hypertrophic scars that are confined to the injury and can partially regress after rapid growth.¹

An unresolved concern remains the treatment of keloids. Intraleional injection, pressure therapy, radiation, excision, and sometimes combining some of the previously listed treatments have been identified in many therapeutic modalities.²

Treatment by intraleional injections have shown some good outcomes over in the form of improvement in keloid appearance and psychological well-being, but there is yet no definite protocol according to which intraleional agents are best for treatment of keloid.³

In recent years, some physicians are using BTX-A as a modality for prevention and treatment of keloids as it decreases itching, discomfort, improves the texture, and decrease the size of keloids.⁴

Methotrexate (MTX) has been reported a few times in the literature as an alternative therapy for keloids. It affects the synthesis of thymidylate synthase which decreases the nucleotides that form DNA and RNA, affecting repair of nucleic acids which suppresses cell proliferation. Keloids are affected the most because of the increased cell growth rate.⁵

Verapamil has also been successfully applied for keloid therapy. Calcium channel blockers have been proven to reduce production of extracellular matrix in scars. Also, they modify fibroblast morphology by depolymerizing actin filaments due to increased secretion of pro-collagenase.⁶

MATERIALS AND METHODS

This is a prospective comparative non-randomized clinical study conducted at Al Azhar University hospitals including 20 patients with 30 keloid lesions. Patients below age of 15 and above age of 50,
patients receiving other treatment for keloid, pregnant, lactating females and patients with lesions more than 20 cm² were excluded from the study. Ethical approval was gained from the ethics unit of the Faculty of Medicine, Al-Azhar University, Cairo and informed agreements were gained from the included participants.

Lesions were divided to three treatment groups A, B and C including ten lesions each. Group (A) received four sessions of intralesional injection with BTX-A 2 U/cm² with a maximum total dose of 50 U/session separated by 2 months interval. Group (B) received 6 sessions of intralesional injection with Methotrexate (MTX) 1 mg/cm² with a maximum total dose of 20 mg/session separated by 1 month interval. Group (C) received 6 sessions of intralesional injection with Verapamil 0.125 mg/cm² with a maximum total dose of 2.5 mg/session separated by 1 month interval. Follow up was done for 1 month after the last session and assessment was done clinically, photographically and statistically according to improvement of Vancouver scar scale (VSS).

**RESULTS**

The study included 20 patients, 11 females (55%) and 9 males (45%), aging from 16-45 years with Mean age of 22.80 ± 8.50 years. Lesion sizes ranged from 5.0-20.0 cm² with the mean size of 11.0 ± 5.04 cm². Scar age ranged from 4.0-12.0 months with a mean of 7.90 ± 2.81 months. (Table 1).

Regarding the total VSS, a statistically significant difference between before and after treatment in group A (p<0.01), group B (p<0.01) and group C (p<0.01). In the post treatment period, there was a statistically significant difference between Group A and C (p=0.012) and between Group B and C (p=0.01), while no statistically significant difference between group A and B was noticed (p=0.625). (Table 2).

Improvement of keloid scars after treatment was noticed clinically as well as statistically by calculating the percentage of improvement of the total VSS in all groups by varying degrees with better improvement in both group A and group B than group C. Good improvement after treatment was noticed in group A treated with BTX-A (figure1) with a mean improvement percentage of (49.83 ± 10.48). Group B treated with MTX also showed good improvement after treatment (figure2) with a mean percentage of (58.73 ± 15.75). While, group C treated with Verapamil showed a slightly less improvement (figure3) with a mean percentage of (27.45 ± 8.10).

The percentage of improvement of VSS was better in group A than group C which was statistically significant (p<0.01). Also, group B was better than group C in the percentage of improvement of VSS which was statistically significant (p<0.01), while there was no statistical difference in the percentage of improvement between group A and group B (p=0.233). (Table 3)

### Table 1: Distribution of the studied lesions regarding characteristics (n = 30)

<table>
<thead>
<tr>
<th>Lesion size (cm²)</th>
<th>No.</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Min. – Max</td>
<td>5.0 – 20.0</td>
<td></td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>11.0 ± 5.04</td>
<td></td>
</tr>
<tr>
<td>Median (IQR)</td>
<td>10.0 (6.0 – 15.0)</td>
<td></td>
</tr>
<tr>
<td>Scar age (months)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Min. – Max</td>
<td>4.0 – 12.0</td>
<td></td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>7.90 ± 2.81</td>
<td></td>
</tr>
<tr>
<td>Median (IQR)</td>
<td>7.50 (5.0 – 10.0)</td>
<td></td>
</tr>
</tbody>
</table>

### Table 2: Comparison between the treatment groups regarding total Vancouver scar scale

<table>
<thead>
<tr>
<th>Total Vancouver scar scale</th>
<th>Treatment</th>
<th>F</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-treatment</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Group A (BTX-A) (n = 10)</td>
<td>Group B (MTX) (n = 10)</td>
<td>Group C (Verapamil) (n = 10)</td>
<td></td>
</tr>
<tr>
<td>Min. – Max</td>
<td>5.0 – 11.0</td>
<td>5.0 – 11.0</td>
<td>5.0 – 11.0</td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>7.60 ± 2.12</td>
<td>8.10 ± 2.02</td>
<td>8.20 ± 1.99</td>
</tr>
<tr>
<td>Median (IQR)</td>
<td>7.50 (6.0 – 9.0)</td>
<td>8.50 (6.0 – 10.0)</td>
<td>9.0 (7.0 – 9.0)</td>
</tr>
<tr>
<td>Post-treatment</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Min. – Max</td>
<td>2.0 – 6.0</td>
<td>1.0 – 5.0</td>
<td>4.0 – 8.0</td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>3.90 ± 1.52</td>
<td>3.30 ± 1.34</td>
<td>5.90 ± 1.45</td>
</tr>
<tr>
<td>Median (IQR)</td>
<td>4.0 (2.0 – 5.0)</td>
<td>3.50 (2.0 – 4.0)</td>
<td>6.0 (5.0 – 7.0)</td>
</tr>
<tr>
<td>Sig. between groups, t6 (p)</td>
<td>p1 = 0.625, p2 = 0.012, p3 = 0.01 ^ *</td>
<td>12.333 ^ (&lt;0.01 ^ *)</td>
<td>7.856 ^ (&lt;0.01 ^ *)</td>
</tr>
<tr>
<td>Total Vancouver scar scale</td>
<td>Treatment</td>
<td></td>
<td></td>
</tr>
<tr>
<td>---------------------------</td>
<td>-----------</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td></td>
<td>Group A (BTX-A) (n = 10)</td>
<td>Group B (MTX) (n = 10)</td>
<td>Group C (Verapamil) (n = 10)</td>
</tr>
<tr>
<td>Improvement</td>
<td>Min. – Max.</td>
<td>2.0 – 5.0</td>
<td>3.0 – 8.0</td>
</tr>
<tr>
<td></td>
<td>Mean ± SD.</td>
<td>3.70 ± 0.95</td>
<td>4.80 ± 1.93</td>
</tr>
<tr>
<td>Median (IQR)</td>
<td>4.0 (3.0 – 4.0)</td>
<td>4.50 (3.0 – 7.0)</td>
<td>2.0 (2.0 – 3.0)</td>
</tr>
<tr>
<td>Sig. between groups.</td>
<td>p₁ = 0.185, p₂ = 0.072, p₃ = 0.01</td>
<td></td>
<td></td>
</tr>
<tr>
<td>% Improvement</td>
<td>Min. – Max.</td>
<td>33.33 – 66.67</td>
<td>37.50 – 80.0</td>
</tr>
<tr>
<td></td>
<td>Mean ± SD.</td>
<td>49.83 ± 10.48</td>
<td>58.73 ± 15.75</td>
</tr>
<tr>
<td>Median (IQR)</td>
<td>47.73</td>
<td>52.78</td>
<td>24.75</td>
</tr>
<tr>
<td>Sig. between groups.</td>
<td>p₁ = 0.233, p₂ = 0.01*, p₃ &lt; 0.01*</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Table 3:** Comparison between the treatment groups regarding improvement in total Vancouver scar scale

**Fig. 1:** before (a) and 1 month after (b) treatment with BTX-A for 4 sessions.

**Fig. 2:** before (a) and 1 month after (b) treatment with MTX for 6 sessions.

**Fig. 3:** before (a) and 1 month after (b) treatment with Verapamil for 6 sessions.
DISCUSSION

Keloid is a benign proliferating tumour of the dermal connective tissue that occurs in genetically susceptible individuals as a result of an excessive tissue reaction to cutaneous trauma and does not disappear spontaneously.¹

Keloid is a common yet difficult-to-treat condition. Keloids have been treated with a variety of methods, however there is no definitive treatment that eliminates keloids.²

This is the first study to compare the efficacy between intralesional injection Botulinum toxin type A (BTX-A), Methotrexate (MTX) and Verapamil in management of keloids.

Twenty patients aging from 16-45 years with thirty keloid lesions were included in this study. Ten lesions were treated with BTX-A every 2 months for four sessions, ten lesions were treated with MTX monthly for six sessions and ten lesions were treated with Verapamil monthly for six sessions. Lesions treated with BTX-A showed (49.83 ± 10.48) percent improvement and lesions treated with MTX showed (58.73 ± 15.75) percent improvement. While, Verapamil treated lesions only showed (27.45 ± 8.10) percent improvement after treatment.

In a prior study by Ghonaim,³ IL BTX-A was administered at one-month intervals (dosage of 2.5 U/cm³) for 3 months, and good results was observed in 48 percent of scars which is agreement with our results.⁴

Other study conducted by Zhibo et al.,⁵ twelve patients with single or multiple keloids were given BTX-A every three months for nine months. After one year of follow-up, excellent results were seen in three patients, good results in five patients, while in four patients, fair results were noticed.⁶

Al-Khateeb et al.,⁷ made a study on 40 patients with hypertrophic scars comparing intralesional injection of TAC and Methotrexate. His results suggested good improvement in both treatment modalities with TAC being more effective than Methotrexate.⁸

A study by Sharquie et al.,⁹ who combined Methotrexate and TAC in treatment of keloids with or without surgical debulking and the result of the intralesional injection treatment without debulking was about 50 percent improvement.¹⁰

A study carried out by Abedini et al.,¹¹ showed that verapamil had very low effects on VSS scores (7.33%) percent compared to triamcinolone (68.81%).¹²

Saki et al.,¹³ in A study comparing the effect of intralesional triamcinolone and verapamil, combined with cryotherapy on scar improvement, showed that both groups had a decrease in height and texture, but better results was obtained with TAC.¹⁴

CONCLUSION

Treatment of keloids is difficult, and no standard treatment has been established yet. Our study supports the effect of intralesional BTX-A, MTX and Verapamil in treatment of keloids with better results obtained from Botulinum Toxin A and Methotrexate than Verapamil. More studies including larger groups and longer follow up periods are required to fully understand the effect of the three mentioned drugs in treatment of keloids.

REFERENCES


