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Comparison of intralesional verapamil versus intralesional corticosteroids in treatment of keloids and hypertrophic scars: A randomized controlled trial

Robabeh Abedini [a], *Pardis Sasani* [b], *Hamid Reza Mahmoudi* [a], *Maryam Nasimi* [a,*], *Amir Teymourpour* [c], *Zahra Shadlou* [b]

[a] *Autoimmune Bullous Disease Research Center, Department of Dermatology, Razi Hospital, Tehran University of Medical Sciences, Tehran, Iran*
[b] *Razi Hospital, Tehran University of Medical Sciences, Tehran, Iran*
[c] *School of Public Health, Tehran University of Medical Sciences, Iran*

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ABSTRACT

Background: Keloids and hypertrophic scars are due to overgrowth of dermal collagen following trauma to the skin that usually cause major physical, psychological and cosmetic problems.
Methods: In this randomized controlled trial, with a paired design, 50 patients with 2 or more keloids were included. In the control group (50 lesions), intralesional triamcinolone acetonide (40 mg/mL) was injected at three-week intervals for a total of 18 weeks. In the other group (50 lesions), lesions were treated by verapamil (2.5 mg/mL) with the same therapeutic sessions. Scar evaluation at each stage and at the end of 3 months follow up was done by serial photographic records as well as by Vancouver Scar Scale (VSS).
Results: Mean zero VSS scores were achieved with only triamcinolone in respect of scar height (week 15th) and pliability (week 15th). No therapeutic event (parameter=0) or significant improvement was seen in verapamil group.
Conclusion: Our results did not support verapamil's capability in treatment of keloid nor hypertrophic scars.

1. Introduction

Hypertrophic scars and keloids are dermal fibro-proliferative disorders which can lead to pruritus, disfigurement and pain. Against hypertrophic scars which are limited to the injury sites and after quick growth can partially regress, keloids extend beyond the extent of the original wound and have a permanent and long evolution [1,2].

Variety of treatment modalities for hypertrophic scars and keloids from surgical to non-surgical have been developed. These modalities include dressings, cryotherapy, intralesional corticosteroid, 5-fluorouracil, bleomycin, interferon alfa-2b and verapamil, pulsed dye laser and surgical removal. Despite

* *Corresponding author at*: Autoimmune Bullous Disease Research Center, Department of Dermatology, Razi Hospital, Tehran University of Medical Sciences, Vahdate Eslami Street, Zip code: 1199663911, Tehran, Iran.
E-mail address: m-nasimi@sina.tums.ac.ir (M. Nasimi).
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many treatment approaches, scar treatment is still challenging with high rate of recurrence [3–6].

Intralesional corticosteroids are the mainstays of intralesional therapies and triamcinolone acetonide is the most widely used agent (10–40 mg/mL) which is injected at 3–6 weeks intervals. Adverse effects of treatment with corticosteroids including hypopigmentation, telangiectasia, dermal atrophy, delayed wound healing, and scar widening [5].

Verapamil is a Ca^{2+} channel blocker with in vitro antifibrotic activity indicating its promising effects for keloid and hypertrophic scar treatment. Predominantly, verapamil has fewer side effects in comparison to corticosteroids that allows longer treatment period and the possibility for using in cases that corticosteroids cannot be used [7–10].

There are several randomized controlled trial to evaluate the efficacy and safety of verapamil, in addition compared to triamcinolone. Studies showed that verapamil alone or after surgical excision reduce the risk of recurrence and resulted in keloids reduction. These studies stated recurrence rates with verapamil (1.4-48%), but they found it to be a safe treatment with a lower incidence of adverse effects compared to triamcinolone [11–17].

Since the results of these reports were inconsistent, and verapamil has not indicated as an alternative approach for corticosteroids in the keloids, we decided to compare the efficacy and safety profile, as well recurrence rates of verapamil with corticosteroid in patients with hypertrophic scars and keloids.

2. Material and methods

This study was a randomized observer blinded controlled trial with a paired design (Clinical Trials. IRCT2016010525871N1). From 2014 to 2015, 50 patients aged 18–65 who accepted to participate in the study were selected with convenience sampling methods. Inclusion criterias were patients with two or more than two keloids and hypertrophic scars but no more than 10 cm^2 total area, without previous treatment of any type and lesions under 5 years duration. Patients with facial lesions, pregnant or lactating women, patients with history of diabetes, cancer and heart disease, patients with darker skin phototype (skin phototype more than 4), and patients with keloidal diathesis on the basis of personal or family history were excluded from study. No attempt was made to consider origin of the lesions and also to distinguish between keloids and hypertrophic scars. This study was approved by the local research ethics board.

Patients' lesions were randomly allocated to two groups (A, B) using a computer generated random sequence, lesions A were treated with triamcinolone and group B with verapamil. If there were more than 2 keloids, other lesions were treated according standard treatment protocol with triamcinolone.

Treatments were injected intradermally into lesions with an insulin syringe and 24 gauge needle to achieve complete blanching of the lesion at endpoint every 3 weeks: triamcinolone acetonide (triamhexal) 40 mg/mL, maximum total dose 20 mg/mL; verapamil hydrochloride (Isoptin® Injection, Abbott, Australasia) 0.5 mg/cm, maximum total dose 2.5 mg. Treatments were continued for a maximum of six sessions or till complete flattening of the scar, whichever came earlier, then patients followed for 3 months regarding recurrence of lesions and side effects. Subjects were withdrawn from study if any side effects appeared during treatment periods.

Lesions were assessed by clinical examination, Vancouver Scar Scale (VSS), digital photograph, and experienced pain during treatment. Lesions' length, width and height were assessed at starting point and height were pointed every treatment session according VSS scale. Pigmentation and vascularity were quantified with clinical examination after blanching with translucent paper: comparing to surrounding skin and blood refilling, respectively [18].

Scar pliability was evaluated by palpation. The clinical improvement defined as decreasing values of the scores and complete recovery consider if scores reach to zero. Scar flattening was considered as <1 mm scar height over 90% of the lesion. Assessments were done by an independent trained dermatologist who was blinded to the treatment groups. Beside the fact that subjects, assessor, and analyzer were blind to therapies, the dermatologist who administrated the study injections was not blinded because of different physical properties of the triamcinolone and verapamil.

Sample size of 50 was calculated by G*Power software for repeated measure, within factors analysis with effect size of 0.136 and significant level of 0.05 and power of 80% for 8 number of measurements. Continuous and categorical variables were reported by mean ± Standard Deviation and frequency (percent), respectively. The Kaplan–Meier survival curve and logrank test was used to depict and test the time to complete recovery in two treatments. Two-way within subject factor repeated measure analysis was used to test the effect of session or time and treatment (drug) on mean of response variable and also repeated contrast was defined for session or time factor to test each session or time against the previous session or time. Appropriate P-value based on epsilon has been reported if Mauchly's test of Sphericity was significant. For comparing categorical variables Chi-square test was used. Data were analyzed by Statistical Package for Social Sciences (SPSS) version 22.

3. Results

During one year, 50 patients were recruited in our study, 3 of them excluded at week 18 because of the responsiveness of verapamil and they did not consent to continue the study. The mean age of patients was 30.26 ± 10.59 (range 18–62 year) and 54% of patients were female. Lesions' location in triamcinolone and verapamil groups were anterior chest (22, 19), extremities (16, 20) and back (12, 11), respectively. The difference between two groups, regarding lesions location ($P=0.7$) and VSS scores were not statistically significant.

The mean VSS scores of two groups during therapy and follow up after 3 months were shown in Table 1. In verapamil group, vascularity and pigmentation did not show any change during study course (Figs. 1 and 2).

Based on two way within subject factor repeated measure analysis, there was significant main effect of treatment factor for VSS, pigmentation, pliability, height and

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