



Comparing Efficacy and Tolerability of Triamcinolone and Verapamil in Treatment of Hypertrophic Scars and Keloids

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Received 2017 July 10; Revised 2017 August 15; Accepted 2017 September 01.

Abstract

Background: Hypertrophic scars (HSC) and Keloids are fibroproliferative dermal lesions resulting in excessive accumulation of extracellular matrix in the dermis and subcutaneous tissue. Corticosteroid, especially triamcinolone acetonide, injections may be the first line treatment for the prevention and treatment of keloids and HSC. Some drugs that inhibit calcium channels, such as verapamil, have also been effective in treatment of these lesions. The present study aimed to assess and compare the efficacy of these two treatment options in patients with HSC and keloids.

Methods: The study used a randomized, single blind, parallel design to compare the effect of verapamil in comparison with triamcinolone on the healing of HSC and keloids in two groups comprising 25 patients. Patients were randomly allocated using random numbers to receive intralesional injection of 1 mL of either verapamil (2.5 mg) or triamcinolone (20 mg) every 3 weeks for 3 months.

Results: Downward trends in all lesion parameters including height of lesion, as well as the scores for erythema, pigmentation in both groups was revealed. The change in characteristics of the lesion within the treatment was independent to patients' gender and age. Regarding drug - related complications, one case of atrophy was reported in triamcinolone group, however, not in the verapamil group.

Conclusions: Both verapamil and triamcinolone have significant therapeutic effects in decreasing the height of the lesion, improving erythema, improving the pliability of the lesion, and improving the hyperpigmentation. It seems that verapamil has less cost and side effects in comparison with triamcinolone, thus, it could be a good choice in treatment of keloids.

Keywords: Verapamil, Hypertrophic Scar, Keloid

1. Background

Hypertrophic scars (HSC) and Keloids are fibroproliferative dermal lesions resulting in excessive accumulation of extracellular matrix in the dermis and subcutaneous tissue (1). These lesions are caused by trauma, surgery, inflammation, burns, or possibly spontaneous (2). HSC lesions are fibrous, itchy, erythematous, and prominent lesions that are caused by damage to the deep dermis, remain within the ulcer zone, and often reducing size over time, while, keloids are lesions with similar characteristics that are caused by surgery, physical shock, and inflammatory reactions, usually extending beyond their primary zone and rarely recurring (3, 4). The pathogenesis of these lesions include migration and cell proliferation, inflammation, increased production of cytokines and proteins in extracellular matrix, as well as newly made from remodeling of the matrix (5, 6). The actual pathogenesis of keloids and HSC is not well defined. Generally, the pathogenesis of keloids and HSC is based on the function of fibroblast

cells (7-9). The prolongation of the inflammatory process of wound healing in an infective scar, deep wound, or burn tissues may results in an exacerbated response of inflammatory cells, resulting in secretion of large amounts of cytokines such as transforming factor beta, which are fibrotic cytokines (10, 11). The excessive synthesis of collagen, fibronectin, and proteoglycans, as an extracellular matrix by fibroblasts, as well as reducing its degradation and remodeling can cause abnormal lesions such as keloids and HSC (12).

The treatment of keloids and hypertrophic scars is challenging and controversial. The first line options include the use of silicone sheets, compression therapy, and corticosteroid injections (13-15). Corticosteroid, especially triamcinolone acetonide, injections may be the first line treatment for the prevention and treatment of keloids and HSC (16). The function of corticosteroids is to inhibit the inflammatory cell migration and also to suppress the proliferation of fibroblasts, especially at high doses of the

drug (17). On the other hand, some drugs that inhibit calcium channels, such as verapamil, have been effective in treatment of these lesions, where the main mechanism of which is to stimulate the synthesis of pro-collagenase in keloids, HSC, and human implanted fibroblasts that finally result in depolarization of actin filaments, changes in cellular shape, and decreased fibrotic tissue production (17-21). The present study aimed to assess and compare the efficacy of these two treatment options in patients with HSC and keloids.

2. Methods

The study used a randomized, single blind, parallel design to compare the effect of verapamil with triamcinolone on the healing of HSC and keloids in two groups comprising 25 patients each. Patients who satisfied the selection criteria and gave written informed consent to participate in the study were chosen for the study. Inclusion criteria for the study included patients between the age of 8 and 60 years, at least one HSC or keloid, size of scar between 2 to 10 cm, and caused by different reasons such as burns, trauma, or surgery. The exclusion criteria used for the study were family history of keloids, dark pigmented skin, pregnancy or lactation, as well as patients with systemic illness such as diabetes mellitus, mental disorder, cancer, and cardiac disease. Patients were allocated using random numbers to receive intralesional injection of 1ml of either verapamil (2.5 mg) or triamcinolone (20 mg) every 3 weeks for 3 months. Clinical assessment of the scars was performed at the beginning of the study and 3 months after starting treatment. The drugs were administered till the scar flattened or for a maximum period of three months. The clinical assessment of the scar was based on the Vancouver Scar Scale, which is the standard scale used universally for scar assessment. This scale was slightly modified for our patients. The scale scores the scars on four parameters namely pigmentation, erythema, pliability, and height. In addition, the scar height was also measured using a centimeter scale. At each visit the patients' scars were photographed on a digital camera. The level of patients' satisfaction was also scaled as 1+ to 3+; a higher scale indicated higher level of satisfaction. The study was approved by the Ethics Committee at Iran University of Medical Sciences.

Results were presented as mean \pm standard deviation (SD) for quantitative variables and were summarized by absolute frequencies and percentages for categorical variables. Normality of data was analyzed using the Kolmogorov-Smirnov test. Categorical variables were compared using Chi-square test or Fisher's exact test when more than 20% of cells with expected count of less than 5

were observed. Quantitative variables were also compared with *t*-test or Mann-Whitney U test. The trend of the change in study parameters was assessed by the Repeated Measure ANOVA test. For the statistical analysis, the statistical software SPSS version 16.0 for windows (SPSS Inc., Chicago, IL) was used. P values of 0.05 or less were considered statistically significant.

3. Results

In total, 50 patients (25 receiving triamcinolone and 25 receiving verapamil) were assessed. There was no difference between the two groups in gender (36% and 32%, $P = 0.765$) and mean age (34.44 ± 13.38 years and 31.28 ± 11.18 years, $P = 0.369$). Regarding the changes in parameters of the lesions including height of lesion, as well as the scores for erythema, pigmentation, and pliability within the follow-up time, although it was revealed downward trends in all parameters in both groups, no difference was found in the trend of the changes in parameters between the two groups (Table 1). With the presence of sex and age variables as the confounders, the change in characteristics of the lesion within the treatment was independent to patients' gender and age (Table 2). The level of satisfaction was shown to be higher in the triamcinolone group than in the verapamil group (mean satisfaction score: 2.28 ± 0.68 versus 1.88 ± 0.60 , $P = 0.036$), which is probably due to the use of lidocaine for diluting the drug and also for lowering the pain caused by injection. Regarding drug-related complications, one case of atrophy was reported in the triamcinolone group, however, not in the verapamil group.

4. Discussion

Various invasive therapeutic protocols and medical treatments are commonly used for treating HSC and keloids. In severe cases, the need for surgical repair is felt. Medical treatments are mainly based on the use of different types of corticosteroids or other local or systemic injection options that have been considered in recent years. Corticosteroid injections, for the prevention and treatment of keloids and hypertrophic scars, may be the first line of treatment. Corticosteroids can suppress inflammation and mitosis as well as increase vascular contraction in the scar tissue. In this regard, triamcinolone suppresses the immune responses by reducing the activity and volume of the lymphatic system, reducing the concentration of immunoglobulin and complement components, reducing the passage of immune complexes through the basement membranes and also the re-activity of the tissue against the antigen-antibody interaction. In total, this

Table 1. The Change in Lesion Characteristics in Both Treatment Groups

Item	Triamcinolone	Verapamil	P Value
Height of lesion			
First assessment	3.07 ± 1.28	3.20 ± 1.23	0.714
Second assessment	2.20 ± 1.16	2.53 ± 1.16	0.330
Third assessment	1.52 ± 1.11	1.94 ± 0.92	0.148
Fourth assessment	0.95 ± 0.88	1.41 ± 0.83	0.065
Erythema score			
First assessment	2.64 ± 0.49	2.44 ± 0.71	0.253
Second assessment	2.24 ± 0.66	2.04 ± 0.74	0.317
Third assessment	1.68 ± 0.69	1.56 ± 0.71	0.548
Fourth assessment	1.24 ± 0.59	1.00 ± 0.58	0.155
Pliability score			
First assessment	2.68 ± 0.48	2.59 ± 0.59	0.570
Second assessment	2.04 ± 0.54	2.05 ± 0.38	0.968
Third assessment	1.48 ± 0.59	1.64 ± 0.49	0.331
Fourth assessment	0.88 ± 0.67	1.18 ± 0.59	0.109
Pigmentation score			
First assessment	2.40 ± 0.58	2.44 ± 0.71	0.828
Second assessment	1.72 ± 0.74	1.72 ± 0.84	0.999
Third assessment	1.36 ± 0.76	1.40 ± 0.76	0.853
Fourth assessment	0.96 ± 0.74	0.88 ± 0.60	0.675

drug is bound to its cytoplasmic receptors to enter the cell nucleus. This complex coupled with specific regions of DNA stimulates the transcriptional process of mRNA and subsequently generates enzymes that are believed to be responsible for inflammatory effects. The metabolism of corticosteroids is mainly found in the skin itself, however, the triamcinolone metabolism is lower than other corticosteroids, thus, its systemic absorption is relatively high. Several studies have been conducted on the effects of triamcinolone on the treatment of HSC and keloids. In particular, the use of this drug has been evaluated in combination with other methods, such as cryotherapy (22), fluorouracil (23), and radiofrequency (24). Nevertheless, the use of localized injection of triamcinolone alone was associated with significant improvements in HSC and keloids symptoms by decreasing the height, erythema, hyperpigmentation of the lesion, and increasing pliability of the lesion. More interestingly, a large proportion of patients had complete satisfaction with their treatment due to the use of lidocaine for diluting the drug and also for lowering the pain caused by injection that was not used for verapamil group. As a second therapeutic option, verapamil injection was also assessed in the treatment of HSC and keloids. In re-

Table 2. The Effect of Treatment Regimen on the Trend of the Change in Lesion Parameters Adjusted for Sex and Age

Item	Mean Square	F	Sig.
Height of lesion			
Intercept	43.666	10.115	0.003
Sex	0.051	0.012	0.914
Age	1.821	0.422	0.519
Group	6.381	1.478	0.230
Erythema score			
Intercept	32.186	24.307	0.000
Sex	0.001	0.001	0.973
Age	1.189	0.898	0.348
Group	1.396	1.055	0.310
Pliability score			
Intercept	32.854	52.032	0.000
Sex	0.476	0.753	0.390
Age	1.511	2.394	0.129
Group	0.915	1.449	0.235
Pigmentation score			
Intercept	33.740	19.915	0.000
Sex	0.465	0.275	0.603
Age	0.372	0.219	0.642
Group	0.013	0.007	0.932

cent meta-analysis on the therapeutic effects of verapamil on HSC, it was found that, although treatment with verapamil was similar in function to other therapeutic options, the side effects and cost of the drug is less than the other (25, 26). In another study, verapamil combination therapy with silicone gel plates was used to treat HSC and keloids, resulting in significant improvements in HSC in the animal model, although results in human samples are still uncertain (27).

4.1. Conclusion

In general, in our study, there was no difference in the therapeutic effect of verapamil and triamcinolone on the treatment of HSC and keloids, however, verapamil was more acceptable with fewer side effects and cost.

As a general result, both verapamil and triamcinolone have acceptable healing effects in the treatment of HSC and keloids, and have significant therapeutic effects in decreasing the height of the lesion, improving erythema, improving the pliability of the lesion, and improving the hyperpigmentation.

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