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A Comparative Study of Efficacy and Safety of Intralesional Triamcinolone with Intralesional Verapamil in the Treatment of Keloid and Hypertrophic Scar at a Tertiary Care Hospital

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Abstract

Introduction: Keloids are abnormal fibrous tissue outgrowth that extends beyond the borders of the wound, whereas hypertrophic scars (HTS) are limited to the boundaries of the wound. Intralesional triamcinolone is the gold standard treatment for keloids and HTS. Intralesional verapamil is an emerging treatment modality. Our study objective is to compare the efficacy and safety of intralesional triamcinolone with intralesional verapamil in the treatment of Keloid and HTS.

Methods: A total of 60 patients with Keloids and HTS were recruited in the study. They were randomized into two groups of 30 patients each. Group-A received intralesional triamcinolone 10mg/ml for a 2-6 cm scar and 20mg/ml for a 6-10cm scar. Group B received intralesional verapamil 1ml(2.5mg/ml) for a 2-6 cm scar and 5mg/ml for a 6-10cm scar. Patients were assessed at the baseline, every 3 weeks till the scar flattened or a maximum period of 6 months. Clinical assessment of the scar was based on the Vancouver scar scale. The mean decrease in the total score was calculated and photographed with a high-quality digital camera with consent.

Results: Out of 60 patients, 34 (56.7%) males and 26(43.3%) females were enrolled. The mean age was 27.3+7.63 years and most of the patients were between 20-29 years. After the completion of the study, a 58.33% reduction in the baseline score was seen in the Triamcinolone group as compared to a 37.38% reduction in the verapamil group. The length of the scar did not change significantly with either drug. The rate of reduction of vascularity, pliability, height, and width of the scar with triamcinolone was faster than with verapamil. Adverse drug reactions were more with triamcinolone than with verapamil

Conclusion: In comparison to intralesional triamcinolone, intralesional verapamil is less efficacious but because of fewer adverse effects and lower chances of recurrence intralesional verapamil can be considered a safe alternative in the treatment of Keloid and HTS.

Keywords: Keloids; Hypertrophic Scar; Triamcinolone; Verapamil

Abbreviations: HTS: Hypertrophic Scars; SPSS: Statistical Package for Social Science; VSS: Vancouver Scar Scale.

Introduction

Keloids and Hypertrophic scars (HTS) are abnormal wound responses in pre-disposed individuals and represent a hyper-proliferative connective tissue response to injury, inflammation, surgery, or burns. Keloidal scarring is one of the most disappointing clinical problems in wound healing. Keloids occur following dermal injury and exhibits exude rant, indefinite growth of collagen [1]. They usually occur in darker-skinned individuals with a familial tendency and not in the extremes of age [2]. The incidence of HTS following injuries is 40-70% and up to 91% following burn injury [3].

Keloids classically occur on certain parts of the body, especially, on the shoulder, sternum, and earlobes. Surface tension and sebaceous gland density are among the characteristics that seem to predispose these anatomical sites to keloid formation [1].

HTS, resulting from alterations in the normal processes of superficial wound healing, is characterized by the multiplication of dermal tissue with excessive deposition of fibroblast-derived extracellular matrix proteins, especially collagen, over long durations and by persistent inflammation and fibrosis [1].

The various treatment modalities for keloids and HTS include compression garments, radiation, surgical excision, intralesional injections, cauterization, cryotherapy, laser surgery, and silicon gel dressings. It is difficult to assess the efficacy of the existing treatment modalities as there are no properly controlled, comparative studies [4].

Multiple modalities of treatment have been advised but most of these modalities have variable and transient success. One of the commonly practiced long-term treatments for keloids is an intralesional steroid injection [1]. The calcium channel blocker, verapamil has been shown to stimulate the synthesis of pro-collagenase thus increasing collagenase activity resulting in the de-polymerization of actin filaments and reducing fibrous tissue production in keloid and HTS [5].

Verapamil is clinically safe, adverse drug reactions are less and economical compared to triamcinolone and other agents used intralesionally [5]. However, there has been limited clinical data showing its efficacy and safety in the treatment of keloid or HTS. Thus more studies are needed before it is recommended as a routine treatment for Keloid and HTS. Hence, the current study was taken up.

Methodology

Patients with HTS and keloid attending Dermatology outpatient department were the study participants. It was a randomized, open-label, prospective comparative study conducted from November 2016 to May 2018. The total sample size was 60 patients. Patients were divided into two groups. 30 patients of keloid and HTS were treated with intralesional triamcinolone and the other 30 patients with intralesional verapamil.

The following were the Inclusion Criteria

- Patients aged above 18 years and below 80 years attending dermatology outpatient department with keloid and hypertrophic scars measuring 2 to 10 cm in length with a duration of less than 5 years
- Patients with keloid and HTS due to acid burns, trauma, surgery, insect bite, and acne
- Patients willing to give written informed consent
- Patients who have not received any kind of treatment for this before

The Following were the Exclusion Criteria

- Patients with systemic illnesses like uncontrolled diabetes, severe hypertension, severe depression/ psychosis, active tuberculosis, fungal infection, acid peptic disease, and cardiac illness
- Pregnancy and lactating mother
- Patients allergic to verapamil /Triamcinolone acetonide
- Patients with a family history of keloid and HTS
- Patients with darkly pigmented skin

Patients who were not willing to give informed consent and were not willing to come for follow up. After obtaining clearance and approval from the institutional ethics committee (Institutional Ethics Committee of Bangalore Medical College and Research Institute Reference no. BMC/ PGs/289/2016-17 dated 03.11.2016) and patients fulfilling the inclusion criteria were included in the study after obtaining informed consent. A detailed history of etiology, duration, site, and family history was recorded in the case record form. Photographs were taken before and after treatment. Treatment regimens were under the direction of the treating dermatologist.

Any recurrence or complications and the patient's scar photograph were taken. Based on the experimental protocol, the participants were divided into two groups, the first group (Group A) was treated with an intralesional injection

of triamcinolone 10 mg for 26 cm scar, 20 mg for 6-10 cm scar, administered at 3 weeks intervals till scar flattens or for a maximum duration of 6 months. The second group (Group B) was treated with an intralesional injection of verapamil 2.5mg/ml for a 2-6cm scar and 5mg/ml for a 6-10cm scar, administered at 3 weeks intervals till the scar flattens or for a maximum duration of 6 months.

Safety assessment was done and the following parameters were looked for - pain, pruritis, sweating, irregular menstruation, and if any other side effects were reported that were assessed and graded by the dermatologist at baseline, once in 3 weeks up to 6 months and was followed up after one year. The pain was assessed by the patients using a visual analog scale.

The following methods of statistical analysis have been used in this study. Statistical analyses were performed using the Statistical Package for Social Science-SPSS for window ver 18.5 (SPSS Inc. Chicago, IL, USA) software. Univariate analyses of the dichotomous variables encoded were performed using the Chi-square test with Yates correction if required. The student's test was used to determine whether there was a statistical difference between male and female subjects in the parameters measured. In all the above tests p-value of less than 0.05 was accepted as indicating statistical significance.

Results

Baseline demographic and clinical parameters are summarised in Table 1. The present study was designed to compare the efficacy and safety of intralesional triamcinolone with intralesional verapamil in the treatment of keloid and hypertrophic scars (HTS) in a tertiary care hospital based on clinical assessment of Vancouver scar scale (VSS) score and the mean VSS is summarised in Table 2 at different time points. This includes vascularity, pigmentation, pliability, and height of the scar.

		Group A (Triamcinolone) N = 30	Group B (Verapamil) N = 30
Age in years (Mean±SD)		27±7.02	27.6±8.31[$]
Sex	Males	17	17
	Females	13	13
Etiology	Trauma	12	11
	Surgery	1	0
	Acne	2	1
	Ear piercing	3	3
	Burns	1	2
	Spontaneous	11	13
Diagnosis	Hypertrophic scar	10	9
	Keloids	20	21
Duration of scar	Upto 1 year	15	15
	1 - 2 years	5	8
	> 2 years	10	7
Number of lesions	1 lesion	21	20
	2 lesions	6	7
	3 lesions	1	2
	4 lesions	2	1

Table 1: Demographic and baseline parameters of patients with keloids and hypertrophic scars. Statistical test used is Chi-square test for all parameters except age ([$] Unpaired t test).

Study time points	VSS scores in Triamcinolone group (n=30) (Mean±SD)	Percentage reduction in VSS scores (Triamcinolone)	VSS scores in Verapamil group (n=30) (Mean±SD)	Percentage reduction in VSS scores (Verapamil)	P value
Baseline	9.17±1.63	0	9.63±0.76	0	0.373
Week 3	8.8±1.30	4.03	9.53±1.45	1.04	0.143
Week 6	7.93±1.78	13.52	9.3±1.88	3.43	0.003*
Week 9	6.97±2.26	23.99	8.73±1.68	9.35	<0.001*
Week 12	6.17±1.92	32.72	7.93±1.65	17.65	<0.001*
Week 15	5.43±0.78	40.79	7.33±0·54	23.88	<0.001*
Week 18	4.9±1.66	46.56	6.73±1.09	30.11	<0.001*
Week 21	4.4±2.60	52.02	6.5±0.38	32.5	<0.001*
Week 24	3.83±0.74	58.23	6.03±0.36	37.38	<0.001*
Week 52	4.13±2.23	54.96	5.93±0.49	38.42	<0.001*

Table 2: Comparison of Mean Vancouver scar scale scores between triamcinolone and verapamil groups at different time points. Unpaired t-test, *P value <0.05 is considered statistically significant.

Our findings suggest that there is a reduction in vascularity, pliability and, the height of the scar with both drugs after 3 weeks of treatment. Scar pigmentation such as hypo and hyperpigmentation is seen with intralesional injection of triamcinolone. The length of the scars did not change significantly with either of the drugs. The rate of reduction in vascularity, pliability, height, and width of the scar is faster with triamcinolone than with verapamil. Adverse drug reactions are more with triamcinolone than with verapamil.

Keloids and HTS are relatively common and very important problems encountered in our routine dermatology outpatient department. In our study, the majority of 65% were keloids and 35% were HTS.

Vancouver scar scale (VSS) consists of four parameters namely vascularity, pliability, pigmentation, and height of the scar. The maximum score for VSS is 13. The score for pliability ranges from 0 to 5, height and vascularity from 0 to 3, and pigmentation from 0 to 2. The decreasing mean value of the score indicates clinical improvement in the scar. The percentage reduction in VSS was graded according to the quartile score with less than or equal to the 25%reduction in VSS, graded as poor, 26-50% reduction as good, 51-75% reduction as very good, and >75% as excellent response [6].

In our study, there was a significant reduction in mean VSS at every visit in both study groups. However, rate of reduction in mean VSS score was much better in patients treated with intralesional triamcinolone than in patients receiving intralesional verapamil as depicted in Table 3. With triamcinolone, hypopigmentation (13.3%) or hyperpigmentation (23.3%) was noticed in some of the patients. The length of the scars did not change significantly in the study groups.

Adverse events	Triamcinolone group (n=30)	Verapamil group (n=30)	P value @
Atrophy	6	0	0.01*
Telangiectasia	2	0	0.15
Hypopigmentation	4	0	0.038*
Hyperpigmentation	7	0	0.005*
Pain	6	6	<0.001*
Pruritis	17	0	<0.001*
Profuse sweating	2	0	0.15

Table 3: Comparison of the number of participants who developed adverse events between triamcinolone and verapamil groups (Safety assessment). @Fischer's Exact test, *P value of <0.05 is considered statistically significant.

Discussion

Margaret Shanthi FX. in their study compared intralesional verapamil with intralesional triamcinolone acetonide in the treatment of keloids. They performed their study on 54 patients (27 in each group) and followed them for one year. They reported that verapamil was equally effective [5].

D'Andrea F, et al. in their study, conducted on 44 patients concluded that verapamil hydrochloride showed poor results when used in the treatment of already-formed keloids even when compared to topical steroids. However, when intralesional verapamil injection was combined with surgical excision and topical silicon application, a 54% cure rate was seen [6].

In the present study, a mean reduction of 58.33% in all the parameters of the VSS was observed in the triamcinolone group at the end of the 8th visit (6 months) and 37.38%at the end of the 8th visit (6 months) in verapamil group. So, intralesional triamcinolone had a faster rate of reduction in VSS score.

The reason that verapamil hydrochloride is less effective than corticosteroids may be that corticosteroids have an additional anti-inflammatory effect on the scar tissue along with inhibition of collagen and glycosaminoglycan synthesis and degeneration of fibroblast/collagen as compared to verapamil.

Uzair et al in a study found a mean decrease in the VSS score of 58.28%reduction from the baseline in the triamcinolone group as compared to 36.75% in the verapamil group [7]. In the study conducted by Shah YM et al, the physician assessment was very good in 32% and excellent in 8% of patients treated with injection verapamil. But Shah YM et al used only intralesional verapamil drug and did not compare it with intralesional triamcinolone in 25 patients with keloid [8].

In our study, intralesional triamcinolone was associated with more adverse effects than intralesional verapamil. Pain during injection was associated with intralesional triamcinolone which was mild to moderate in nature and some required analgesics for relief of pain. In 56.7% of patients in the triamcinolone group experienced itching, pigmentary changes (hypopigmentation 13.3%/ hyperpigmentation 23.3%) were seen with triamcinolone injection, 20% of patients showed profuse sweating.

Almost 20% of the patients receiving intralesional verapamil experienced pain during injection mild to moderate in nature which persisted for 24 - 48 hours, some required analgesics for relief. Atrophy, pigmentary changes, and sweating which are common with intralesional triamcinolone are not seen with intralesional verapamil injection. In our study (26.7%) of patients treated with intralesional triamcinolone had to recurrence whereas none of the patients treated with verapamil had a recurrence.

Prevention in people who are predisposed to develop hypertrophic scars and keloids should avoid the preventable cause which is surgery. During surgery, reducing strain on the incision with proper surgical technique is a crucial part of preventing hypertrophic scars [9-11]. Although there are several therapies available, most of them result in less than optimum care; this is a difficult condition to cure. There is no better therapy than another, and each has the potential to make the scar worse [12,13]. Verapamil with advantages over triamcinolone may be considered a more preferable alternative.

The prospective, randomized study design and use of standard validated tools for assessing the efficacy of treatments have added strength to the study. The study was limited by its relatively smaller sample size. Therefore, further studies with a larger sample size are required to evaluate the efficacy and safety of intralesional Triamcinolone and Verapamil in the treatment of keloids and HTS.

Conclusion

There was a reduction in vascularity, pliability, and height of the scar at every visit however the rate of reduction in VSS scores was faster with intralesional injection of triamcinolone compared to intralesional injection of verapamil. When compared to intralesional triamcinolone, intralesional verapamil is less efficacious but because of less adverse effects and lower chances of recurrence intralesional verapamil can be considered a safe alternative in the treatment of keloid and HTS.

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