Original Article

Comparison of efficacy and safety of intralesional verapamil hydrochloride and intralesional triamcinolone acetonide in the treatment of keloids

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Abstract

Objective The purpose of this study was to evaluate the effectiveness and safety of intralesional verapamil hydrochloride versus intralesional triamcinolone acetonide for the treatment of keloids.

Methods Total 88 (44 in each group) patients were enrolled. Group A (44 patients) was treated with intralesional verapamil hydrochloride (2.5mg/ml) through an insulin syringe. Group B (44 patients) was treated with 0.1ml/cm^2 intralesional triamcinolone acetonide (20mg/ml). In both groups, site of lesion was draped with alcohol solution. The patients were treated every two weeks for 10 sessions or until the resolution of keloid. Response to treatment was assessed by VSS score by two blinded qualified dermatologists at 2-weeks follow up visit and inter-observer agreement was calculated. Follow up was done one month after the last treatment session and percentage reduction in VSS score from baseline was calculated and efficacy was assessed.

Results In intralesional verapamil group, the mean age of the patients was 34.93±12.42 years and in intralesional triamcinolone group, the mean age of the patients was 34.45±11.80 years. In intralesional verapamil group 25 (56.8%) patients were male and in intralesional triamcinolone group, 24 (54.5%) patients were male. At baseline; the mean VSS was 8.98±1.66 with intralesional verapamil, and 9.52±1.21 with intralesional triamcinolone (p-value=0.082). At the 18th week; the mean VSS was 5.68±1.58 vs. 4.91±0.83 (p-value=0.006). After 4 weeks of cessation of trial drugs, the mean VSS was 3.7±1.60 vs. 1.73±1.04, respectively (p-value=0.000). In intralesional verapamil group, the mean percentage reduction was 64.24±15.72% and in intralesional triamcinolone group it was 82.34±10.46%, p-value<0.001. In intralesional verapamil group, efficacy was noted in 10 (22.7%) patients and in 28(63.6%) patients in intralesional triamcinolone group (p-value=<0.001). No side effects were observed with intralesional verapamil and with intralesional triamcinolone, side effects were absent in 26 (60.5%) patients, p-value=<0.001.

Conclusion Intralesional triamcinolone acetonide is significantly more efficacious as compared to Intralesional verapamil hydrochloride for the treatment of keloids; however, intralesional verapamil hydrochloride is safer.

Key words
Efficacy; Safety; Verapamil; Triamcinolone acetonide; Keloids.

Introduction

Keloid is an abnormal proliferation of dense fibrous tissue that grows beyond the boundaries of the original wound usually after cutaneous insult and is a benign dermal fibro-proliferative tumor with no malignant potential.[1]

The exact incidence and prevalence of keloids is still unknown especially in our population. There is 5-16% increased incidence of keloid formation in dark-skinned individuals especially of African and Asian descent.[2] A study conducted in Taiwan has reported an annual incidence of 15 per 10,000.[3] A familial tendency

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has been suggested by some studies with an autosomal dominant pattern of inheritance to develop keloids.[4-6]

The disease pathophysiology is complex and not completely understood and involves an imbalance between tissue repair and regeneration at the site of deep cutaneous trauma. Eventually there is increased collagen synthesis in the scar tissue.[7]

Various treatment modalities have been employed in the treatment of keloids e.g. intralesional corticosteroids, intralesional verapamil, intralesional 5-flourouracil, silicone gel sheets, pressure therapy, cryotherapy, surgical excision, radiation therapy and laser therapy etc., but none has found to be the most effective due to lack of complete understanding of disease pathophysiology and targeted therapies. Amongst various modalities, intralesional triamcinolone acetonide is considered to be the most effective therapy especially for both minor (<0.5cm) and major (>0.5cm) keloids.[8,9]

Triamcinolone acetonide intralesionally is a powerful corticosteroid with long-lasting effects, including anti-inflammatory, antipruritic, and vasoconstrictive effects. Lipocortins are peptides induced by corticosteroids at the cellular level; they inhibit phospholipase A2, an enzyme that catalyses the synthesis of arachidonic acid, the precursor molecule of endogenous inflammatory mediators.[10] It has been found to reduce the amount of collagenase inhibitors (alpha2-macroglobulin and alpha2-antitrypsin) in keloids, leading to a corresponding reduction in collagenase breakdown and therefore the abundant collagen that characterizes keloids.[10]

Boggio *et al.*[11] demonstrated that verapamil, a calcium channel blocker, leads to decreased extracellular matrix production in scars. Verapamil acts by depolymerizing actin filaments and modifying the fibroblast morphology with consequently increased pro-collagenase secretion.

Since then, several studies have been done to evaluate these medications side by side. Margaret *et al.* selected 54 patients in India to take part in a research of intralesional verapamil hydrochloride vs. triamcinolone acetonide.[12] The Vancouver Scar Scale (VSS) revealed that both medicines led to improvements in the scar's vascularity, pliability, height, and breadth.[13] Intralesional triamcinolone accelerated the decrease in these measures.[12]

Similar results were shown in a research published by Ahuja *et al;* which demonstrated that intralesional injections of triamcinolone acetonide or verapamil hydrochloride may reduce the elevation of hypertrophic scars and keloids. The quick and successful response to intralesional triamcinolone has kept it as the therapy of choice for acute inflammation of the joint. Verapamil, on the other hand, has a similar impact and provides other therapy options for bigger (or many) scars when triamcinolone may not be enough.[14]

The purpose of this study is to compare the efficacy and safety of intralesional triamcinolone acetonide and intralesional verapamil hydrochloride in the treatment of keloids. As limited number of studies are available which compared both the efficacy and safety of these drugs, sample size in the previous studies was small and study duration was short which couldn’t predict the outcome. Moreover, owing to the low cost of verapamil hydrochloride, it can be a great treatment modality in resource-limited settings.

Material and Methods

It was a comparative interventional study conducted at the Dermatology Department Unit-

II, KEMU/ Mayo Hospital, Lahore during period of one year after the approval from Hospital Ethics Committee. Data was collected using a pre-designed proforma. Patients fulfilling the inclusion criteria, after acquiring detailed history and performing a clinical examination, were enrolled in the study. Informed consent was taken. Randomization into two groups was done by lottery method. For sampling, Simple randomization by lottery method was used. Patients aged between 18–60 years of either sex having Keloids of 2–5 cm in maximum dimension, regardless of the site and shapes were enrolled. The pregnant and lactating females were excluded. The patients having active infection at the lesional site, with history of systemic illness like diabetes mellitus, uncontrolled hypertension, psychosis and underlying malignancy were also excluded. Patients with keloids who have any topical or intralesional therapy in the last 3 months and having history of any bleeding diathesis had also been excluded.

Group A (44 patients) was treated with intralesional verapamil hydrochloride. Site of lesion was draped with alcohol solution and inj. verapamil hydrochloride (2.5mg/ml) was filled in an insulin syringe and 0.1ml/cm^2 of the drug was injected slowly until the skin rose and blanched completely.

Group B (44 patients) was treated with intralesional triamcinolone acetonide. Site of lesion was draped with alcohol solution. Inj. triamcinolone acetonide (40mg/ml) was mixed with inj. Lignocaine in an insulin syringe in the ratio of 1:1 and 20mg/ml strength of triamcinolone acetonide was achieved. The amount of drug to be given was 0.1ml/cm^2. In both groups, by adopting the aseptic measures, the needle was inserted into the lesion at an angle of 45 degrees to the level of mid-dermis and the drug was injected slowly until the skin rises and blanches completely. For larger lesions, needle was withdrawn and reinserted into other sites of the lesion until enough drug was injected at lesional site. Caution was needed to avoid injecting into the subcutaneous tissue and resistance was felt while injecting drug into the dermis. At the end of the procedure, mild pressure was applied with the help of a gauze piece until the bleeding stopped from needle sites. The patients were treated every two weeks for 10 sessions or until the resolution of the scar.

Response to treatment was assessed by VSS score by two blinded qualified dermatologists at 2-weeks follow up visit and inter-observer agreement was calculated. Patients were told about the side effects of intralesional therapies and these were noted on each visit. Follow up was done one month after the last treatment session and percentage reduction in VSS score from baseline was calculated and efficacy was assessed.

Assessment was done according to improvement in VSS score[13] at two-week follow up visit. Grading was done as excellent, good, satisfactory and unsatisfactory when ≥75%, 50-69%, 25-49% and <25% reduction in baseline VSS score respectively. Treatment causing 50% or more reduction in baseline VSS score was considered as effective. Safety was measured clinically on the basis of number of patients having the side effects like pain requiring analgesia, telangiectasia, skin atrophy and local infection. The drug having minimal frequency of side effects was considered safe.

VSS Score Includes following four variables, i.e.

Height of keloid (H), Range: 0-3
Pliability (P), Range: 0-5
Vascularity (V) Range: 0-3
Pigmentation (Pg) Range: 0-2

VSS= H+P+V+Pg; VSS Score ranges from 0-13.

VSS Grading Scale.

Score	*Height (H)*	*Pliability (P)*	*Vascularity (V)*	*Pigmentation (Pg)*
0	Normal (Flat)	Normal	Normal	Normal
1	Less than 2 mm	Supple	Pink	Hypopigmentation
2	2-5 mm	Yielding	Red	Hyperpigmentation
3	Greater than 5 mm	Firm	Purple	-
4	-	Banding	-	-
5	-	Contracture	-	-

Table 1 Descriptive statistics of age (years).

N	88
Mean	34.69
Standard Deviation	12.045
Minimum	18.00
Maximum	56.00

$$\frac{\text{Baseline VSS score} - \text{Post treatment VSS score}}{\text{Baseline VSS score}} \times 100$$

Data was entered in to SPSS-26. Quantitative variables like age were presented as mean±standard deviation. Qualitative variables like gender were presented as frequency and percentages. Chi-square test was applied for the comparison of two groups (intralesional triamcinolone acetonide and intralesional verapamil hydrochloride). A P-value of ≤ 0.05 was taken as significant.

Results

In this study total 88 patients participated after meeting inclusion and exclusion criteria. The mean age of the patients was 34.69±12.04 years with minimum and maximum ages of 18 and 56 years respectively (**Table 1).**

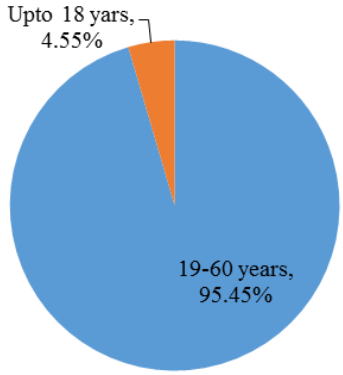

Figure 1 Frequency distribution of age groups.

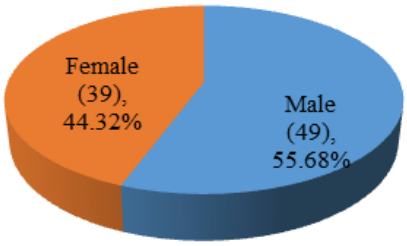

Figure 2 Frequency distribution of gender.

According to this study, 84(95.45%) patients were between age ranges of 19-56 years **(Figure 1)**.

According to this study 49(55.68%) patients were male and 39(44.32%) patients were females. Male to female ratio of the patients was 1.2:1 **(Figure 2)**.

At baseline; in intralesional verapamil group, the mean VSS of the patients was 8.98±1.66 and in intralesional triamcinolone group, its mean value was 9.52±1.21 (p-value=0.082). At 2nd week; in intralesional verapamil group, the mean VSS of the patients was 8.93±1.66 and in intralesional triamcinolone group, its mean value was 9.23±1.18 (p-value=0.339). At 4th week; in intralesional verapamil group, the mean VSS of the patients was8.52±2.02 and in intralesional triamcinolone group, its mean value was 8.50±1.17 (p-value=0.949). At 6th week; in intralesional verapamil group, the mean VSS of the patients was 8.16±1.68 and in intralesional triamcinolone group, its mean value was8.16±1.08 (p-value≥0.999). At 8th week; In intralesional verapamil group, the mean VSS of the patients was 7.82±1.66 and in intralesional triamcinolone group, its mean value was 7.66±1.03 (p-value=0.591). At 10th week;

Table 2 Comparison of VSS score from baseline to 10th week follows up between study groups.

VSS	*Study Groups*	*n*	*Mean*	*SD*	*p-value*
At baseline	Verapamil hydrochloride	44	8.98	1.66	0.082
	Triamcinolone acetonide	44	9.52	1.21	
2nd Week	Verapamil hydrochloride	44	8.93	1.66	0.339
	Triamcinolone acetonide	44	9.23	1.18	
4th Week	Verapamil hydrochloride	44	8.52	2.02	0.949
	Triamcinolone acetonide	44	8.50	1.17	
6th Week	Verapamil hydrochloride	44	8.16	1.68	>0.999
	Triamcinolone acetonide	44	8.16	1.08	
8th Week	Verapamil hydrochloride	44	7.82	1.66	0.591
	Triamcinolone acetonide	44	7.66	1.03	
10th week	Verapamil hydrochloride	44	7.50	1.75	0.126
	Triamcinolone acetonide	44	7.02	1.04	

In intralesional verapamil group, the mean VSS of the patients was 7.50±1.75 and in intralesional triamcinolone group, its mean value was 7.02±1.04 (p-value=0.126) **(Table 2)**.

At 12th week; in intralesional verapamil group, the mean VSS of the patients was 7.14±1.66 and in intralesional triamcinolone group, its mean value was 6.70±1.00 (p-value=0.145). At 14th week; in intralesional verapamil group, the mean VSS of the patients was 6.52±1.70 and in intralesional triamcinolone group, its mean value was 6.02±0.93 (p-value=0.092). At 16th week; in intralesional verapamil group, the mean VSS of the patients was 6.23±1.61 and in intralesional triamcinolone group, its mean value was 5.64±0.75 (p-value=0.031). At 18th week; in intralesional verapamil group, the mean VSS of the patients was 5.68±1.58 and in intralesional triamcinolone group, its mean value was 4.91±0.83 (p-value=0.006). After 4 weeks of cessation of trial drugs, in intralesional verapamil group, the mean VSS of the patients was 3.27±1.60 and in intralesional triamcinolone group, its mean value was 1.73±1.04 (p-value=0.000) **(Table 3)**.

In our study, in intralesional verapamil group, the mean percentage reduction was 64.24±15.72% and in intralesional triamcinolone group, the mean percentage reduction was 82.34±10.46%. This difference was statistically significant i.e. p-value<0.001 **(Table 4)**.

Table 3 Comparison of VSS score from to 12th week to 18th week follows up between study groups.

VSS	*Study Groups*	*n*	*Mean*	*SD*	*p-value*
12th week	Verapamil hydrochloride	44	7.14	1.66	0.145
	Triamcinolone acetonide	44	6.70	1.00	
14th week	Verapamil hydrochloride	44	6.52	1.70	0.092
	Triamcinolone acetonide	44	6.02	0.93	
16th week	Verapamil hydrochloride	44	6.23	1.61	0.031
	Triamcinolone acetonide	44	5.64	0.75	
18th week	Verapamil hydrochloride	44	5.68	1.58	0.006
	Triamcinolone acetonide	44	4.91	0.83	
22nd week	Verapamil hydrochloride	44	3.27	1.60	0.000
	Triamcinolone acetonide	44	1.73	1.04	

Table 4 Comparison of percentage reduction in VSS score between study groups

	Study Groups	*n*	*Mean*	*Standard Deviation*	*p-value*
Percentage reduction	Verapamil hydrochloride	44	64.24	15.72	<0.001
	Triamcinolone acetonide	44	82.34	10.46	

Table 5 Comparison of efficacy between study groups.

		Study Groups		*Total*	*p-value*
		Verapamil hydrochloride	*Triamcinolone acetonide*		
Efficacy	Yes	10 (22.7%)	28 (63.6%)	38 (43.2%)	
	No	34 (77.3%)	16 (36.4%)	50 (56.8%)	<0.001
Total		44 (100.0%)	44 (100.0%)	88 (100.0%)	

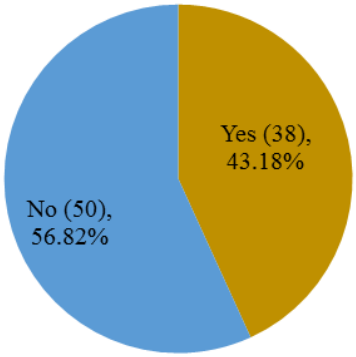

Figure 3 Frequency distribution of efficacy.

According to this study, efficacy was observed in 38 (43.18%) patients (**Figure 3)**.

In intralesional verapamil group, efficacy was noted in 10 (22.7%) patients and in intralesional triamcinolone group, efficacy was noted in 28(63.6%) patients (p-value=<0.001) **(Table 5)**.

In intralesional verapamil group, no side effects were observed in 44(100%) patients and in intralesional triamcinolone group, no side effects were observed in 26(60.5%) patients. This difference was statistically significant i.e. p-value=<0.001 **(Table 6)**.

Discussion

Keloids are skin lesions characterized by aberrant and excessive scar growth, with collagen deposition and irregular fibrous tissue extending beyond the boundaries of the initial cutaneous injury. Itching and soreness are common symptoms, and they tend to return often. Keloid development has been linked to postoperative healing, acne, burns, trauma, piercings, and inflammation, yet the precise mechanism behind this phenomenon is still poorly understood. Even though they may show up everywhere, the most typical spots are the chest, the shoulders, and the earlobes.[15]

In this study the mean age of the patients was 34.69±12.045 years, 49(55.68%) patients were male and 39(44.32%) patients were females. One study by Abedini *et al.*[16] in a randomized control trial showed that the mean age of the patients was 30.26±10.6 years and most of the patients were females. One more study by Aggarwal *et al.*[17] done a randomized control trial and presented that the mean age of the patients was 30.41±8 years. While one study by Margaret *et al.* showed lower age group in their study. They showed that the mean age of the patients was 23±10 years.[18] Srivastava *et al.*[19] demonstrated that the mean age of the patients was 29.95±8.7 years and also showed that the female patients were more as compared to male patients. The males outnumbered in this study when compared to all other studies. The reason might be traditional and cultural differences in our country due to which females present less in outpatient department than males.

Table 6 Comparison of side effects between study groups.

Side Effects	*Study Groups*		*Total*	*p-value*
	Verapamil hydrochloride	*Triamcinolone acetonide*		
No	44 (100.0%)	26 (60.5%)	70 (80.5%)	
Hypo pigmentation	0 (0.0%)	3 (7.0%)	3 (3.4%)	
Hyper pigmentation	0 (0.0%)	7 (16.3%)	7 (8.0%)	<0.001
Telangiectasia	0 (0.0%)	4 (9.3%)	4 (4.6%)	
Total	44 (100.0%)	44 (100.0%)	88 (100.0%)	

In this study at baseline the mean VSS of the patients was 9.25±1.47 and at 18th week its mean 5.29±1.31 respectively. At 18th week; in intralesional verapamil group, the mean VSS of the patients was 5.68±1.58 and in intralesional triamcinolone group, its mean value was 4.91±0.83 (p-value=0.006). The effectiveness of intralesional verapamil has been shown in a number of investigations.[18,20,21] One study indicated a 54% cure rate when chemotherapy was used in conjunction with surgical excision, and 36% of patients who had a recurrence reported a reduction in tumour size.[21] After therapy, the VSS has been shown to considerably reduce in many studies.[18,20]

In Intralesional triamcinolone acetonide group, efficacy was noted in 28(63.6%) patients and in Intralesional verapamil hydrochloride group efficacy was noted in10 (22.7%) patients (p-value=<0.001). More side effects were observed in Intralesional triamcinolone acetonide group patients as compared to Intralesional verapamil hydrochloride group patients. Some other studies are discussed below.

In their research, Klomparens *et al*. found that patients treated with triamcinolone acetonide improved more quickly than those given verapamil. Consistent with our findings, however, these enhanced outcomes came with a greater incidence of unfavourable events.[22]

According to the data given by Pu Wang *et al.* Verapamil might be a viable alternative to Triamcinolone acetonide.[23] The overall rate of side effects did not differ between the two treatments, although verapamil was associated with a reduced rate of telangiectasia and skin atrophy than Triamcinolone acetonide. Total adverse effects (RR=0.42; P=0.1) were not significantly different, in the subgroup analysis the incidence of telangiectasia (RR=0.04; P<0.05) and skin atrophy (RR=0.10; P<0.05), but not pain (RR=1.27; P=0.77), was significantly lower with verapamil than with Triamcinolone acetonide.

Additional proof that verapamil may reduce the prominence of scars was found in a research by Rajeev B. Ahuja and Pallab Chatterjee. Due to its cheap price and lack of side effects, this treatment option for hypertrophic scars should be given more prominence. As an alternative to triamcinolone or in conjunction with it for bigger (or many) scars, it provides a number of treatment options.[24]

In their research, Radwa O. Mohamed *et al.* found that although Verapamil significantly improved the pigmentation score of keloids and hypertrophic scars, triamcinolone did not. Four triamcinolone patients reported adverse symptoms, but no verapamil patients did. Several low-cost therapeutic options, including verapamil, exist for the treatment of keloids and hypertrophic scars.

In a meta-analysis, Li *et al*. and Wang *et al*. found no discernible difference between intralesional verapamil and Triamcinolone acetonide for the treatment of HSs and keloids.[25,26]

Intralesional injections of triamcinolone acetonide or verapamil hydrochloride have been shown to reduce the elevation of scar tissue in hypertrophic scars and keloids, according to a research published by Ahuja *et al*. Due to its quick and successful response, intralesional triamcinolone remains the gold standard for first-line therapy. On the other hand, verapamil is almost as effective as triamcinolone and provides other treatment options, especially for bigger (or many) scars.[14]

Verapamil and triamcinolone were shown to have the same therapeutic impact on the treatment of HSs and keloids in another investigation; however, verapamil was more

acceptable due to its lower side effect and cost profiles.[27]

In contrast, Margaret *et al*. did a research in India, randomly assigning 54 patients to intralesional verapamil hydrochloride or triamcinolone acetonide.[12] The VSS revealed that both medicines led to improvements in the scar's vascularity, pliability, height, and breadth.[13] Intralesional triamcinolone accelerated the decrease in these measures.[12] A meta-analysis found that triamcinolone therapy was more beneficial than verapamil in increasing height, flexibility, and vascularity. Furthermore, verapamil had much less adverse effects than triamcinolone did, including skin shrinkage, telangiectasia, and hyperpigmentation.[28] Similarities between their findings and ours may be attributed to the same geographical and environmental influences.

Our results should be evaluated by future research with bigger samples and in a multicenter environment since there is so little information currently available on this issue.

Conclusion

Intralesional triamcinolone acetonide is significantly more efficacious as compare to Intralesional verapamil hydrochloride for the treatment of keloids. However, Intralesional verapamil hydrochloride has a better safety profile than triamcinolone acetonide. Thus in the future, use of triamcinolone acetonide as first-line treatment of keloids is recommended. Verapamil hydrochloride can be a safer alternative to triamcinolone acetonide or can be used as an effective adjuvant.

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