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Comparison of efficacy of intralesional vitamin D3 versus intralesional triamcinolone acetonide in keloid – A randomized double-blinded non-inferiority study

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ABSTRACT

Objectives: Keloids are often difficult to treat and have a high chance of recurrence. Multiple modalities of therapy have been tried with variable success rates. Intralesional triamcinolone acetonide (TA) remains the most common modality of treatment of keloids. We have conducted a randomized controlled trial comparing the efficacy of intralesional injection TA versus intralesional vitamin D3 (VD3) in keloids.

Material and Methods: Group TA (n = 30) received an intralesional TA 40 mg/mL, and group vitamin D (VD) (n = 30) received intralesional VD3 (cholecalciferol) 60000 IU every 4 weekly till 12 weeks and all the patients were followed up for another 4 weeks. At each session, the scar size was assessed by the Vancouver Scar Scale (VSS), and the Visual Analog Scale assessed the pain.

Results: The mean score of VSS was significantly decreased in both group TA (7.91 ± 1.5–4.9 ± 1.6, $P < 0.001$) and group VD (7.84 ± 0.8–5.0 ± 1.6, $P < 0.001$). The pain was severe in group VD compared to group TA. There was fluid discharge with severe itching and pain in one keloid site in the VD group. The keloids reduced faster in size in the TA group compared to the VD group. There was no significant difference in response to TA versus VD.

Conclusion: Both intralesional triamcinolone and VD3 were found to be efficacious with triamcinolone achieving a faster effect. The pain was a limiting factor in the intralesional VD group.

Keywords: Keloid, Intralesional vitamin D3, Intralesional triamcinolone acetonide

INTRODUCTION

Keloid is an abnormal, benign, well-demarcated growth caused by the deposition of collagen by dermal fibroblasts that extend beyond the original site of the skin injury (e.g., ear piercing, surgical injury, burns, or any type of inflammation due to trauma wounds, insect bites, acne, chickenpox, and herpes zoster infection).[1-3] Keloid frequently occurs in high-tension body surfaces, such as the chest and upper back.[4] It clinically appears as raised amorphous growth and is frequently associated with contractures, pruritus, and pain. Larger keloids may cause physical/functional disability, cosmetic deformation, and psychological distress and hamper the quality of life. The prevalence of keloid is not gender or skin-type dependent but may occur more in dark individuals, with an incidence rate of 16% in Hispanic, African American, or black cohorts.[2,3]

Many researchers described a significant association between keloid scars, obesity, and hypertension.[5,6]

The exact patho-mechanism behind the keloid formation is still unclear.[7] There is a strong association between dysregulation of transforming growth factor beta (TGF-β) isoform levels (TGF-β1, -β2, and -β3), cytokines (interleukin [IL]-4, IL-5, IL-10, and IL-13), elastin, and fibrillin-1, mediating the tissue repair and regeneration processes.[8-10]

Interestingly, various treatments were used to treat keloids with varying degrees of success. However, the recurrence of the disease is the most challenging thing to manage. Keloids can be treated with medical and surgical interventions and combination therapies. Topical treatments (mitomycin C, imiquimod, and topical silicone), intralesional injections (triamcinolone acetonide [TA], verapamil, 5-fluorouracil [5-FU], etc.), radiations, laser-based therapy, and combination therapies have been tried for keloids.[7,11,12] Numerous clinical trials have reported the effectiveness of various treatments on keloid scarring. Yet, most treatment for keloid remains empirical and unsatisfactory.[13] The gold standard of treatment, which is the need of the hour, should be minimally invasive, cost-effective, with very few side effects, and a low recurrence. Among all of these, intralesional TA is the most widely used treatment in keloid.[7,14,15] It is considered to be the gold standard in the non-surgical management of hypertrophic and keloid scars. It suppresses the collagen and glycosaminoglycan synthesis level and decreases fibroblast development and the collagen degradation process.[7,14,15] Previously, vitamin D3 (VD3) has been documented as having anti-inflammatory, anti-proliferative, and anti-cancerous properties. A limited number of studies have found VD3 to be effective in the treatment of keloid.[16] Therefore, this study was undertaken to compare the efficacy of intralesional injection of VD3 and intralesional TA.

Aims and objective

Primary

To compare the efficacy of 3 weekly intralesional TA injections versus 3 weekly intralesional VD3 injections in keloids at the end of 12 weeks.

Secondary

To compare the side effect profile and recurrence during follow-up of either group.

MATERIAL AND METHODS

The study was a randomized, non-inferiority trial. This study was approved by the Institutional Ethical Committee and registered with the Clinical Trials Registry-India bearing number REF/2022/09/058153. Patients with clinically diagnosed keloid attending the dermatology outpatient department in a tertiary healthcare center in the eastern part of India were assessed for eligibility. The sample size was determined to be 60 based on the percentage of success in the control group being 73.1%, and 54.68% in the experimental group, with a non-inferiority limit of 40 with a significance level of 0.05 and power of 80%. A total of 15 patients with 76 numbers of clinically confirmed keloids were enrolled of which 9 patients with 60 numbers of keloids satisfying the eligibility criteria were included in this study after obtaining consent. Six patients were excluded. The clinicodemographic data, such as age, gender, disease duration, family history, triggering factor, and affected sites, were recorded in a case report form. A total of sixty (n = 60) keloids were included in the study, randomly divided into two groups: Group TA (n = 30) keloids were treated with intralesional TA and group vitamin D (VD) (n = 30) received intralesional VD3. A computer-generated software was used to generate a random allocation sequence. Allocation concealment was done using a similar-looking syringe for both medications. Both the patient and assessor were blinded. A flowchart of the treatment assigned to both groups is shown in Figure 1.

Inclusion criteria

- All patients with keloids above 18 years of age
- Patients having a minimum of two keloids not more than 5 cm
- Keloids without any treatment in the past 6 months.

Exclusion criteria

- Pregnancy and lactation
- Diabetes mellitus
- Systemic disorder, immune-compromised status
- Retinoid use in previous 6 months.

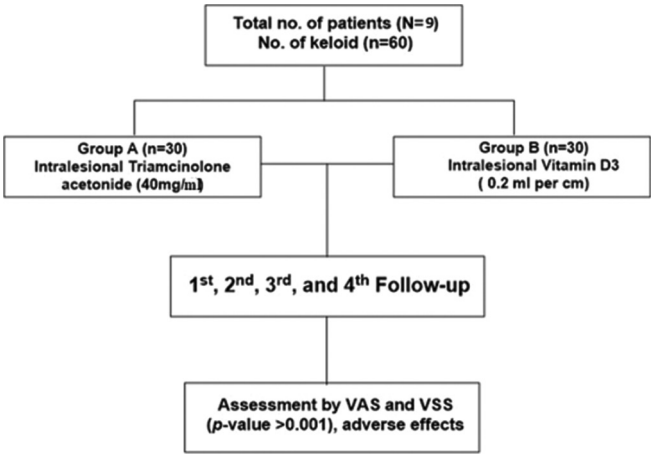

Figure 1: Treatment allocation flow chart. VSS: Vancouver scar scale, VAS: Visual analog scale.

Group TA received intralesional TA 40 mg/mL till blanching was seen with a maximum total dose of 80 mg for sizes up to 5 cm, using 1 mL U-100 insulin syringe every 4 weekly and group VD received intralesional injection VD3 (cholecalciferol) 60000 IU at a dose of 0.2 mL/cm up to a maximum of 1 mL. Treatment was continued for three 4 weekly sessions. Patients were followed for 1 month after the last injection.

This study used two scoring systems to assess the pre and post-treatment results. The Vancouver Scar Scale (VSS) score [Figure 2] was evaluated for vascularity, pigmentation, pliability, and height.[17,18] The pain score was determined through self-assessment using the Visual Analog Scale (VAS), a 0–10 scale ranging from no to extremely unbearable pain.[17,19] The comparison of VSS scores among the two groups is depicted in Figure 3.

Scar features	Scores
Vascularity	
Normal	0
Pink	1
Red	2
Purple	3
Pigmentation	
Normal	0
Hypopigmentation	1
Hyperpigmentation	2
Pliability	
Normal	0
Supple	1
Yielding	2
Firm	3
Ropes	4
Contracture	5
Height (mm)	
Flat	0
<2	1
2-5	2
>5	3
Total score	**13**

Figure 2: Vancouver skin scar scale.

All the baseline data were presented as percentages (%) for categorical variables and continuous variables by mean ± Standard deviation. The chi-square test was used to compare data between groups before and during every session of follow-up periods. All the statistical analyses were performed using IBM Statistical Package for the Social Sciences software, version 26.0. A $P < 0.05$ was considered significant. The primary investigator did the group allocation, and the second investigator assessed the effectiveness and safety parameters at baseline and during the follow-up procedure.

RESULTS

Five males and four females with a total of sixty ($n = 60$) keloids were included in the study and were randomly divided into two groups: Group A ($n = 30$) keloids were treated with intralesional TA and Group B ($n = 30$) received intralesional VD3. A family history of keloid was found in two cases (28.57%). The majority (63.33%) of keloids were distributed either on the chest or around the waist [Table 1]. The VSS score for group TA was 7.91 ± 1.5 and 4.9 ± 1.6 at baseline and fourth follow-up, respectively [Table 2]. The baseline VSS score of the VD group reduced from 7.84 ± 0.8 to 5.0 ± 1.6 at the end of the fourth follow-up visit [Table 3]. The difference was found to be statistically significant ($P < 0.001$) with both modalities of treatment [Table 4]. VAS score was used to analyze injection pain. Patients in

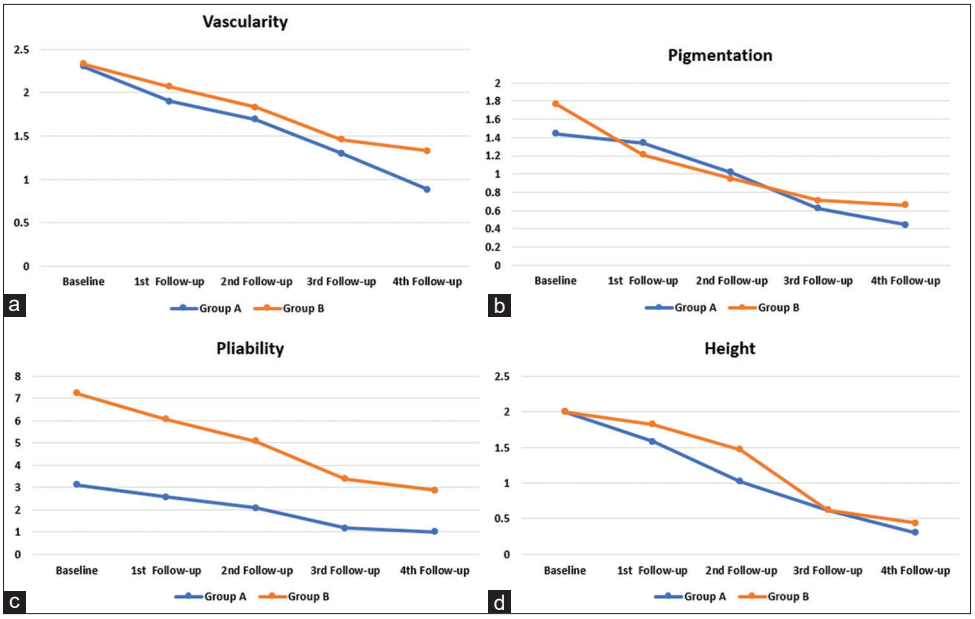

Figure 3: Comparison of individual parameters of Vancouver Scar Scale score among the two groups. (a) Line graph comparing vascularity. (b) Line graph comparing pigmentation. (c) Line graph comparing pliability. (d) Line graph comparing height.

Group VD experienced a more severe form of pain than the group TA. 5 out of 9 patients in group VD had a score of "Hurts even more or score value 3." Injection pain and mild itching were the commonly reported adverse effects in the VD group. However, 3 patients developed atrophy in group TA after the second visit, and 5 patients developed depigmentation after the third visit. One case in group VD experienced sterile fluid discharge from the keloid after the third injection. The discharge was sent for culture sensitivity, which showed no growth. Clinical images comparing the response are shown in Figure 4a and b.

The pliability of the keloids was the first to improve in the TA group as early as 1st week, and the last parameter to improve significantly was the height of keloids at the fourth follow-up visit. Contrarily, vascularity was the last facet of keloids to improve in the VD group, and pigmentation and pliability showed significant improvement by the second follow-up. By the third follow-up in the VD group, there was a significant decrease in the height of keloids.

Table 1: Demographic data.

Characteristics	*n*	%
Gender		
Male	5	71.42
Female	4	28.57
Duration of disease		
1–5 years	5	60
5–10 years	4	10
Family history		
Mother	1	14.28
Father	1	14.28
None	7	71.42
Trigger		
Spontaneous	16	25
Trauma	41	68.33
Post acne	4	5
Immunization/None	1	1.66
Sites affected		
Chest	25	38.33
Waist	18	25
Bilateral arms	13	20
Upper back	10	16.66

DISCUSSION

Keloids are stubborn scars that are difficult to treat and manage. Corticosteroids remain the gold standard among the myriad treatment modalities.[20] At the end of this study, we found a noticeable improvement in the keloids, as demonstrated by the significant reduction in VSS scores in both groups. There was a faster improvement in the intralesional TA group by the 1st month itself; however, subsequently, the change was gradual. In the VD group, the decline in VSS was slow in onset and gradual in nature. Pain was the most common side effect in the VD group in our study compared to Mamdouh *et al.*, where redness, swelling, and tenderness were reported.[21] We presume that the oily nature of the VD3 injection may be the cause of the pain. VD plays an important role in cell proliferation and differentiation, has an anti-fibrotic effect, and inhibits collagen synthesis in dermis fibrosis. The African American population has an increased incidence of keloids and hypertrophic scars. Interestingly, the same ethnic black population has VD3 deficiency due to decreased synthesis of VD3 in the skin and genetic defects

Table 2: Group A (intralesional corticosteroid) (*P*-value).

VSS	Baseline versus 1st follow-up	Baseline versus 2nd follow-up	Baseline versus 3rd follow-up	Baseline versus 4th follow-up
Vascularity	0.320	0.001	<0.001	<0.001
Pigmentation	0.603	0.012	0.001	<0.001
Pliability	<0.001	<0.001	<0.001	<0.001
Height	0.401	0.023	0.01	<0.001

VSS: Vancouver scar scale

Table 3: Group B (intralesional vitamin D3) (*P*-value).

VSS	Baseline versus 1st follow-up	Baseline versus 2nd follow-up	Baseline versus 3rd follow-up	Baseline versus 4th follow-up
Vascularity	1.008	0.086	0.012	<0.001
Pigmentation	0.033	<0.001	<0.001	<0.001
Pliability	0.083	0.002	<0.001	<0.001
Height	0.950	0.102	0.003	<0.001

VSS: Vancouver scar scale

Table 4: A comparison between baseline and 4th follow-up post-treatment intralesional TA and VD3, assessment scoring through VSS.

VSS assessment	Baseline		4th follow-up	
	Mean±SD	*P*-value	Mean±SD	*P*-value
TA	7.91±1.5	<0.001	4.9±1.6	<0.001
VD3	7.84±0.8		5.0±1.6	

VSS: Vancouver scar scale, TA: Triamcinolone acetonide, VD3: Vitamin D3, SD: Standard deviation

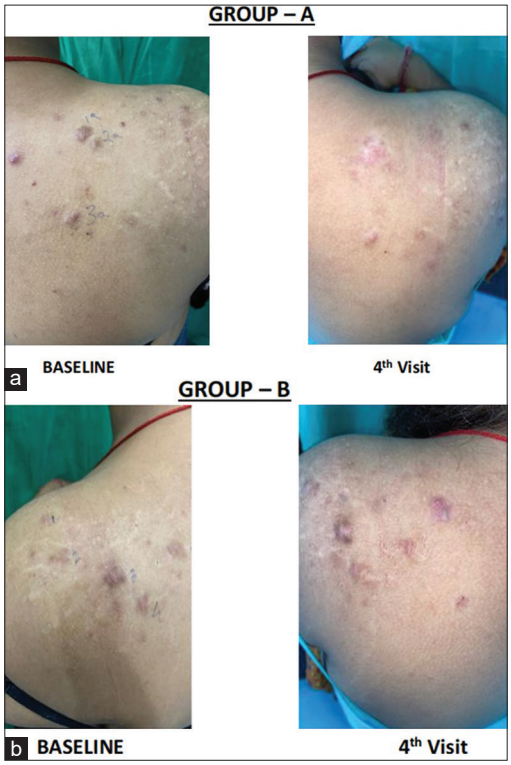

Figure 4: (a) Clinical images showing the response of each visit in the triamcinolone acetonide group. (b) Clinical images showing the response of each visit in the vitamin D group.

in VD3 metabolism.[22] This hypothesis can be extrapolated to the fact that VD3 prevents the formation of scars. Yu *et al.* compared serum 1,25-dihydroxyvitamin D level and VD3 gene polymorphism among 261 patients with keloids to a control group of 261 healthy people without keloids. Patients with keloids had significantly lower levels of circulating serum 1,25-dihydroxyvitamin D than the healthy controls.[2] A cross-sectional study by Cho *et al.* reported higher pigmentation and low scar elasticity in hypertrophic burn scar cases having VD3 deficiency.[23] The severity of keloid has been found to be higher in patients with a deficiency of VD3.[24-26]

Intralesional TA has long been the mainstay in the management of keloid, alone or in combination with other therapeutic or non-therapeutic procedures.[27,28] However, corticosteroids come with their own set of adverse effects, limiting their prolonged usage. Various newer treatment modalities are being tried to match the efficacy and response rate of intralesional TA. Botulinum toxin type A, corticosteroids (including diprospan and TA), verapamil, and 5-FU are the main drugs for local injection in the treatment of pathological scars.[7] TA was associated with a significant improvement in vascularity over the medium-term and long-term follow-up. There was no significant difference in pliability across TA and verapamil in the medium-term and long-term follow-up.[29] In our study also, there was a significant increase in pliability as early as 4 weeks in TA and 8 weeks in the VD group. In our study, both the groups showed a statistically significant reduction in all the parameters of the VSS score; however, the pliability component responded as early as 4 weeks in the steroid group. In terms of patient safety, studies have shown that TA often causes adverse effects like skin atrophy and telangiectasia in up to 63% of patients. TA was more effective in improving scars than silicone gel sheets, verapamil, and cryotherapy. In addition, combining 5-FU with TA showed a significant improvement in keloid in comparison with TA alone. Although TA treatment could lead to complications, including skin atrophy and telangiectasia, the difference was not statistically significant compared to 5-FU or verapamil.[30] A systematic review has concluded that multiple injections of TA and doses of more than 40 mg per session are known to cause hypothalamic-pituitary-adrenal axis suppression and subsequent development of Cushing syndrome.[31] This may be attributed to the slow release of triamcinolone from the injection site. Patients receiving 75–100 mg (40 mg/mL) intralesional TA can have adrenal suppression for as long as 5 days.[32] Patients receiving successive injections can have adrenal suppression for up to 8 months. This study supports the potential role of VD as an alternative, practical, and safe method in the treatment of keloid. There is delay in response with intralesional vitamin D3 as compared to intralesional steroids. Our results were comparable with the findings of the study by Mamdouh *et al.* However, in their study, the treatment interval was weekly for 4 weeks, in contrast to the 4 weekly gap in our study.[21]

Limitation

Shorter follow-up time.

CONCLUSION

We did not find any significant difference in the efficacy of intralesional TA and VD in the treatment of keloids. Intralesional TA as opposed to intralesional VD3 has a faster effect; however, VD3 is a safe and effective option. The side effects were atrophy and depigmentation in the intralesional

steroid group, whereas pain was the major adverse effect in the VD3 group. However, the pain associated with the injection was transient and subsided without any medication. A large-scale study with a more extended follow-up period is recommended to assess the efficacy of VD3 as a keloid treatment and its role in preventing relapses in keloids.

Authors' contributions

Liza Mohapatra: Concepts, design, definition of intellectual content, literature search, clinical studies, experimental studies, data acquisition, data analysis, statistical analysis, manuscript preparation, manuscript editing and review. Bikash Ranjan Kar: Concepts, design, definition of intellectual content, clinical studies, experimental studies, and manuscript review. Surabhi Singh: Concepts, design, definition of intellectual content, clinical studies, experimental studies, data analysis, statistical analysis, manuscript editing and review. Bhabani STP Singh: Concepts, design, definition of intellectual content, data acquisition, and data analysis. Nibedita Dixit: Statistical analysis, Manuscript editing and manuscript review.

Ethics approval

The research/study was approved by the Institutional Review Board at IMS AND SUM HOSPITAL, Reg. No. DRI/IMS.SH/SOA/2021/176, dated 21/7/21.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent.

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Nil.

Conflicts of interest

There are no conflicts of interest.

Use of artificial intelligence (AI)-assisted technology for manuscript preparation

The authors confirm that there was no use of artificial intelligence (AI)-assisted technology for assisting in the writing or editing of the manuscript and no images were manipulated using AI.

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