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Efficacy & Safety of Intralesional Vitamin D3 in the Treatment of Cutaneous Verrucae

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Abstract

Background: Verruca is one of the common dermatopathologies which has multiple therapeutic options but with variable success rates, refractory cases and high recurrence rates. Nowadays, treatment with intralesional injections has gained recognition due to its effectiveness in clearing verrucae. These act by stimulating the cell-mediated immunity. Out of scores of options available for intralesional therapeutics, Vitamin D3 appears to be more promising but least evaluated. Therefore, we planned to evaluate the efficacy and safety of intralesional Vitamin D3 in various types of cutaneous verrucae.

Methods: A total of 100 patients of cutaneous verrucae with varying size and duration were included in the experimental randomized comparative study. About 0.2-0.5 ml intralesional Vitamin D3 (600,000 IU, 15mg/ml) into the base of verrucae. A maximum of 5 verrucae were injected per session at 3 weeks interval until resolution or for a maximum of 4 sessions. Patients were followed up for 6 months after the last injection to assess the clearance status and detect any recurrence.

Results: Complete response', 'Partial response' and 'No response' were observed in 85.07%, 6.74% and 8.17% respectively after 4 sessions. Recurrence rate was 0.81% after 6 months. The average number of injections required to achieve a complete resolution was 3.55. Complete resolution of distant warts was noticed in all patients.

Conclusion: Intralesional vitamin D3 is a safe, effective, and an inexpensive treatment option for recalcitrant warts. We purpose its use, as a primary mode of treatment in various types of cutaneous verrucae.

Keywords: Bleomycin, Vitamin D3, Verrucae.

Introduction

Verrucae are the benign epidermal growths with focal extension of epithelial cells of skin and mucosa caused by human papillomavirus (HPV). It affects all age

groups.[1] HPV has 200 phenotypes and 100 sequenced types as per genotyping.

There are numerous methods for treating the verrucae. But none, is labelled as gold standard treatment. It is very difficult to treat when these are numerous or present on unreachable sites.

Local destruction of verruca is the most commonly used modality; performed by electrocoagulation, chemical cautery, curettage, cryotherapy, laser therapy but these all require expensive equipments and can remove only the visible infected lesions, leaving the invisible infected tissue behind resulting in higher chances of recurrence. [2] All these modalities may end with disfiguring scar marks.

In immunotherapy; the cell-mediated immunity stimulates, patient's immune system to eradicate HPV. Immunotherapy is cost-effective choice with high rate of resolution of both lesional and distant sites (lesions at different anatomical sites, away from injected one) with minimal side effects.[1]

Different types of immune stimulants are available, e.g. pro inflammatory cytokines like interferons and interleukin(IL)-2; intralesional antigens like purified protein derivative; *Candida* and Trichophyton; vaccines like the mumps, measles, and rubella (MMR) vaccine; *Mycobacterium w* and Bacillus Calmette-Guerin (BCG) vaccine; topical contact sensitizers like diphencyclopropenone and dibutyl ester; and immune enhancers like zinc sulfate.[2]

Vitamin D has the property to regulate the epidermal proliferation and cytokine production and, when used as an intralesional injection, it acts as an immuno therapeutic agent.[3]

It has immunomodulatory effects by inhibiting the expression of interleukin-6(IL-6), IL-8, TNF-alpha-gama, mediated by VDR-dependent pathway. Activation of Toll-like receptor (TLR) of human macrophages upregulates the expression of Vitamin D receptor and Vitamin D1- hydroxylase genes, leading to induction of the antimicrobial peptide.[4] The prospective study was undertaken, to evaluate the efficacy of intralesional Vitamin D3 in various types of cutaneous verrucae.

Materials and methods

An experimental study was conducted on 100 patients of cutaneous verrucae, attending the outpatient department from July 2018 to June 2019. This study was approved by the Institutional Ethics & Research Board of our institute. An informed written consent was obtained from all the patients, as per institutional regulation prior to initiation of the treatment. Cases were diagnosed on the basis of typical clinical manifestation.

The characteristics of the verrucae for each patient such as, type, size, number, duration, presence or absence of side effects and photographs were recorded at the start of the study and at each follow-up visit. Three weeks washout period was allowed if the patients were still on any therapy before coming to the out patient department. They were also instructed not to use any other verruca therapies during the course of the study.

Patients were included, who had extra genital verrucae and above the age of 18 years. Patients who were on immunosuppressive drugs and had systemic illness, history of peripheral vascular disease; the pregnant and lactating females were excluded from study.

A maximum of 5 verrucae were injected per session. The injections were repeated at 3 weekly intervals until complete resolution or for a total 4 sessions, at the most. Using a 26-gauge needle insulin syringe with bevel upward, 0.2 to 0.5ml vitamin D3 solution

(600,000 IU; 15mg/ml) was slowly injected in base of verruca.

After each injection antibiotics and anti-inflammatory agents were prescribed for 5 days to prevent superadded bacterial infection and post injection pain. Patients were followed up on 21st day of injection till 6 months after the last injection to detect any recurrence.

The response status on the basis of decrease in verruca size was created. The response rate is classified as follows:

1. Complete Response (CR) -If all verrucae showed complete or 100% disappearance.
2. Partial Response (PR) - If some verrucae show decrease in size and the number is more than 50% but less than 100% as compared to the pre-procedural status.
3. No Response (NR)- If some verrucae improve in size but the number is less than 50% as compared to the pre-procedural status.

Chi square statistical test were applied to analyse the results, 'p values' less than 0.05 were consider statistically significant.

Results

Present study was conducted on 200 fresh cases with a total of 956 cutaneous verrucae.

Following observations were made during the study:

Most of the patients were in age group of 18-30 years. Cutaneous verrucae were more common in males with male: female ratio of 1.32:1.

Response of Intralesional Vitamin D3 in Cutaneous verrucae are tabulated in table 1.

Type of Verrucae	Complete Response (CR)					Partial Response (PR)	No Response (NR)	Total
	IL-1 (n)	IL-2 (n)	IL-3 (n)	IL-4 (n)	Total (n)			
Common Verrucae	120 (83.33%)	06 (4.16%)	05 (3.47%)	03 (2.08%)	134 (93.05%)	04 (2.77%)	06 (4.16%)	144
Plantar Verrucae	89 (84.76%)	03 (2.85%)	02 (1.90%)	02 (1.90%)	96 (91.42%)	05 (4.76%)	04 (3.80%)	105
Palmar Verrucae	77 (84.61%)	03 (3.29%)	02 (2.19%)	01 (1.09%)	83 (91.20%)	03 (3.29%)	05 (5.49%)	91
Filiform Verrucae	38 (66.66%)	02 (3.50%)	02 (3.50%)	02 (3.50%)	44 (77.19%)	05 (8.77%)	08 (14.03%)	57
Verruca Plana	36 (44.44%)	06 (7.40%)	04 (4.93%)	04 (4.93%)	50 (61.72%)	15 (18.51%)	16 (19.75%)	81
Periungual Verrucae	06 (54.54%)	01 (9.09%)	01 (9.09%)	01 (9.09%)	09 (81.81%)	01 (9.09%)	01 (9.09%)	11
Total	366 (74.84%)	21 (4.29%)	16 (3.27%)	13 (2.65%)	416 (85.07%)	33 (6.74%)	40 (8.17%)	489

Table 1: Response rates of cutaneous verrucae with Intralesional Vitamin D3

The abbreviations in the tables stands as;

IL-1; Post intralesional at 3 weeks

IL-2; Post intralesional at 6 weeks

IL-3; Post intralesional at 9 weeks

IL-4; Post intralesional at 12 weeks

PR & NR; After 12 weeks

n; Number of cases

All verrucae of different morphology showed 75 % complete response after a single injection. Additional 10% verrucae showed complete response after 2nd, 3rd and 4th injection as depicted in table 1. 'Partial response' in 7% and 'No response' in 8% patients.

Response of Intralesional Vitamin D3 in combination of different types of Cutaneous Verrucae is summed up in table 2.

Type of Verrucae	Complete Response (CR)					Partial Response (PR)	No Response (NR)	Total
	IL-1 (n)	IL-2 (n)	IL-3 (n)	IL-4 (n)	Total (n)			
Palmo-Plantar Verrucae	30 (93.75%)	00	02 (7.25%)	00	32 (100%)	00	00	32
Periungual-Plantar Verrucae	09 (100%)	00	00	00	09 (100%)	00	00	09
Periungual-Common Verrucae	05 (100%)	00	00	00	05 (100%)	00	00	05
Periungual- Palmar Verrucae	05 (100%)	00	00	00	05 (100%)	00	00	05
Filiform-Common Verrucae	07 (46.66%)	00	00	00	07 (46.66%)	05 (33.33%)	03 (20%)	15
Palmar-Common Verrucae	07 (66.67%)	00	00	00	07 (66.67%)	00	02 (33.33%)	09
Total	63 (84.33%)	00	02 (2.67%)	00	65 (86.67%)	05 (6.67%)	05 (6.67%)	75

Table 2: Response distribution amongst various combinations of verrucae.

A total of 87 % showed complete response, 5% 'Partial response' and 5% 'No response' after a single injection.

Patients felt pain during intralesional procedure and the pain persisted for few days. Patients felt swollen sites, pruritus which was with in tolerable limits and none of them required any interventional medication for the adverse reaction. None Of the patients complained any systemic adverse event.

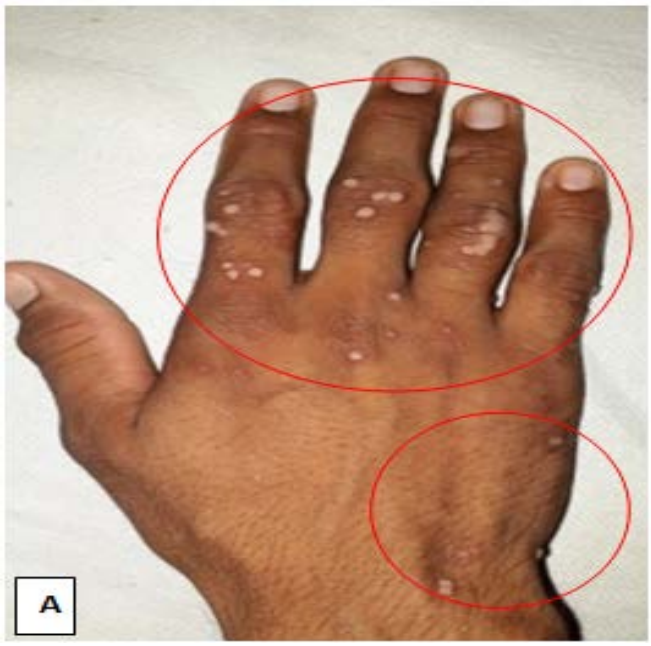

Fig A:1st visit: Week 0

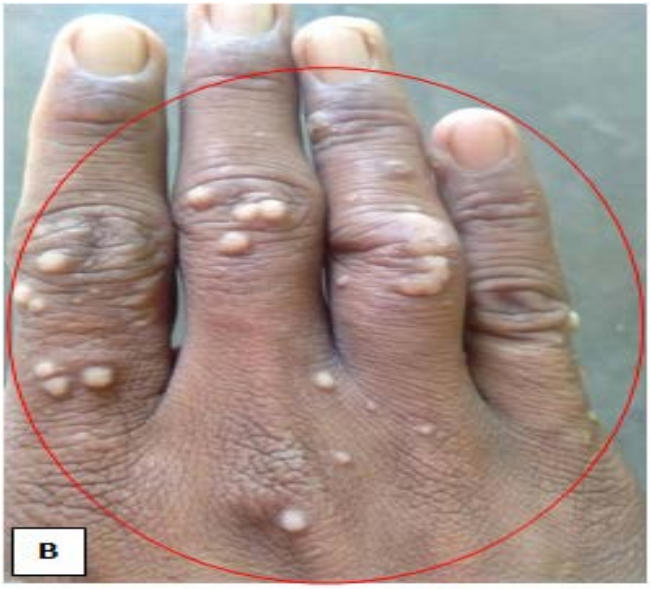

Fig B: 2nd visit: Week 3

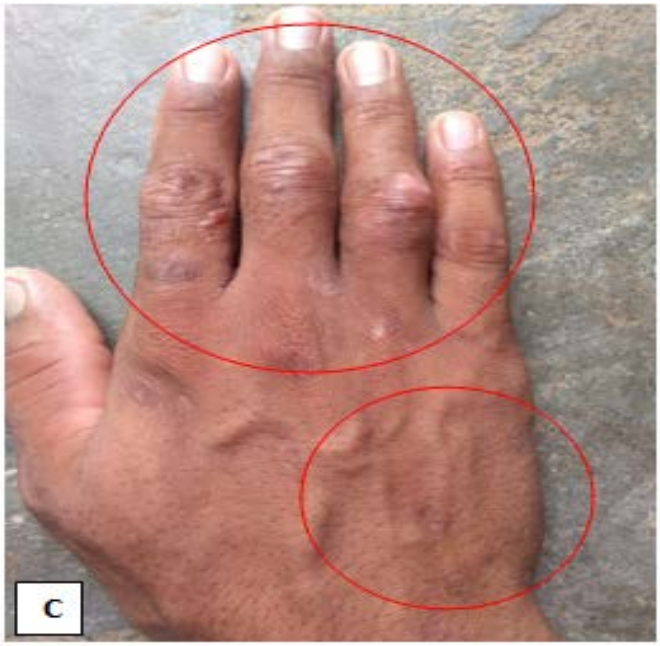

Fig C: 3rd Visit: Week 6

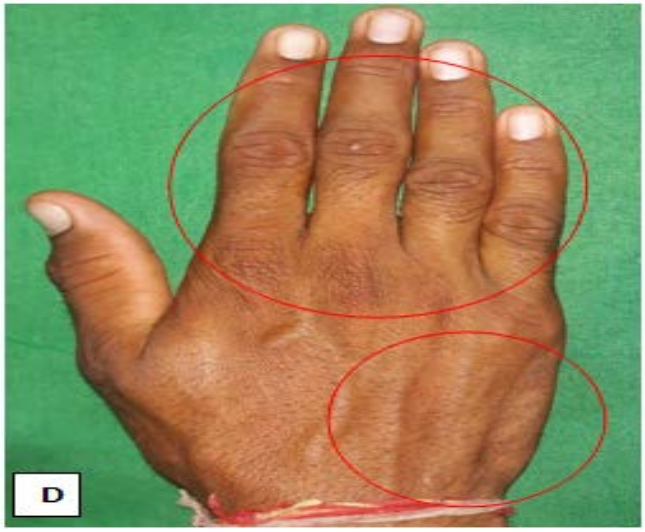

Fig D- 4th Visit: Week 9 Complete Response

1.Verruca Vulgaris

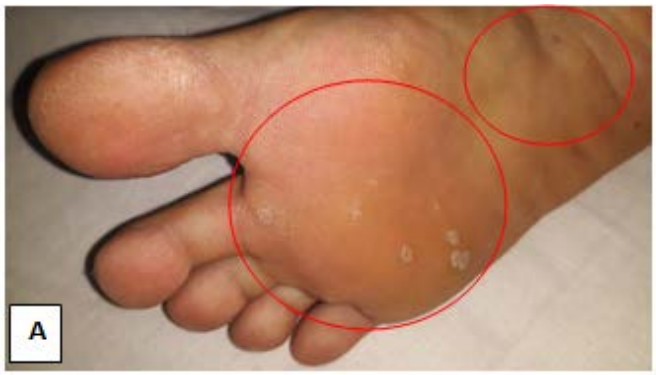

Fig A: 1st Visit: Week 0

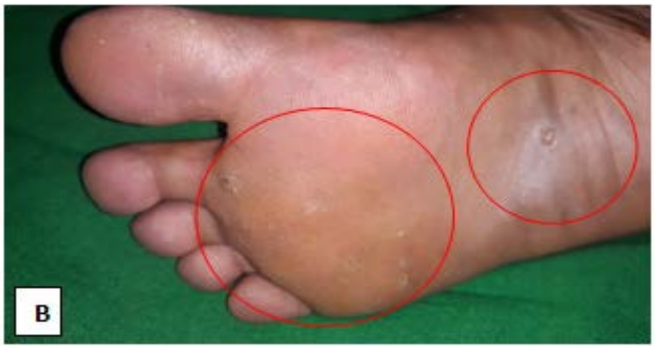

Fig B: 2nd Visit: Week 3

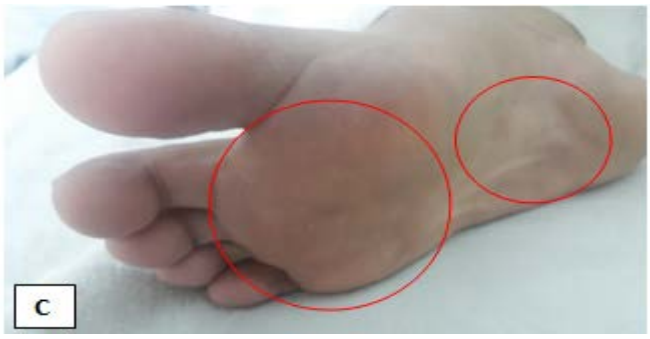

Fig C: 3rd Visit: Week 6, Complete Response

2. Plantar Verrucae

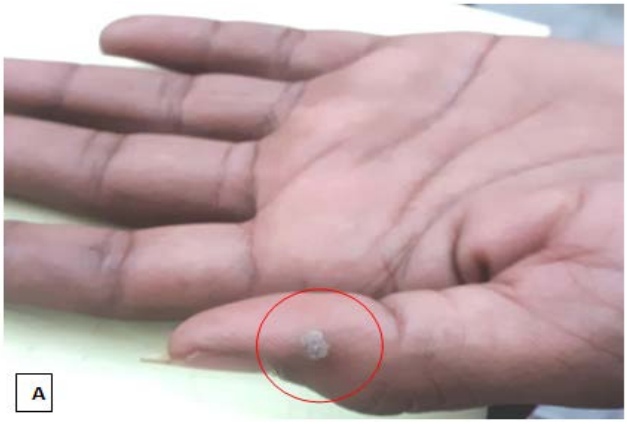

Fig A: 1st Visit: Week 0

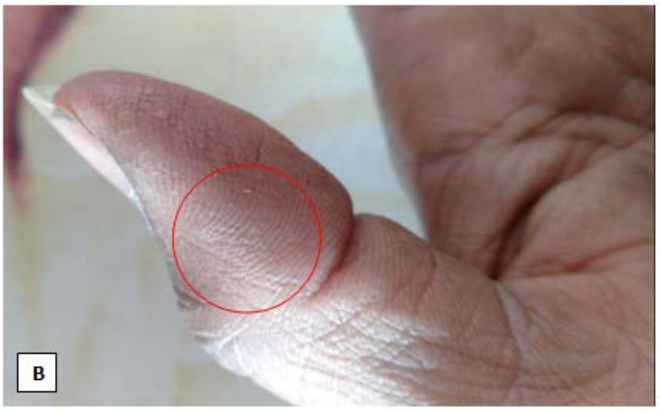

Fig B: 2nd visit: Week 3, Complete Response

4.Palmar Verrucae

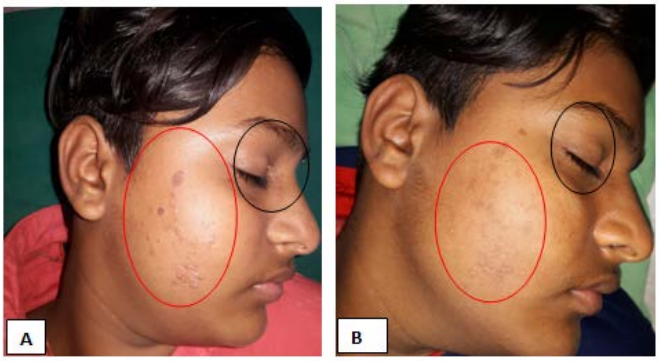

Fig. A:1st Visit: Week 0; Red circle- Plain verrucae & Black circle Filiform verrucae,

Fig. B: 3rd Visit: Week 6- Complete Response in both circle

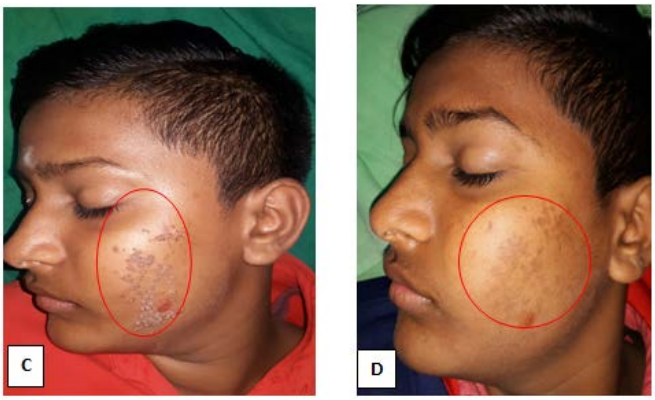

Fig C: 1st Visit: Week 0

Fig D:3rd Visit: Week 6- Complete Response

5.Filiform Verrucae & Verruca Plana

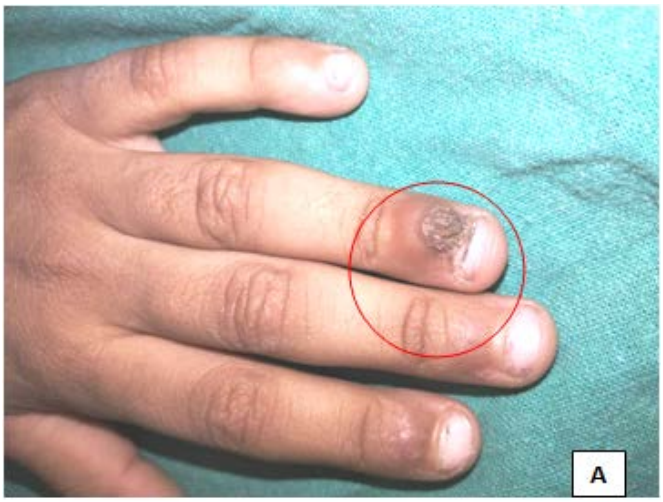

Fig A: 1st Visit: Week 0

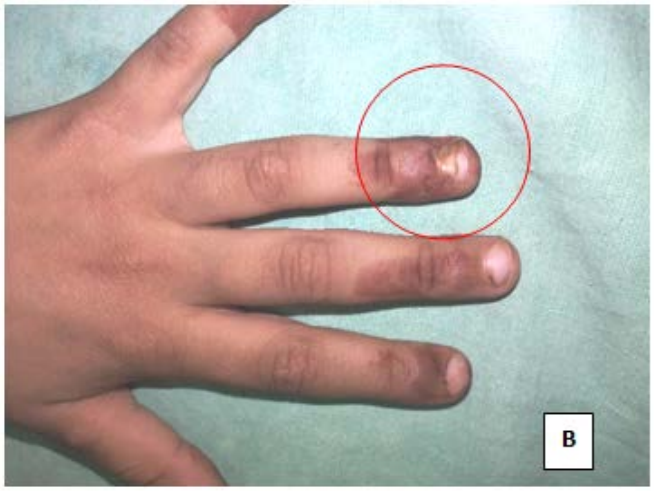

Fig B: 2nd Visit: Week 3

Discussion

None of the patients had serious side effects including scarring, change in pigmentation, nail damage or Raynaud's phenomenon in our study. The only side effect noted was pain at the site of injection during the procedure which varied in intensity according to the perception of the patients from mild to severe.

Aktas et al, used intralesional Vitamin D3 for plantar verrucae. Twenty patients were included in thier study, and 7.5 mg of Vitamin D3 injection was given at monthly interval for a maximum of 2 sessions. They reported[3] complete clearance in 80% of patients while one patient had partial response and 3 failed to show any response at the end of 8 weeks. The complete response of plantar verrucae observed in our study was 91.42% which is quite high as compared to above mentioned study, by Aktas et al.

Raghu Kumar et al, on 64 patients having recalcitrant verrucae (i.e. showing no response to conventional therapies) [5] gave intralesional vitamin D3. 'Complete response' was seen in 54 of 60 (90%) of the patients, 'Partial response' in 4 of 60 (6.66%), and 'No response' in 2 of 60 (3.33%). In our study the sample size was quite large than above the mentioned study and our study design was comparative, one.

Kavya, et al used intralesional Vitamin D3 for various cutaneous verrucae, [6] observed Complete clearance in 19 (82.60%) out of 23 patients. Six patients (14.28%) showed moderate response and three patients (7.14%) had mild response. The complete response in plantar verrucae group was observed in our study, 91.42% patients and in common verrucae, it was 93.05% which is quite high as compared to above mentioned study.

In the present study, a total of 489 verrucae were treated with intralesional Vitamin D3 and complete response, partial response and no response after 4 sessions were observed in 85.07%, 6.74% and 8.17% of each category. Recurrence rate 0.81% was seen.

Therefore, from above discussion we propose the use of intralesional Vitamin D3 in the treatment of cutaneous verrucae because it is safe, inexpensive and more effective.

Conclusion

This study proves that intralesional Vitamin D3 is highly effective and safe for the treatment of cutaneous verrucae which usually do not respond to other modalities of treatment.

The efficacy of intralesional Vitamin D3 was found significantly higher as compared to intralesional Bleomycin in the treatment of cutaneous verrucae. Vitamin D3 has an additional advantage of cost-effective treatment over Bleomycin and we suggest its use, as a primary mode of treatment in all cases of cutaneous verrucae.

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