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Original Article

Intralesional Vitamin D3 for palmoplantar warts : A novel modality

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Abstract

Background Palmoplantar warts is a common condition with many treatment options having different success rates. Intralesional Vitamin D3 for treatment of palmoplantar warts is an upcoming concept as very few studies have been done in this regard. We have tried to explore the efficacy of this new modality for treatment of palmoplantar warts.

Aims and Objective To study the efficacy and safety of intralesional Vitamin D3 in palmoplantar warts.

Materials and Methods Twenty patients having palmoplantar warts of variable duration were enrolled. 0.3 to 0.5 ml of intralesional injection of Vitamin D3 (15 mg/ml, 600,000 IU) was given in the base of maximum 5 warts at each visit. Four such visits at 3 weeks interval were scheduled. Post treatment follow up was done for 6 months. Improvement and adverse effects were noted at every visit.

Results Out of 20 patients, 18 patients completed the study. 15 patients (83.3%) had "good" to "very good" response while 3 patient had "mild' to "moderate" response. No respone was seen in uninjected warts. P value was significant.

Conclusion Intralesional Vitamin D3 is a novel modality and it can be used as an effective and safer option for treatment of palmoplantar warts.

Key words
Palmoplantar warts, intralesional injections, vitamin D3.

Introduction

Immunotherapy has been tried in the past for warts using various antigens including measles, mumps, rubella (MMR), tuberculin purified protein derivative (PPD), Mycobacterium *w* vaccine and Candida antigen.[1-4] *Trichophyton* and autoimplantation are the other available options. The basic principle of using immunotherapy in warts is to enhance cell mediated immunity for the clearance of warts.[5] Immunotherapy is indicated in a patient with recalcitrant warts, recurrent warts, extensive warts, warts in difficult to treat areas-periungual and palmoplantar sites.[6] Human papilloma virus causing the warts is epitheliotropic and results in hyperproliferation of epithelium. The effect of vit. D is speculated to be due to study by Rind *et al*.[7] that reported complete clearance of anogenital warts in an infant by calcipotriene ointment and another study of refractory wart in a 41-year-old renal transplant patient that was treated successfully with calcitriol solution by Moscarelli *et al.*[8] Recently, it was observed that there is toll-like

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receptor activation of human macrophages which upregulated the expression of Vitamin D receptor (VDR) and Vitamin D-1-hydroxylase genes, leading to induction of the antimicrobial peptide.[9] Most common employed methods like, topical cryotherapy, electrocoagulation and laser therapy have shortcomings of long duration of treatment, multiple sittings, recurrence and expensive. Although spontaneous resolution occurs within 2 years in 65%–78% of warts, most patients seek treatment of warts as they are cosmetically disfiguring and sometimes painful, especially on the soles.[10] The treatment of palmoplantar warts require the method that does not result in local wound as it leads to limitation of daily activity of patient and moreover the treatment should be offered for early resolution as the warts on palms can spread due to high chance of autoinoculation by the use of hands. Immunotherapy for warts has been performed with diphenylcyclopropenone (DCP), squaric acid dibutyl ester (SADBE), imiquimod, tuberculin jelly, and autologous vaccines. The use of DCP and SADBE is limited by allergic contact dermatitis, urticarial reactions and pigmentary disturbances. Autologous vaccine therapy is limited by the oncogenic potential of the virus. Therefore, a safe, inexpensive, effective and simple immunotheurapeutic agent is needed for the management of warts.[11] Local signs of necrosis, pigment change, scarring, pain, Raynaud's phenomenon and nail dystrophy resulted with another intralesional therapy of bleomycin though in some patients. Not many studies have been done in regard of use of intralesional vit. D in warts. It is an emerging modality for treatment of warts. Hence, present work was done to study the efficacy and safety of intralesional vit. D in palmoplantar warts.

Materials and Methods

The study was conducted in Department of Dermatology, Venereology and Leprology of our institute. 20 clinically diagnosed patients of palmoplantar warts with no prior treatment history for 3 months were enrolled for the study after explaining the procedure in detail and obtaining a written consent. Pregnant, lactating, immunosuppressed patients and those with any history of hypersensitivity to vit. D were excluded from the study. Response was documented by change in size of lesions. 4 such sittings of vit D at 3 weeks interval. 0.3 to 0.5 ml intralesional intralesional injection of Vitamin D3 (15 mg/ml, 600,000 IU) was given in the bases of 2 to 5 warts with insulin syringe. No further injection of intralesional vit D3 was given if the lesion cleared before the duration of study. Improvement and adverse effects were noted at every visit. Post treatment follow up was done after 3 and 6 months of last injection for any recurrence of the lesions. Patients were advised not to use any other treatment for the condition. Any change in the distant lesions was also noted. Change in size of lesions was recorded and was graded as described below:

- *No response*: Grade 0 = No decrease in size of lesion from the baseline size.
- *Mild response*: Grade 1= ≤ 25% decrease in size of lesion from the baseline size.
- *Moderate response*: Grade2 = 26-50% decrease in size of lesion from the baseline size.
- *Good response*: Grade 3=51-75% decrease in size of lesion from the baseline size.
- *Very good response*: Grade 4=76-100% decrease in size of lesion from the baseline size

Results

18 out of 20 patients completed the study. 15 patients (83.3%) had "good" to "very good" response while 3 patients (16%) had "mild" to "moderate" response. Grades of response in patients at different time intervals, comparison

Table 1 Grades of response in different patients at different time interval

	No. of patients			
	at 3 wks	*at 6 wks*	*at 9 wks*	*at 12 wks*
Grade 0 (no response)	5	2	1	-
Grade 1 (mild response)	5	3	1	2
Grade 2 (moderate response)	8	9	3	1
Grade 3 (good response)	-	-	9	1
Grade 4 (very good response)	-	4	4	14
Total	18	18	18	18

Table 2 Comparison of response at different weeks

Comparison	*P value*	*Significance*
At 3 wks vs At 6 wks	0.001	Significant
At 3 wks vs At 9 wks	<0.001	Highly significant
At 3 wks vs At 12 wks	<0.001	Highly significant
At 6 wks vs At 9 wks	<0.001	Highly significant
At 9 wks vs At 12 wks	0.001	Significant

Table 3 Side effects

Side effect	*No. of patients*
Pain during injection	18
Swelling	4
Systemic side effets	0
Any other	0

of response and side effects are given in **Tables 1-3**.

In some patients, clearance of the lesions was observed before completion of total 4 injections. No further injection of intralesional vit. D was given if the lesion cleared before the duration of completion of study.

- After first sitting, i.e, after 3 weeks of first injection, Grade 0 and Grade 1 response was observed in 5 patients each whereas 8 patients had Grade 2 response.
- After second sitting of intralesional injection of vit. D, Grade 0 was observed in 2, Grade 1 in 3, Grade 2 in 9 and Grade 4 in 4 patients.
- At the follow up visit of third injection i.e. at 9 weeks, Grade 0 was observed 1, Grade 1 in 1, Grade 2 in 3, Grade 3 in 9 and Grade 4 in 4 patients.
- At 12 weeks, all the patients responded with Grade 1 in 2, Grade 2 in 1, Grade 3 in 1 and Grade 4 in 14 patients.

P value was significant at every visit. The p value came to be highly significant with more visits.

There was no improvement seen in the lesions which were present adjacent or distant from the injected wart.

Side effects like pain at injection site while giving injection and swelling were recorded as adverse affects in almost all patients, tenderness remained for a day or two and these side effects were relieved with NSAIDs

Discussion

Immunotherapy with the aim of inducing cell mediated immunity can have edge in clearance of palmoplantar warts than other modalities as recurrence rate is very high in the therapies which are non immunogenic. The exact mechanism behind the clearance of warts by intralesional vit. D has not yet been established, though the experimental evidence suggests that it has immunomodulatory effects by inhibiting the expression of interleukin-6 (IL-6), IL-8, tumour necrosis factor (TNF)-α and TNF-γ mediated through VDR-dependent pathway.[12]

Topical vitamin D can be used in combination with corticosteroids and phototherapy in vitiligo and as monotherapy for various ichthyoses, morphea, pityriasis alba, prurigo nodularis, and polymorphous light eruption.[13] VDR activators (VDRAs) have been shown to inhibit cell

Table 4 Comparison of response of various antigens in different studies

Study	*Antigen /vaccine*	*Number of sessions given*	*Clearance rate (%)*
Garg & Baveja[3]	Mycobacterium w	10	93
Saoji *et al.*[15]	PPD	4	76
Lee *et al.*[16]	Bleomycin	6	73
Nofal *et al.*[17]	MMR vaccine	5	63
Majid *et al.*[4]	Candida albicans	3	56
Singh *et al.*[18]	Mycobacterium nidicus pranii vaccine	10	54
Present study	Vit D3	4	78

replication and have immunomodulatory properties. An important observation was reported which suggested that toll-like receptor (TLR) activation of human macrophages upregulated expression of vitamin D receptor and vitamin D-1-hydroxylase genes, leading to induction of the antimicrobial peptide. This suggests an association of TLRs and vitamin-D-mediated innate immunity.[8]

Vitamin D, when applied topically, regulates epidermal cell proliferation and is involved in the formation of antimicrobial peptides. Intralesional use of vitamin D3 is to exploit its reported action as an immunotherapeutic molecule in addition to its topical effects.[14] Various other antigens/vaccines used for immunotherapy and their response rate are shown in **Table 4** given below. The maximum response rate with complete cure achieved in our study was 77.78% in total 4 sessions which was superior to the results achieved with PPD, Bleomycin, MMR vaccine, C. Albicans antigen and Mycobacterium indicus pranii vaccine. However, treatment with Mycobacterium w vaccine was superior to that of Vitamin D3, but the number of sessions was more i.e., 10 as compared to our study which was 4. Hence, higher response rate i.e. 93% reported in the Garg and Baveja study[3] can be attributed to more number of sessions. Furthermore, they reported systemic and local complications such as high-grade fever and redness, swelling, induration and ulcer which were not in our study. Hence, intralesional vit D can be safer and effective option requiring more comparable studies with larger sample size and standardization of dose and duration is required with less painful method of drug delivery.

Conclusion

Intralesional vit D can be safer and effective method of treatment for palmoplantar warts.

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