

Role of Intralesional Vitamin D3 in the Treatment of Cutaneous Warts

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ABSTRACT

Warts are the benign cutaneous manifestations caused by human papillomavirus (HPV). All currently available treatment modalities are associated with significant side effects and frequent recurrences. As intralesional vitamin D3 is a new immunotherapeutic agent in practice, we conducted this study to determine its safety and efficacy as an immunotherapeutic agent in the treatment of cutaneous warts. We conducted this study on 60 patients. The selected warts were slowly injected with 0.1-0.5 ml of Vitamin D3 (15 mg/ml) into the base of each wart with a 26-gauge insulin syringe. A maximum of 5 warts were injected per session. The injections were performed at 2 weekly intervals until complete resolution or for a total of 4 sessions. It resulted in complete clearance in 38 out of 60 patients, while moderate response was seen in 4 patients and mild response was observed in 3 patients in terms of number of warts. Fifteen patients did not demonstrate any decrease in number of warts even after 4 sittings of intralesional Vitamin D3. In terms of size of warts, moderate response was seen in 8 patients and mild response was observed in 5 patients. Nine patients did not demonstrate any reduction in size of warts even after 4 sittings of intralesional Vitamin D3. Immunotherapy with vitamin D3 seems to be a promising, effective, simple, inexpensive and safe treatment modality for the treatment of cutaneous warts. Due to low recurrence rates, it can be considered to have potential advantages of widespread and sustained effects against HPV.

KEY WORDS: intralesional immunotherapy, vitamin D3, warts

INTRODUCTION:

Warts are the benign cutaneous manifestations caused by human papillomavirus (HPV)^[1]. Most patients seek treatment of warts since they are cosmetically disfiguring and sometimes painful, especially on the soles^[2,3]. Local destruction of warts is a commonly employed treatment modality performed by using either electrocoagulation, cryotherapy, laser therapy or by topical keratolytics like salicylic acid and trichloroacetic acid^[4]. All these treatment options can be painful and may be associated with scarring and frequent recurrences. In addition, destructive modalities are not suitable for the treatment of multiple warts as they clear only treated lesions and have no effect on the distant ones^[5,6].

Various agents have been tried for intralesional immunotherapy including measles, mumps, rubella vaccine (MMR), Bleomycin, Tuberculin purified protein derivative (PPD),

Bacillus-Calmette-Guerin (BCG) vaccine, Mycobacterium w vaccine and Candida antigen. Other immunotherapy agents include *Corynebacterium parvum*, contact immunotherapy, glycyrrhizic acid, Echinacea, green tea extracts, and intralesional vitamin D with variable results. Among these, contact immunotherapy with dinitrochlorobenzene (DNCB), diphencyprone and squaric acid dibutyl ester (SADBE) have also been used but their use was limited by adverse effects like allergic contact dermatitis, urticaria and pigmentary disturbances^[7,8,9,10].

In order to improve the outcome, intralesional immunotherapy is being tried widely for the treatment of multiple cutaneous warts over the last few years. It acts on the basic principle of enhancing the cell-mediated immunity against HPV and results in clearance of warts^[11]. The role of vitamin D3 in the treatment of warts is still not well understood. The probable mechanism of vitamin D3 in the treatment of warts was proposed to be due to its ability to regulate epidermal cell proliferation and differentiation and modulate cytokine production. It can also lead to induction of anti-microbial peptide expression in the skin^[3,12].

Intralesional immunotherapy reportedly causes the resolution of these longstanding benign

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proliferations at the primary as well as distant sites. The exact mechanism of immunotherapy has not been completely elucidated but is believed that the injection to the HPV-infected tissue induces a strong nonspecific pro-inflammatory signal and attracts the antigen-presenting cells. This is associated with the release of different cytokines such as IL-2, IL-8, IL-12, IL-18, tumor necrosis factor- α , and interferon- γ . Significant peripheral mononuclear cell proliferation promotes a Th1 cytokine response. This successively activates the cytotoxic T cells and natural killer cells to eradicate the HPV-infected cells^[2,9,13,14].

As intralesional vitamin D3 is a new immunotherapeutic agent in practice, there is paucity of literature regarding its effectiveness. Therefore, we conducted this study to determine the safety and efficacy of vitamin D3 as an immunotherapeutic agent in the treatment of cutaneous warts.

MATERIALS AND METHODS:

The study was conducted on 60 patients over a period of 18 months. The study started after obtaining approval from the Research Advisory Committee (RAC) and the Institutional Ethics Committee (IEC) of People's College of Medical Sciences & Research Centre, Bhopal. (Code number IEC-2017/37).

The procedure was performed on all adult patients presenting to dermatology OPD with cutaneous warts, which were either newly diagnosed or left untreated for the past 6 months. Written Informed consent was obtained from all the patients after detailed explanation of the procedure prior to commencement of treatment.

The characteristics of the warts such as size and number of warts, type of warts, presence or absence of side effects, and clinical photographs were recorded at the start of the study and at each follow-up visit.

Vitamin D3 for injection, available in vials containing 6,00,000 IU of cholecalciferol in 1 ml (15 mg) was used to treat the patients. The selected warts were slowly injected with 0.1-0.5 ml of Vitamin D3 (15 mg/ml) into the base of each wart with a 26-gauge insulin syringe. Post-treatment, the patients were advised not to use any topical and oral medications. A maximum of 5 warts were injected per session. The injections were performed at 2 weekly intervals until complete resolution or for a total of 4 sessions.

If complete clearance was achieved before four injections, the treatment was stopped and all

patients were followed up for two months after complete clearance to check for recurrence. Clinical response was documented by recording the decrease in number and size of warty lesions at each visit i.e., at 2 weekly intervals for 4 sessions. Clearance was considered in terms of reduction in both size and number of lesions. Response for further categorized accordingly: Complete response: 100%; Moderate response: between 50 to 99% and Mild response: between 1% to 49%. Data was compiled using MS Excel and statistically analyzed using SPSS/PC (Statistical Package of social sciences for personal computer) software version 20.

RESULTS:

Most common type of cutaneous wart observed in present study was palmoplantar (63.3%) followed by mixed warts in 13.3%. Common and flat warts were observed in 6.7% patients each. Mosaic type was the least common type of cutaneous wart observed in only 1.7% patients.

Mean number of injections administered in present study were 2.92 ± 1.03 (range-1 to 4). About 38.3% patients required 4 sittings which also includes those patients who had partial clearance as well as no response. (Table 1).

In present study, 100% resolution in warts was seen in 63.3% patients following intralesional injection of vitamin D3 whereas no resolution was observed in 25% patients. More than 50% and less than 50% resolution in number of warts was observed in 6.7% and 5% patients respectively.

Complete resolution in size of warts was observed in 63.3% patients. However no resolution in size was observed in 15% patients following intralesional injection of vitamin D3. More than 50% reduction in size was observed in 13.3% patients whereas less than 8.3% reduction was observed in 8.3% patients only. In present study, we observed statistically highly significant reduction in number as well as size of warts at final follow up following intralesional vitamin D3 ($p < 0.01$) (Table 2). The most common side effect observed in present study was pain during injection (100%) followed by hypopigmentation (6.7%), granuloma and swelling in 3.3% patients each. Secondary infection was observed in only 1.7% patients (Table 3). Recurrence of cutaneous warts was observed in only 2 (5.3%) patients following vitamin D3 injection. In present study, no significant association was observed between percentage reduction in number of warts and pattern of warts ($p > 0.05$).

Table 1: Number of Injections administered at 2 weeks interval

Number of injections	Frequency (n=60)	Percentage	Outcome
1	6	10.0	Complete clearance
2	16	26.7	Complete clearance
3	15	25.0	Complete clearance
4	23	38.3	Complete + Partial + No clearance

Table 2: Reduction in mean number and size of warts.

Warts	At presentation		At final follow up		t- test	p-value
	Mean	SD	Mean	SD		
Number	5.13	8.02	1.58	3.74	3.98	0.001
Size	3.14	1.99	0.65	1.12	9.46	0.001

Table 3: Distribution according to side effects.

Side effects	Frequency	Percentage
Pain during injection	60	100
Hypopigmentation	4	6.7
Granuloma	2	3.3
Swelling	2	3.3
Secondary Infection	1	1.7


Figure 1: pre-treatment photograph showing plantar warts over left great toe (patient 1).

Figure 2: Post-treatment photograph showing complete resolution (patient 1).

DISCUSSION:

The effect of vitamin D3 derivatives on verruca is speculated from its potential to regulate epidermal cell proliferation and differentiation and to modulate cytokine production. Labaindera J et al (2005) suggested that toll-like receptor (TLR) activation of human macrophages upregulated the expression of vitamin D receptor and vitamin D-1-hydroxylase genes, leading to induction of the antimicrobial peptide. Thus suggesting an association of TLRs and vitamin D-mediated innate immunity and their possible role in antiviral efficacy^[15].

In our study all the 60 patients presenting with cutaneous warts were given intralesional Vitamin D3 injections. Injections were repeated at 2 weekly intervals for a maximum of 4 injections and resolution was noted. If complete resolution was obtained before completion of 4 injections, the treatment was stopped. Mean number of injections required in present study were 2.92 ± 1.03 (range-1 to 4) which were less as compared to study by Raghukumar S et al (2017)^[16] and Kavya M et al (2017)^[3].

Most common type of cutaneous wart observed in present study was palmoplantar followed



Figure 3: Pre-treatment photograph showing plantar warts over right first toe cleft space (patient 2).



Figure 4: Post-treatment photograph showing complete resolution (patient 2).

by mixed warts. These findings were similar to study by Kavya M et al (2017)^[3] and Naresh M et al (2019)^[2].

Mean number and size of warts at presentation and that following intralesional vitamin D3 injection at final follow up showed a difference that was statistically highly significant ($p < 0.01$). We observed complete resolution in size as well as number of warts in 63.3% patients following intralesional vitamin D3 injection.

The complete resolution observed in present study was somewhat less as compared to complete resolution reported in 80% patients by Aktas H et al (2016)^[17]. Kavya M et al (2017) observed complete resolution of warts in 78.6% cases similar to present

study^[3]. Akula ML et al (2018) also reported complete resolution of warts in 70% patients following intralesional vitamin D3 injections^[18].

Minimal side effects were observed in our study, the most common being pain during injection followed by hypopigmentation, granuloma, swelling and secondary infection. Singh SK et al (2018) also documented only pain at the site of injection^[19]. Our findings were similar to findings of Banoth S et al (2019) documented like pain, redness and swelling at the site of injection^[20].

Recurrence of cutaneous warts was observed in only 2 patients. Our findings were in concordance to findings of Kavya M et al (2017) and Naresh M et al (2019) who reported recurrence in 1 and 4 cases respectively.

Immunotherapy with vitamin D3 seems to be a promising, effective, simple, inexpensive and safe treatment modality for the treatment of cutaneous warts. Due to low recurrence rates, it can be considered to have potential advantages of widespread and sustained effects against HPV.

So it may be considered as a first line therapy for multiple warts and a second line therapy for warts recalcitrant to standard treatment modalities because of its low cost, good tolerability and widespread effect involving both treated as well as untreated warts and low recurrence rates.

CONCLUSION:

Immunotherapy with vitamin D3 seems to be a promising, effective, simple, inexpensive and safe treatment modality for the treatment of cutaneous warts. Due to low recurrence rates, it can be considered to have potential advantages of widespread and sustained effects against HPV. So it may be considered as a first line therapy for multiple warts and a second line therapy for warts recalcitrant to standard treatment modalities because of its low cost, good tolerability and widespread effect involving both treated as well as untreated warts and low recurrence rates.

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Cite this article as: Parikh S. Role of Intralesional Vitamin D3 in the Treatment of Cutaneous Warts. *PJSR*; 2020;13(2):51-55.

Source of Support: Nil, Conflict of Interest: None declared.