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Intralesional Vitamin D3 in Recalcitrant Palmoplantar and Periungual Warts: A Prospective, Observational Study

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ABSTRACT Cutaneous warts are particularly difficult to treat with conventional treatment on sites such as the palms, soles, and periungual region. Immunotherapy boosts the host immune response and helps clear warts with less chance of recurrence. Vitamin D plays an important role in proliferation and differentiation of keratinocytes. The aim of this observational study was to study the efficacy and safety of intralesional vitamin D immunotherapy in the treatment of recalcitrant palmoplantar and periungual warts. Patients who had palmoplantar and periungual warts for more than 6 months and were non-responsive to at least two conventional treatment modalities were selected for the study. A maximum of four warts were injected with 0.2 mL of lignocaine (20 mg/mL), followed by intralesional injection of 0.2-0.5 mL of vitamin D3 (15 mg/mL), every 2 weeks for a maximum of four sessions. Response was assessed based on the reduction in the number of warts. A total of 63 patients were included in the study. The mean number of intralesional vitamin D3 injections required for complete clearance was 3.05±0.83 (mean ± Standard Deviation). Complete response was observed in 56 (88.9%) patients. Maximum clearance was observed in periungual warts (92.9%), followed by palmar warts (90.0%) and plantar warts (86.2%). The most common adverse effect was pain during injection (100.0%) and local swelling (25.4%). Two patients developed recurrence during follow-up. Immunotherapy with vitamin D3 appears to be an effective, inexpensive, and safe treatment in recalcitrant palmoplantar and periungual warts.

KEY WORDS: warts, verruca, immunotherapy, vitamin D3

INTRODUCTION

Cutaneous warts are caused by human papillomavirus (HPV) and their prevalence has been reported to be around 2-30% in different age-groups (1). Cutaneous warts have varied clinical presentations that include verruca vulgaris, verruca plana, verruca palmaris and plantaris, and genital warts. More than a hundred different types of HPV have been implicated in the causation of warts; the most common types of cutaneous warts are caused by HPV 1, 2, 3, 4, 7, 10, 27, and 57. Rate of spontaneous clearance of the warts is quite low in adults and persistence for 5-10 years is not unusual (2). Myriad of treatment modalities are available but none of them is completely effective. These include topical trichloroacetic acid and

salicylic acid, cryotherapy, radiofrequency ablation, LASER ablation, photodynamic therapy, 5-fluorouracil, imiquimod, bleomycin sulphate, interferons, contact sensitizers like dinitrochlorobenzene, oral drugs such as zinc sulphate, levamisole, cimetidine, systemic retinoids, etc. (3,4). The main disadvantages of local destruction of warts are scarring and/or dyspigmentation and high frequency of recurrences. Palmoplantar warts and periungual warts are difficult to manage due to their location. Recalcitrant warts cause psychological distress and embarrassment to the patients and are a therapeutic challenge for the treating dermatologist.

Immunotherapy is a promising modality for the treatment of resistant and recurrent warts without any disadvantage of scarring and also boosts the host's immunity against the causative organism, thus leading to complete resolution and fewer recurrences. Several agents have been used for immunotherapy such as Tuberculin Purified Protein Derivative (PPD), Bacillus Calmette Guerin (BCG) vaccine, Measles Mumps and Rubella (MMR) vaccine, *Mycobacterium w*, *Candida albicans*, *Trichophyton*, etc. (5). Vitamin D plays an important role in the proliferation and differentiation of keratinocytes and induces antimicrobial peptides (6). In our study, we evaluated the response of intralesional vitamin D3 in recalcitrant palmoplantar and periungual warts.

Table 1. Baseline characteristics of the study population

Characteristics	Number of Patients (%)
Gender	
Men	42 (66.7%)
Women	21 (33.3%)
Age (years)	
≤20 y	10
21-30	30
31-40	17
41-50	6
Duration of warts (years)	
<1	29 (46.0%)
1-2	26 (41.3%)
2-5	6 (9.5%)
>5	2 (3.2%)
Sites involved	
Palmar	20 (31.8%)
Plantar	29 (46.0%)
Periungual	14 (22.2%)

PATIENTS AND METHODS

This was a prospective, observational study carried out at the Out-Patient Department of Dermatology if our Medical College and Hospital from January 2018 to December 2018. Ethical approval was obtained from the Institutional Ethics Committee and an informed consent was taken from all patients.

Sixty-three patients who were clinically diagnosed with palmoplantar and periungual warts and were refractory to the previous conventional modalities were recruited for the study. These patients had one or more recalcitrant warts in the above-mentioned sites (defined in this study as warts present for a duration of more than 6 months and non-responsive to at least two conventional treatment modalities). Exclusion criteria comprised pregnant and lactating women,

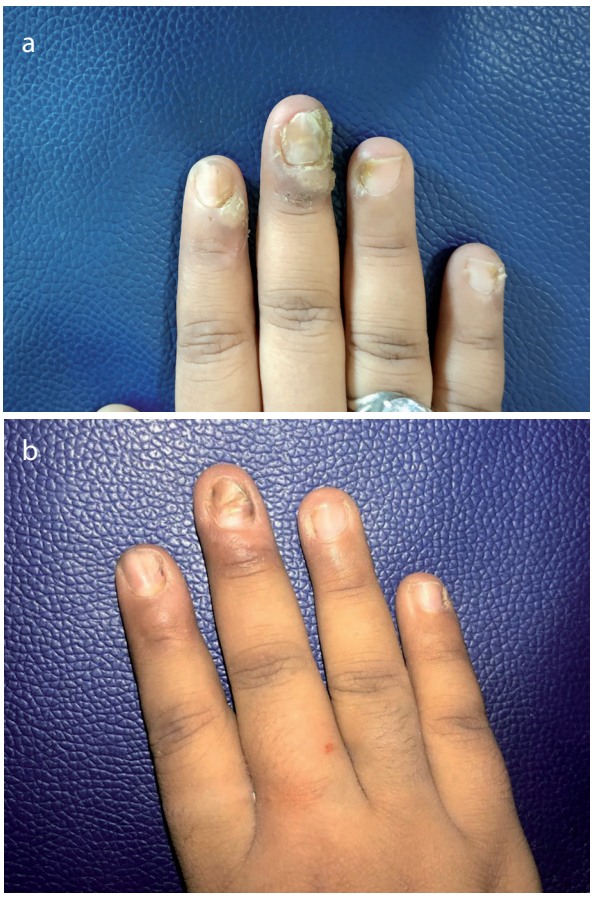

Figure 1. (a) Multiple periungual warts on the fingers of the right hand. (b) Complete resolution of warts after vitamin D3 immunotherapy.

Table 2. Distribution of patients according to response

Site of warts	Number of patients	Outcome		
		Complete response	Moderate response	Mild response
Periungual warts	14	13 (92.9%)	1 (7.1%)	0 (0.0%)
Plantar warts	29	25 (86.2%)	2 (6.9%)	2 (6.9%)
Palmar warts	20	18 (90.0%)	1 (5.0%)	1 (5.0%)
Total	63	56 (88.9%)	4 (6.3%)	3 (4.8%)

patients on immunosuppressants, and patients with prior history of hypersensitivity to vitamin D3. Demographic data and a baseline evaluation regarding the site, number, and size of the warts was recorded at each visit for every patient. Pre- and post-treatment photographs were taken for comparison. The patients were instructed not to use any other treatment modality during this therapy, and there was a waiting period of 1 month before commencing this therapy if the patients were receiving any other treatment.

Vitamin D3 is available in vials containing 600,000 IU of cholecalciferol in the dose of 15 mg/mL. The warts were first injected with 0.2 mL of plain lignocaine (20 mg/mL) and then after a few minutes with a 0.2-0.5 mL injection of vitamin D3 was very slowly administered at the base of each wart with a 27-gauge insulin syringe. A maximum of 4 warts were treated at each session. The sessions were performed in regular 2-week intervals for a maximum of 4 sessions, until complete resolution. Patients were monitored for any adverse effects and attended monthly follow-up for the next 6 months after the last injection to look for recurrences.

Clinical response for each patient was recorded in terms of decreased number of warts. Complete clearance was noted if all the warts resolved completely; moderate response if there was a 50% to <100% reduction in number of warts; mild response indicated <50% reduction.

RESULTS

Out of total 63 patients, 21 (33.3%) were women and 42 (66.7%) patients were men. The age ranged from 12 to 49 years; the largest proportion of patients was in the second decade of life and the mean age

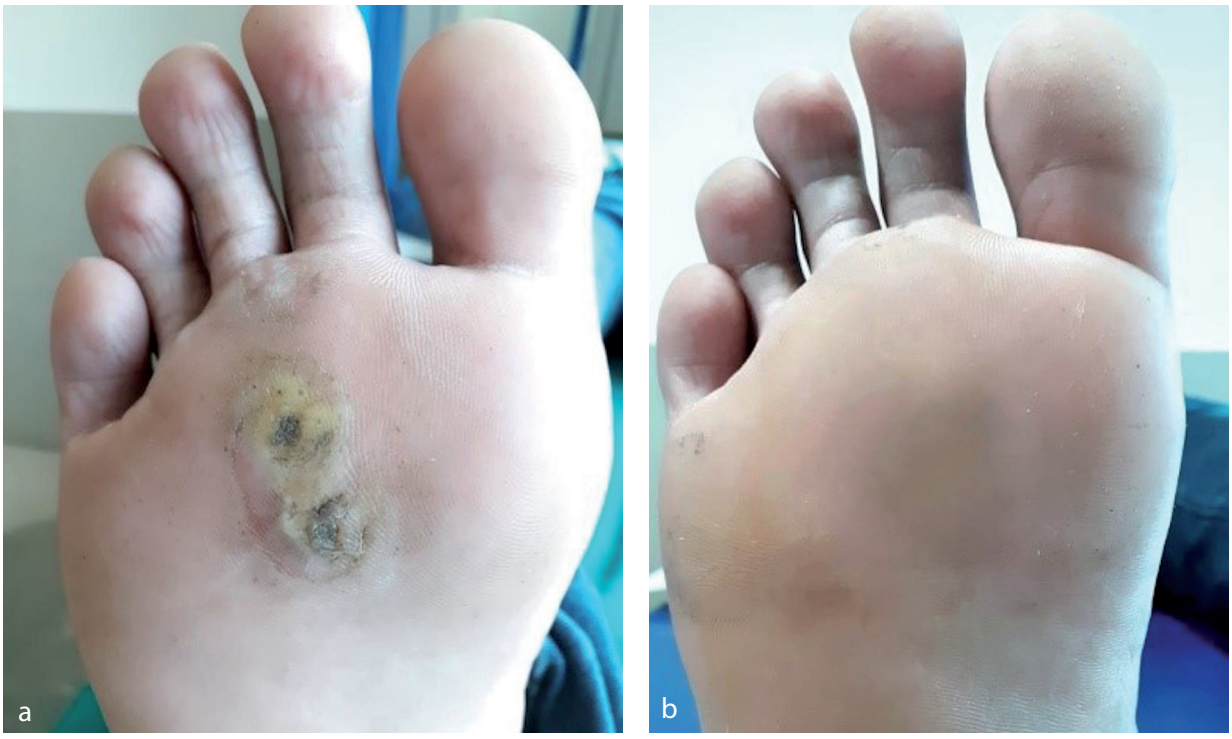

Figure 2. (a) Plantar warts on the sole. (b) Resolution of the warts with vitamin D3 immunotherapy.

was 28.57±8.22 years (mean ± Standard Deviation). The mean duration of disease was 1.47±1.19 years. Plantar warts were most prevalent (29, 46.0%), followed by palmar warts (20, 31.8%) and peri-ungual warts (14, 22.2%). The number of warts varied from 2 to 7 in each patient. The demographic details of patients are enumerated in Table 1. The total number of warts included in the study were 159, out of which 73 were plantar, 49 were palmar, and 37 were periungual in location. The mean number of intralesional vitamin D3 injections in the study for achieving complete clearance was 3.05±0.83.

Complete response was observed in 56 (88.9%) patients, moderate in 4 (6.3%), and mild in 3 (4.8%) patients (Figures 1-3). The maximum number of complete clearances was observed in periungual warts (92.9%), followed by palmar warts (90.0%) and plantar warts (86.2%). The response rate of various types of warts is shown in Table 2.

The most common adverse effect was transient pain, which was present in almost all patients and was managed by pre-injection with lignocaine. The next

Table 3. Response rate of vitamin D3 (topical and intralesional) in the treatment of cutaneous warts in previous studies

Studies	Modality	Site	Response Rate (complete clearance)	Recurrence	Adverse effects
Topical vitamin D3					
Moscarelli *et al.* (14)	Topical calcitriol 0.5 µg solution	Single wart on the right index finger in a renal transplant patient	100%	None	None
Rind *et al.* (15)	Calcipotriene ointment	Anogenital wart in an infant	100%	None	None
Egawa and Ono (16)	Maxacalcitol (25 µg/g) or calcipotriol (50 µg/g) ointment with half-day occlusive dressing	Hands and feet of 3 immunocompromised patients	100%	None	None
Imagawa and Suzuki (6)	Maxacalcitol ointment (25 µg/g)	Hands and feet	100%	None	None
Intralesional vitamin D3 injection					
Aktas *et al.* (17)	Vitamin D3 (0.2 mL, 7.5mg/mL)	Plantar warts	80%	Minimal to moderate pain during injection	None
Kavya *et al.* (18)	Vitamin D3 (0.2 mL, 15 mg/mL)	Cumulative Palmoplantar Verruca vulgaris Filiform wart	78.57% 82.60% 77.77% Mild Response	Swelling (78.57%) Dyspigmentation (2.38%)	2.38%
Raghukumar *et al.* (19)	Vitamin D3 (0.2-0.5 mL, 15 mg/mL)	Cumulative Palmoplantar Common Periungual Filiform Plane	90% 100% 88% 50% No response No response	Transient mild to moderate pain Transient edema (3.33%) Mild erythema (5%)	3.33%
Singh *et al.* (20)	Vitamin D3 (0.5 mL, 15 mg/mL)	Cumulative Palmoplantar Filiform Verruca vulgaris	72.5% 80% 80% 72%	Pain at the time of injection	None
Our study	Vitamin D3 (0.2-0.5 mL, 15 mg/mL)	Cumulative Plantar Palmar Periungual	88.9% 86.2% 90.0% 92.9%	Pain and transient swelling	3.2%

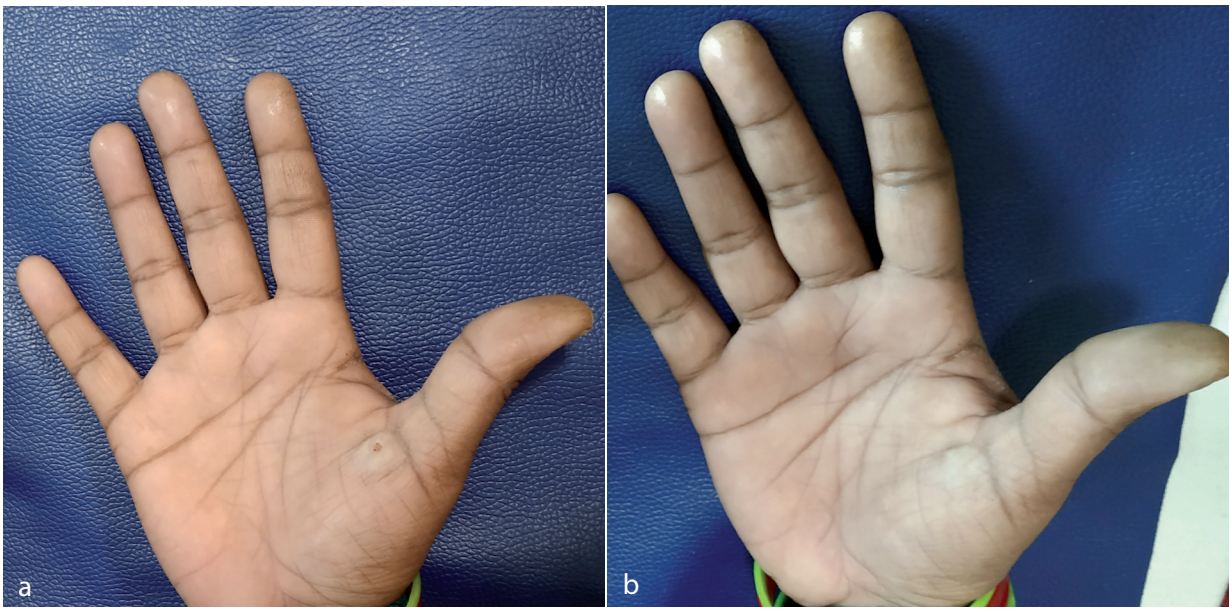

Figure 3. (a) Palmar wart present at the base of the thumb. (b) Resolution of the wart after vitamin D3 immunotherapy.

most common adverse effect was swelling, found in 16 (25.4%) patients in whom it subsided within a week. None of the patient had any serious/systemic side-effects.

The patients attended follow-up for the next 6 months after the last injection, during which 2 (3.2%) patients presented with recurrence (1 each of plantar and palmar warts).

DISCUSSION

Recalcitrant warts cause both physical as well as psychological distress to patients. Following trauma to the skin, HPV infects the basal layer of keratinocytes where it remains latent in the cell for 1-8 months (7). Epidermal cell differentiation and migration triggers the virus to undergo replication until it is shed from the stratum corneum. In most viral infections, the viral proteins cause damage to the host cell leading to stimulation of cytotoxic T-cells which then destroy the virally infected cells (7). However, HPV prevents cell lysis during replication and there is consequently no release of viral proteins into the circulating dendritic cells and thus no antigen presentation to the immune system (8). Recalcitrant warts may present a localized or systemic cell-mediated immune deficiency to HPV. The absent or decreased cellular response due to lack of production of memory T-cells to target HPV infection, failure of clonal expansion of lymphocytes to adequate stimulation, inability of T-lymphocytes to access the sites of infection, and weak effector response mechanism (9) may explain the lack of complete clearance or recurrence of warts seen with conventional treatment modalities.

In view of these shortcomings of conventional treatment, immunotherapy seems to be the best available option for the treatment of recalcitrant warts as it boosts the immune system against HPV, leading to clearance of both treated as well as untreated lesions. Intralesional immunotherapy induces a strong non-specific proinflammatory signal and attracts the antigen-presenting cells at the site of infection, thereby leading to release of different cytokines such as interleukin (IL)-2, IL-8, IL-12, IL-18, tumor necrosis factor (TNF)-α, and interferon-γ. A Th1 cytokine response is initiated due to peripheral mononuclear cell proliferation. This leads to the activation of natural killer cells and cytotoxic T-cells to eradicate the virus-infected cells. (10) Furthermore, the trauma due to injection may lead to resolution of lesions in previously sensitized individuals (11). Intralesional immunotherapy also has other advantages, such as low recurrence rate and almost no physical changes like scarring. In our study, we evaluated the effects of intralesional vitamin D3, which is a new drug in the armamentarium of immunotherapy, and found that the recalcitrant warts present on difficult to treat sites such as the palms, soles and periungual areas can be treated successfully with the use of vitamin D3.

The exact mechanism of action of vitamin D3 against warts is not clearly known, but it has immunoregulatory activities and controls the cellular proliferation and differentiation while also modulating cytokine production. Its effects are mediated through the vitamin D receptor (VDR), which is present in keratinocytes, fibroblasts, melanocytes, and immune cells of the skin. Experimental evidence suggests it

Table 4. A comparison of the various common treatment modalities used in palmoplantar and periungual warts

Modality	Site	Response rate	Recurrence rate	Hazards and complications
Destructive methods				
Salicylic acid	Plantar warts	14% (22) - 33% (23)	25%	Modest efficacy Skin irritation Chemical burns Contact allergy Not to be used in neuropathic foot
Cryotherapy	Plantar warts	14% (23) - 65% (24)	25%	Pain, blistering, scarring, hypo and hyperpigmentation, caution in patients with impaired circulation and near nerves
Cantharidin	Plantar and periungual warts	80% (25)	-	Pain, blistering
Formic acid	Palmoplantar warts	73% (26)	-	Minimal pain, minimal scarring
Surgical excision	Plantar warts	65-85% (27)	30%	Scarring, infection, hypo- or hyper-pigmentation
Electrocautery	Plantar warts	67% (28)	-	Pain, ulcer, infection
CO2 laser	Plantar warts	89.7% (29)	10.7%	Transmission through CO2 laser plumes, infection, pain, cosmetic disfigurement,
Long pulsed 1064 nm Nd:YAG laser	Plantar warts Periungual warts	44% (30) - 56% (31) 64.7% (30)	-	Pain, transient internal hemorrhage and hemorrhagic blisters, nail dystrophy Expensive
Pulsed Dye laser	Palmar warts Plantar warts Periungual warts	75% (32) 20% (32) 50% (32)	-	Pain, erythema, expensive
Photodynamic therapy	Plantar warts	75% (33)	-	Burning sensation, edema, erythema
Virucidal agents				
Formaldehyde	Plantar warts	80% (34)	-	Allergic contact dermatitis, burning sensation
Glutaraldehyde	Palmoplantar and Periungual warts	80% (35)	-	Pigmentation
Anti-proliferative agents				
Dithranol	Plantar warts	71% (36)	-	Irritation, burning, pain, stinging, staining of clothes
Podophyllin	Plantar warts	67% (37)	-	Unsafe in pregnant women, associated with intense irritation
5-fluorouracil (topical)	Plantar warts	95% (38)	15%	Pain, blistering, erosions, local irritation, nail detachment, hyper and hypo pigmentation
5-fluorouracil (intralesional)	Plantar warts Periungual warts	54% (39) 0% (39)	22%	Pain, erythema, edema, blistering, scarring, hyper and hypo pigmentation
Bleomycin (intralesional)	Palmoplantar Periungual	96.1% (40) 100% (40)	0%	Scarring, dyspigmentation, nail changes, Raynaud's phenomenon
Retinoids (topical)	Plantar warts	96% (41)	-	Erythema, irritation

Cidofovir (intralesional)	Palmoplantar and periungual warts	98% (42)	-	Pain, burning at time of injection, erythema, itching, hyperpigmentation
Immunological therapy				
Contact immunotherapy with diphencyprone	Palmoplantar warts	88% (43)	0%	Generalized allergic contact dermatitis, bulla formation, lymphadenopathy, urticaria, erythema multiforme
Auto-implantation therapy	Palmoplantar warts Palmar warts Plantar warts	83.3% (44) 36.1% (45) 16.1% (45)	- 3.33%	Post procedure infection, erythema, induration, post-inflammatory hypopigmentation
Tubercular Purified Protein Derivative (intralesional)	Plantar warts Periungual warts	83% (46) - 100% (47) 0 (48) - 100% (47)	0%	Pain, swelling, erythema, caution advised in immunocompromised patients
Measles, mumps, and rubella vaccine (intralesional)	Palmoplantar warts Plantar warts	70.9% (49) 65% (50) - 82% (51)	2.9%	Flu like symptoms- rhinitis, headache, erythema, edema, caution advised in immunocompromised patients
Killed *Mycobacterium indicus pranii* vaccine (intralesional)	Palmoplantar and periungual warts	25% (52) - 93.3% (53)	14.3%[32]	Pain, nodule, ulceration, scarring, paresthesia, fever
Candida (intralesional)	Plantar warts	76.7% (54)	-	Pain, erythema, flu-like illness
Vit D3 (intralesional): Discussed in table 3				
Alternative therapy				
Thuja occidentalis	Plantar warts	80% (55)	0%	Burning sensation, erythema

*References indicated in parentheses

has an immunomodulatory effect by inhibiting the expression of TNF-α and β, IL-6, and IL-8 acting via a VDR-dependent pathway (12). It has recently been observed that there is Toll-like receptor activation of human macrophages which up-regulates the expression of VDR and vitamin D-1-hydroxylase genes, leading to production of antimicrobial peptide (13).

Several studies have reported the efficacy of topical vitamin D in the treatment of warts. Moscarelli *et al.* demonstrated the effectiveness of topical calcitriol 0.5 µg solution for treating refractory warts in a renal transplant recipient (14). Rind *et al.* reported complete clearance of anogenital wart in an infant with topical calcipotriene ointment applied twice daily for 3 months (15). In both of these case reports, the mechanism of action of vitamin D3 was presumably based on its ability to regulate epidermal cell proliferation and differentiation and enable cytokine production. In their study, Egawa and Ono successfully treated three immunocompromised patients with recalcitrant warts with a vitamin D3 derivative using a half-day occlusive dressing technique and reported complete regression of the lesions without any recurrence in the follow-up period. No adverse effects or abnormal serum levels of calcium were observed (16). The effect of vitamin D3 on cell death and angiogenesis is probably also responsible for the efficacy of vitamin D3 in warts (16). Similarly, Imagawa and Suzuki showed complete regression of refractory palmoplantar warts in all 17 patients (4 adults and 13 pediatric patients) following application of topical maxacalcitol 25 µg/g ointment, applied thrice daily over 6 months (6).

The efficacy of intralesional vitamin D3 injection in the treatment of warts has also been demonstrated in several studies. Aktas *et al.* reported 80% complete clearance of palmar warts with intralesional vitamin D3. No recurrences were noticed in their 6-month follow-up period and no allergic or systemic adverse effects and no signs or symptoms of hypervitaminosis D were observed (17). Kavya *et al.* demonstrated complete clearance of cutaneous warts in 78.5% patients

(both treated as well as distant warts) by intralesional vitamin D3. Complete clearance was observed in 19 (82.60%) out of 23 patients with palmoplantar warts. The mean number of intralesional injections required for complete clearance was 3, and recurrence was observed in one patient with a palmoplantar wart during 6-month follow-up period (18). Raghukumar *et al.* reported complete clearance of recalcitrant warts in 90% patients, partial response in 6.66%, and no response in 3.33% patients using intralesional vitamin D3. They also noted clearance of distant warts. Two patients presented with recurrence in the follow-up period. These results were similar when compared to our study (19). Singh *et al.* performed a comparative study between intralesional PPD and vitamin D3 in the treatment of viral warts. Amongst the total of 80 patients, group 1 patients received 10 TU of intralesional tuberculin PPD (0.1 mL), while group 2 patients were injected with 0.5 mL of vitamin D3. In group 1, 80% (32 patients) had complete clearance while in group 2, 72.5% (29 patients) presented complete disappearance of warts. However, side-effects noted with tuberculin PPD were pain (75%), nodule formation (25%), hyperpigmentation (30%), swelling, fever, blister formation, and erythema (10%) with induration (10%), whereas pain was the most common side-effect with intralesional vitamin D3, which was managed by injecting local anesthetic prior to injecting vitamin D3 (20). The efficacy of vitamin D3 in the treatment of cutaneous warts (topical as well as intralesional) has been summarized in Table 3.

Various other treatment modalities such as cryotherapy, LASER, contact sensitizers, and antigens / vaccines have been used for the treatment of warts, and their response rates in palmoplantar / periungual warts are shown in Table 4 for comparison. The response rate achieved in our study is superior to the results achieved with most of the conventional treatments. Many of these treatments have the potential for adverse effects such as irritation, scarring, or pigmentation. Intralesional immunotherapy has a low recurrence rate and clears the warts even at remote locations.

This was an observational unblinded study limited by the absence of a control group and by a small sample size, and therefore a larger and a double-blind study is needed in future to confirm the efficacy of intralesional vitamin D3.

CONCLUSION

Vitamin D immunotherapy appears to have high efficacy in clearing warts and is largely free of severe adverse effects. Furthermore, vitamin D3 is an inexpensive drug that has proven to be very beneficial especially in developing countries. Since it boosts specific immunity against HPV the need to treat individual lesions is obviated, making it a novel therapy for treatment of warts on sites such as the palms, soles, and periungual region.

Declaration of patient consent: The authors certify that they have obtained all appropriate patient consent forms. In the form the patients have given their consent for their images and other clinical information to be reported in the journal. It was made clear that their name and initials will not be published and that due efforts will be made to conceal identity, but that anonymity cannot be guaranteed.

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