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Case Series

A novel case study on safety and efficacy profile of intralesional vitamin D3 in the treatment of multiple cutaneous warts

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ABSTRACT

Immunotherapy has now become one of the emerging therapeutic tools for treatment of multiple warts. In this case series we tried to analyse the safety and efficacy profile of intralesional vitamin D3, a novel immunotherapeutic agent. A total of 24 patients between 12 to 60 years having more than 3 cutaneous warts were included. Four patients lost follow up and 20 patients were studied. Each patient received 0.1 ml of vitamin D3 (15 mg/ml, 6L IU/ml) injected intralesionally into one wart, with a maximum of 5 warts treated. The injection is repeated 2 weeks once until complete resolution or total of 4 injections. The primary outcome measure is complete resolution of warts and return of normal skin markings. Out of 20 patients, 15 (75%) showed complete clearance. One patient showed recurrence during follow up period. Adverse effects are all minimal including erythema, induration and pain at the injection site. Injection vitamin D3 is a safer, inexpensive, easily available and effective immunotherapeutic agent for treatment of multiple warts. The injection site must be carefully selected to avoid disfiguring induration.

Keywords: Immunotherapy, Verrucae, Induration

INTRODUCTION

Verruca vulgaris or cutaneous viral warts are the common cause of viral infection of skin and other mucosa, caused by multiple strains of human papilloma virus (HPV). Though many modalities are available, treatment of warts is challenging especially for multiple warts. Main aim of the treatment is to eradicate warts without recurrence, improve specific lifelong immunity against HPV and avoid procedures that are mutilating. Immunotherapy is defined as a type of biological therapy that uses a substance to stimulate or suppress the immune system thereby helping the body fight against cancer, infection and other diseases.[1]

Immunotherapy utilizes the ability of our immune system in mounting type IV hypersensitivity response to various antigens and the wart tissue.[2] This is achieved by producing a Th1 type of response which stimulates natural killer cells and cytotoxic T lymphocytes against HPV virus. This clears not only the treated verrucae but also distant verrucae unlike conventional destructive wart therapies.[3] It works better for young patients as older patients produce a weaker immune response. Its advantages are minimally invasive, less pain, low recurrence rate, more effective in recalcitrant warts, no scarring and induces complete resolution. Till now there are no specific indications or criteria for starting immunotherapy. Multiple, recurrent, treatment resistant, periungual and palmoplantar warts are the considerations.

This study assessed the safety and efficacy of intralesional vitamin D3 as a potential treatment for multiple recalcitrant warts, an area with limited existing research.

CASE SERIES

After obtaining ethical committee approval, a study was conducted on 24 patients aged 12-60 years with multiple warts (>3 lesions) attending Thanjavur medical college hospital from February 2021 to April 2022. Patients with immunosuppression, keloidal tendency, or recent wart treatment were excluded. Participants received intralesional vitamin D3 injections (6L IU/ml, 0.1ml/ lesion, up to 5 warts, into superficial dermis using insulin syringe) every 2 weeks for a maximum of 4 sessions or until complete resolution. Patients were followed up every 2 weeks for 3 months and monthly for the next 3 months, with clinical photographs taken at each visit. Treatment success was defined as complete clearance of warts with no recurrence during the 6-month follow-up period. Results were evaluated as follows, complete clearance-100%, good response-75-99%, moderate response-50-75%, mild or nil response<50%.

Data were entered in MS excel sheet and analyzed using statistical packages for social sciences (SPSS) version 16. Spearman's rho correlation test was used to find the strength of association between the variables. P<0.05 was considered statistically significant.

Out of 24 patients who gave consent, 4 lost follow up and 20 patients were studied with a predominance in males (n=18, 90%) than females (n=2, 10%). Majority of the cases were below 35 years (n=17, 85%). We came across more of palmoplantar warts (n=12, 60%) and students are most commonly affected by warts in our study (Table 1).

At the end of 8 weeks, 15 patients (75%) showed complete clearance, 1 patient (5%) showed good response, 2 patients (10%) showed moderate response and 2 patients (10%) showed mild/nil response. All complete responders (n=15, 75%) were under 35 years. Whereas all patients over 35 years (n=3) had mild or moderate responses (Table 1).

Vitamin D3 have shown better results for common, palmoplantar warts showing 70% and 75% response rate respectively. One patient with plane warts have shown 100% clearance rate whereas periungual warts have shown 66.7% clearance rate (Table 1 and Figure 1 A-F).

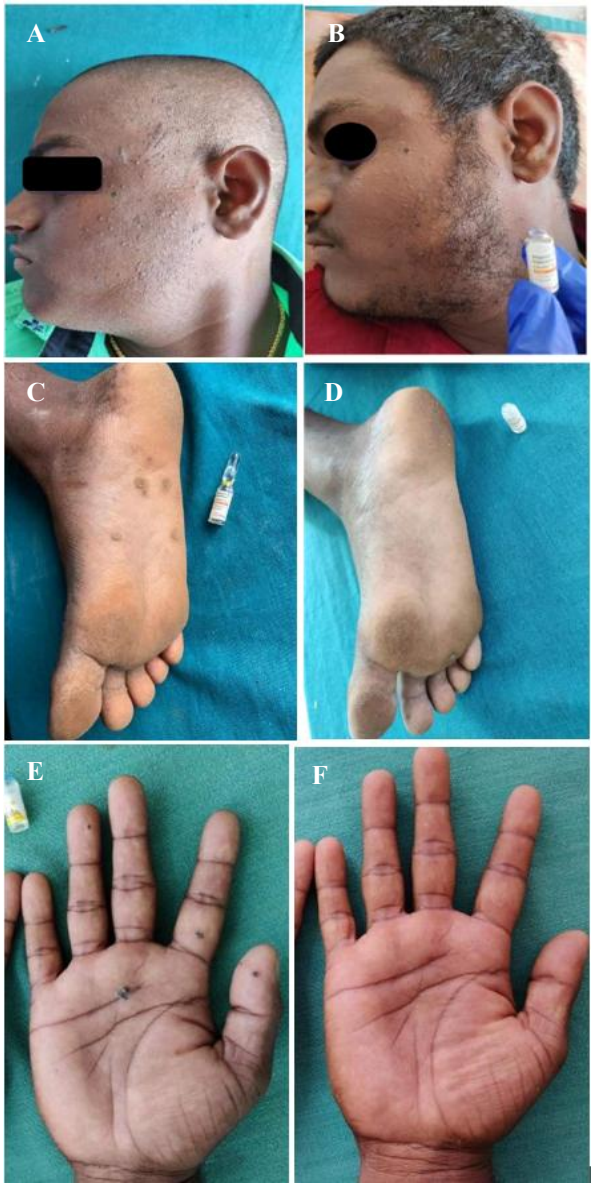

Figure 1 (A-F): Complete clearance of different types of warts (A and B) plane warts, (C and D) plantar warts and (E and F) palmar warts.

*Multiple plane warts (A) before and (B) after treatment with 3 injections of IL vitamin D3; multiple plantar warts (C) before and (D) after 3 injections of IL vitamin D3; multiple palmar warts (E) before and (F) after 4 injections of IL vitamin D3.

Table 1: Patient characteristics and treatment outcomes.

Category	N	Percentage (%)
Age (in years)		
<35	17	85
>35	3	15
Gender		
Male	18	90
Female	2	10
Duration of warts		
<6 months	10	50
6-12 months	6	30
>12 months	4	20

Continued.

Category	N	Percentage (%)
Number of warts		
3-10	16	80
10-20	1	5
>20	3	15
Type of wart		
Common	10	50
Plane	1	5
Palmoplantar	12	60*
Periungual	3	15
Clinical response (8 weeks)		
Complete clearance	15 #	75
Good response	1	5
Moderate response	2	10
Mild/nil response	2	10
Complete clearance by wart type		
Common wart	7/10	70
Plane wart	1/1	100
Palmoplantar wart	9/12	75
Periungual wart	2/3	66.7
Sessions for complete clearance		
1 session	1	5
2 sessions	6	30
3 sessions	3	15
4 sessions	5	25
Correlation with response	**Correlation coefficient**	**P value**
Age (in years)	-0.541	0.014 (significant negative)
Duration of wart	0.051	0.835 (not significant)
Number of wart	-0.148	0.534 (not significant)
Number of sessions	-0.537	0.015 (significant negative)

*Note that the percentages for wart types may not add up to 100% due to overlapping categories. # All complete responders (n=15) were under 35 years old.

Table 2: Comparison with various studies using IL vitamin D3.

Parameters	Present study	Raghukumar et al[14]	Kavya et al[15]	Abou-Taleb et al[16]	Shaldoum et al[17]
No. of patients	20	60	42	23	30
Dosing	0.1 ml/lesion max of 5 warts, 2 weeks once	0.2-0.5 ml, max of 5 warts, 3 weeks once	0.2 ml into max of 2 warts, 2 weeks once	0.6 ml into max of 3 warts, 3 weeks once	0.4 ml/lesion, max of 5 warts, 3 weeks once
No. of injections	4	4	4	3	6
Clearance rate (%)	75	90	78.57	21.7	66.7
Recurrence	1	1	1	Nil	Nil
Adverse effects	Pain, erythema, induration	Pain, erythema, induration, edema	Swelling, pigmentary changes	Pain, itching	Erythema, nail dystrophy, vasovagal attack
Remarks	6L IU/ml 15 mg/ml	6L IU/ml 15 mg/ml	6L IU/ml 15 mg/ml with lignocaine	2L IU/ml 5 mg/2 ml with lignocaine	2L IU/ml 5 mg/2 ml with lignocaine

In 15 patients who had achieved complete clearance, the number of sessions required was one in 1 patient (5%), two in 6 patients (30%), three in 3 patients (15%) and four in 5 patients (25%). Variables such as fewer sessions and younger age were associated with better treatment response (Table 1).

Erythema (n=1, 5%) and induration (n=4, 20%) are the adverse effects noted with IL vitamin D3 apart from pain (n=3, 15%). No serious adverse events had occurred. Recurrence is noted with one patient during 4 months of follow up (Figure 2 A-D).

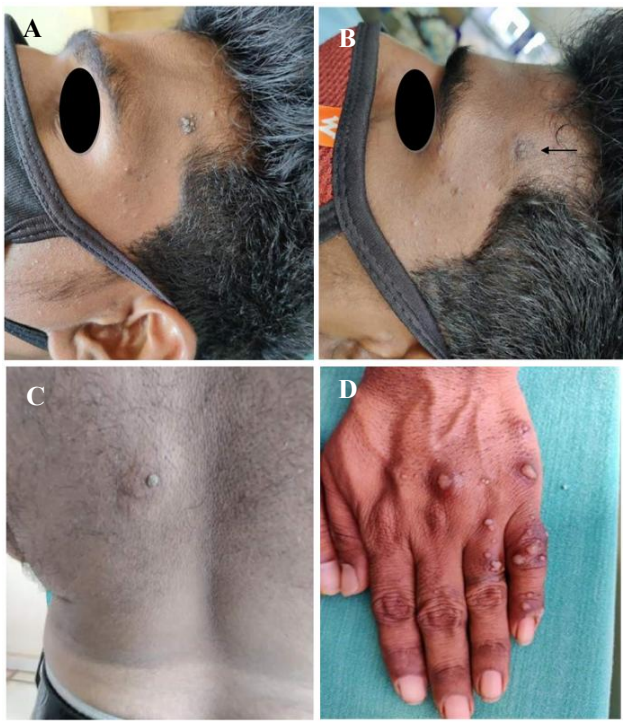

Figure 2 (A-D): Cutaneous adverse effects observed in our study. (A and B) induration at injection site, (C and D) erythema and induration at injection site.

*Multiple common warts over temple (A)at 0 weeks, (B) at 4 weeks showing complete clearance after 2 injections of IL vitamin D3. Note the induration around the injection site [black arrow]. Erythema and induration noted around the common wart in one patient over back (C) treated with 1 injection and in other patient over dorsum of hands (D) after 2 injections.

DISCUSSION

Cutaneous warts are one of the most common infectious dermatoses encountered in dermatology clinics. Though benign, they can cause significant emotional distress due to their appearance and contagious nature, making timely and effective treatment crucial. Spontaneous clearance of warts occurring after CD4 + T cell invasion into the skin, unchecked proliferation of verrucae in patients infected with HIV, organ transplant recipients and epidermodysplasia verruciformis suggests the significance of T cell immune response in clearance of warts. This has led to the concept of immunotherapy in the treatment of warts.[4,5] Numerous immunotherapeutic modalities have been used including topical contact immunotherapy, oral zinc sulphate, cimetidine and levamisole, the results of which were below expectation.[6] Lately intralesional immunotherapy using antigens and vaccines have gained attention in accelerating the clearance of multiple treatment resistant warts. It can be tried either individually or merged with other modalities such as topical or surgical intervention.

Vitamin D3 regulates keratinocyte proliferation and differentiation and acts as an important immunomodulator. It activates TLR on macrophages similar to imiquimod. Vitamin D receptor and vitamin D1 hydroxylase genes gets stimulated thereby induces the production of antimicrobial peptide.[7] This mechanism explains the association between TLRs and innate immunity mediated by vitamin D.[8] It can be used both topically and intralesionally. Rind et al reported resolution of anogenital warts with topical calcipotriene ointment in an infant.[9] Maxacalcitol ointment and salicyclic acid sticking plaster which works under occlusion is a good option for recalcitrant cutaneous warts.[10] There are limited studies on the efficacy of intralesional vitamin D3 which contains calcitriol [active vitamin D]. It carries the advantage of inducing less hypersensitivity as they are dormant containing no organisms.

Students are the most common population affected by warts accounting for 40% of cases (n=8). This may be because of sharing clothes, involving themselves in traumatic and contact sports activities. In our study, most of the cases (n=10, 50%) had warts of less than 6 months duration which was similar to Singh et al.[11] Our study's median wart count was 6, whereas Mittal et al reported a mean count of 14.16.[12] The most common type of wart observed in this study palmoplantar warts (n=12, 60%) whereas plane warts (n=1, 5%) least common type which was similar to Singh et al and Rehna et al.[11,13]

Table 2 shows the comparison of IL vitamin D3 with various other studies. Only few have chosen vitamin D3 injection as immunotherapeutic agent. Kavya et al and Raghukumar et al have 78.57% and 90% clearance rate respectively.[14,15] In contrast, Abou-Taleb et al and Shaldoum et al reported lower response rates (21.7% and 66.7%), possibly due to differences in dosing schedule and vitamin D3 dosage. Both have used only 2L IU/2 ml or 5 mg/2 ml vitamin D3. Abou-Taleb et al had given 0.6 ml only into maximum of 3 warts once in three weeks for a total of only 3 sessions whereas Shaldoum et al had given 0.4 ml/lesion into maximum of 5 warts (total of 2 ml) for 6 sessions (higher than Abou-Taleb et al) and this may be the reason for better results in the latter.[16,17] Other studies counting ours, despite giving only 4 sessions, we used more dosage of the drug {6L IU/ml or 15 mg/ml} given more frequently {2 weeks once} providing better results.[14,15] Few studies had given lignocaine prior to IL vitamin D3 and no studies have done prior sensitization (Table 2).[16,17]

Considering the response with different types of warts, vitamin D3 had worked better for common warts and PPW showing 70% and 75% response rate respectively whereas PUW have shown only 66.7% clearance. Kavya et al have produced 77.77% and 82.60% clearance with common warts and PPW respectively [slightly higher than ours].[15] Samta et al in their study on PPW and Aktas et al [who was leading us all in intralesional vitamin D3] on plantar warts have produced 77.77% and 80% clearance rate respectively.[18,19] Priya et al in their study on PPW and PUW showed clearance in 90% palmar,

86.2% plantar and 92.9% PUW respectively, which are higher than ours.[20] Similarly, Fathy et al have reported better results with vitamin D3 [70%] than candida antigen [27%] in treating plantar warts.[21] Only one patient with plane warts was included in our study who have shown 100% clearance. More patients have to be included to ensure these results.

Fewer injections correlated with better treatment response and vitamin D3 worked better for young people as opposed to Shaldoum et al who had no relationship.[17] Regarding the duration and number of warts, we observed no relationship which is in agreement with others.[17]

Induration was the most common side effect (20%), followed by pain and erythema, highlighting the importance of careful patient selection and site-specific considerations, especially for facial areas. All these side effects are minimal which are in agreement with few studies.[14-16] Other studies reported side effects including cutaneous necrosis, pigmentary changes, nail dystrophy (6.7% in PUW treatment) and vasovagal attacks (26.7%).[13,15,7] One recurrence was noted during follow up period.

Other immunotherapeutic agents such as *Mycobacterium* W vaccine produced many side effects like severe high-grade fever, erythema, induration, swelling and injection site ulcer in one study.[22] *Mycobacterium indicus pranii* vaccine also have shown severe adverse effects like injection site atrophic scar and paresthesias distal to injection site in majority of their patients.[23]

CONCLUSION

Immunotherapy has now become one of the emerging therapeutic tools for the treatment of cutaneous warts. Intralesional vitamin D3 is promising, safe, and effective immunotherapeutic agent for treating multiple warts with minimal adverse effects. Further studies with larger sample sizes and standardized dosing schedules are needed to confirm its efficacy and determine long-term outcomes.

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