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Original Research Article

Evaluation of effectiveness of intralesional vitamin D3 injections in the treatment of warts

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Abstract

Introduction: Immunotherapy is emerging as a new modality of treatment for cutaneous warts by enhancing cell mediated immunity. Immunotherapy is replacing destructive modalities such as electrocautery and cryotherapy due to its advantages over former, such as affordability, easy availability and minimal downtime. The most common immunotherapeutic agents for warts include intralesional vitamin D3, Measles Mumps Rubella (MMR), Bacille calmette-Guerin (BCG) and Purified protein derivative (PPD).

Aim: This study aims to evaluate the safety and efficacy of intralesional vitamin D3 for the treatment of cutaneous warts.

Objectives

1. To provide better quality of life.
2. To assess the clinical response regarding the treatment given.

Material & Methods: This is a prospective observational study conducted from February 2021 to January 2022. Forty clinically diagnosed patients with cutaneous warts were taken up for the study after taking written informed consent. Patients were injected with vitamin D3 (0.2 mL, 15mg/mL) at the base of the wart after injecting with lignocaine earlier. The injections were repeated at an interval of 2 weeks for a maximum of 4 sessions or until clearance of warts, whichever was earlier. A maximum of 2-3 warts were treated per session, and patients were followed up for 6 months after the last injection.

Results: Forty patients with multiple warts were recruited for the study. Of these, 26 (65%) had palmoplantar warts, 8 (20%) were verruca vulgaris, 4 (10%) had filiform warts, and 1 (3%) periungual wart. One patient had all the types of warts. Out of these, 26 (65%) showed complete resolution, 9 (22.5%) showed moderate response and 5 (12.5%) had a mild response. Recurrence was observed in 5 (13%) patients during 6 months of follow-up. Serum vitamin D3 levels were found to be low in most patients.

Conclusion: Intralesional vitamin D3 is safe, effective, affordable and hassle-free procedure both for patients and dermatologists with minimum downtime.

Keywords: Cutaneous warts, immunotherapy, intralesional vitamin D3

Introduction

Cutaneous warts or verrucae are one of the most common skin infections caused by the human papilloma virus (HPV) [1]. Verrucae are benign epidermal proliferations of skin and mucosa. Spontaneous resolution occurs within 2 years in 65-75% of warts. Cosmetic disfigurement and pain are the major concerns to undertake treatment [1]. Various treatment modalities are available with different efficacy rates to treat verrucae, including electrocoagulation, cryotherapy, laser therapy, or topical keratolytics, which can be painful

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and may be associated with scarring and frequent recurrences [2, 3, 4, 5]. Despite having various treatment options, they are recalcitrant and frequently recur. In addition, destructive modalities are not suitable for the treatment of multiple and refractory warts as they clear only the treated lesions and not the distant ones. Hence, to overcome these shortcomings, immunotherapy is being widely for the treatment of warts [6]. Thus, there is a need to evaluate various treatment modalities.

Immunotherapy acts on the principle of enhancing cell mediated immunity for the clearance of warts [7]. Immunotherapy is a promising modality for the treatment of resistant and recurrent warts without any disadvantage of scarring and boosts the host immunity, leading to complete resolution and fewer recurrences. Immunotherapy agents that have been tried including cimetidine, imiquimod, interferons, candida albicans antigens, measles mumps rubella (MMR) vaccine, tuberculin (purified protein derivative) and intralesional vitamin D3 [8-11]. Intralesional Vitamin D3 can be an effective therapy to treat warts as few of its mechanisms of action reveal that it can alter the epidermal cell proliferation, cause upregulation of vitamin D receptor and hydroxylase genes to stimulate cytokine release and block the cytotoxic cell T cells and natural killer cells [12, 13]. So, we undertook a study to evaluate the safety and efficacy of intralesional vitamin D3 in the treatment of warts.

Material & Methods

This was a prospective observational study conducted between February 2021 and January 2022 after proper ethical committee clearance. Forty (40) clinically diagnosed patients with cutaneous warts, attending the DVL outpatient department of Mallareddy medical college, Suraram, Hyderabad were taken up for the study. Clinical history with detailed examination, relevant investigations like CBP, ESR, Vit D3 levels and written informed consent were obtained from all the patients. A total of 40 patients between 19 years to 70 years of age with single or multiple cutaneous warts with no other concurrent systemic or topical treatment were included in the study. Patients with active systemic or local infection, pregnant and lactating women patients on immunosuppressive drugs, patients with genital warts and those with keloidal tendency were excluded from the study.

The characteristics of warts such as type, size, number, presence or absence of side effects, and clinical photographs were recorded at the start of the study and at each follow up visit. A vitamin D 3 solution (6,00,000 IU, 15 mg/ml) of 0.2 -0.4ml was slowly injected into the base of each wart using an insulin syringe after infiltration with lignocaine. A maximum of 3 warts were injected per session. The injections were performed every 2 weeks until complete resolution, or for a total of 4 sessions.

Depending upon the degree of decrease in the size of the wart, the response rate was classified as a complete response, moderate response, or mild response. Complete resolution of warts was taken as a complete clearance (100%). A clearance ranging from 50% - 99% was considered a moderate response, and a mild or no response if the clearance was less than 50% [14]. Patients were followed up monthly for a period of 6 months after the last injection to detect any recurrence.

Statistical analysis

Appropriate statistical tests were applied to analyze the results. Graph pad software was used to evaluate the data significance. The results were statistically significant, with a p-value less than 0.05.

Results

Out of 40 enrolled patients, 22 were males (55%) and 18 were females (45%), with a ratio of 1.2:1. Most patients were between 18 -23 years old (53%), followed by 24-30 years (28%), with a mean age of 26 years $\pm$ 10.42. (Table 1).

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Table 1: Age and Sex distribution of study population

Age in years	Female	Male	Total	Percentage
18-23	10	11	21	53
24-30	5	6	11	28
31-40	1	2	3	8
41-65	2	3	5	13
Total	18	22	40	100
Percentage	45	55	100	

The duration of warts ranged from 1 month to 36 months, with a mean duration of 8 months $\pm$ 7.53 months. The number of warts ranged from 1 to 40. The mean number of warts was about 6 $\pm$ 8.08 (Table 2).

Table 2: Summary of demographic and clinical data

Total No of patients	40
Gender ratio (Male: Female)	1.2:1
Mean age in years	26 $\pm$ 10.42
Mean duration of disease in months	8 $\pm$ 7.53
Mean number of warts	6 $\pm$ 8.08
Mean size of warts	2 cm $\pm$ 0.73

Based on the area of distribution, 26 (65%) had palmoplantar warts, 8 (20%) patients had verruca vulgaris, 4 (10%) patients had filiform warts, 1 (3%) patient had periungual warts, and one patient had multiple warts of all four types (Table 3).

The mean range of serum vitamin D was 16.66ng/dl, with the lowest being 3ng/dl and the highest being 50ng/dl. The size of warts varied ranging from 1 cm to 3 cm, with an average of about 2 cm $\pm$ 0.73 cm seen in 70% of warts.

Complete clearance was observed in 19 out of 26 patients (73.07%) in palmoplantar warts, 4 out of 8 patients (50%) in verruca vulgaris, and 1 out of 4 in filiform warts (25%). A 100% response was noted in one case of periungual warts taken up for the study. Palmoplantar warts in a patient having all types of warts showed complete clearance. Moderate response was noted in 5 out of 26 patients (19.2%) in the palmoplantar warts, 2 out of 8 patients (25%) in verruca vulgaris, and 2 out of 4 (50%) in the filiform warts. Mild response was noted in 2 out of 26 patients (7.6 %) in the palmoplantar warts, 2 out of 8 patients (25%) in verruca vulgaris, 1 out of 4 patients (25%) in filiform warts (Table 4).

Overall, complete resolution of warts was seen in 26 out of 40 patients (65%), moderate response was seen in 9 out of 40 patients (22.5%), and a mild response was seen in 5 out of 40 patients (12.5%).

Warts were limited to one site in 11 out of 40 patients (28%) and in 29 out of 40 patients

(73%) more than one site was involved. About 7 patients (18%) had a positive family history of warts.

10 patients (25%) and 11 patients (28%) had swelling following intralesional injections.

During 6 months of follow up, 5 patients (13%) had recurrence.

Table 3: Percentage of various types of warts

Type of wart	F	m	Total	Ratio
Palmoplantar	11	15	26	65%
V. vulgaris	5	3	8	20%
Filiform wart	2	2	4	10%
Periungual	0	1	1	2.5%
Multiple	0	1	1	2.5%
Grand Total	18	22	40	100%

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Table 4: Resolution in different warts after 4 sessions of intralesional vitamin D3

Response to IL vit D3	Palmoplantar	Verruca vulgaris	Filiform	Periungual	Multiple warts	Total	%
Complete (100% clearance)	19	4	1	1	1	26	65.0%
Moderate (50-99% clearance)	5	2	2	0	0	9	22.5%
Mild (<50% clearance)	2	2	1	0	0	5	12.5%
Total	26	8	4	1	1	40	100%
Percentage	65.0%	20.0%	10.0%	2.5%	2.5%	100%	

Fig 1a: Wart over the Palmar aspect of index finger-before treatment

b) after 4th session

Fig 2a): Wart over the Plantar aspect of Great toe-Before treatment

b) after 4 sessions of treatment

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Fig 3a): Wart over the Plantar aspect of Left Foot- before treatment **b)** after 4 sessions of inections

Fig 4a): Warts over the dorsal aspect of Left foot and Left hand-before treatment **b)**

Discussion

Cutaneous warts, especially palmoplantar warts, are a major source of distress for both practitioners and patients, as no single treatment is completely effective. The destructive modalities of treatment most used are cryotherapy and electrocautery, which are usually associated with scarring and pigmentation. To overcome these side effects, immunotherapy was introduced, as it boosts the immune system against the HPV virus, leading to the clearance of both treated and untreated warts. Hence, it is replacing the other modalities and is considered an available option. Immunotherapy has a low recurrence rate.

In this present study, we used intralesional vitamin D3 injections, which is relatively a new treatment option for warts. It is believed that the vitamin D3 injection into HPV infected tissues induces a strong nonspecific proinflammatory signal and attracts the antigen presenting cells. There is a release of cytokines such as IL-2, IL-8, IL-12, IL-18, tumor necrosis factor, and interferon gamma. 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 [15]. Recently, it was observed that there is toll like 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 [16].

In our study, out of 26 patients with palmoplantar warts, 19 patients (65%) had complete resolution. Out of 8 patients with verruca vulgaris, 4 (50%) showed complete response. Out of 4 patients with filiform warts, 1 patient (25%) had complete clearance. Immunotherapy with vitamin D3 is well tolerated with minimal side effects. The common side effects noted were pain and swelling.

In a study conducted by Aktas *et al*. [17], twenty patients were given intralesional vitamin D3 for plantar warts at monthly intervals for a maximum of 2 sessions. They reported complete clearance in 80% of patients at the end of 8 weeks, which is like our study. In an open uncontrolled trial conducted by Kavya *et al*. [18], forty-two patients with multiple warts were recruited and given intralesional vitamin D. Complete response was noted in 78.6% cases. The results were comparable to our study. In a study conducted by Naresh *et al*. [19], sixty patients with multiple cutaneous warts were included in the study. 80% of patients showed complete response.

In our study complete clearance 73% was seen with palmoplantar, 100% in periungual warts, 50% in verruca vulgaris and 25% in filiform warts. Palmoplantar and periungual warts showed good response when compared to verruca vulgaris and filiform warts (Table 5).

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Table 5: Showing various studies warts prevalence, treatment modalities and outcome

Study	Year	Place	No. of patients	Type of warts	Treatment	Interval between sessions	No. of sessions	Adverse effects
Aktas *et al.,* [17]	2016	Turkey	20	Plane warts	Vitamin D3+lignocaine	4 weeks	2	Pain
Kavya *et al.* [18]	2016	Karnataka	42	Verruca vulgaris Palmoplantar warts	Vitamin D3+lignocaine	2 weeks	4	Swelling pigment on
Naresh *et al.* [19]	2019	Vijayawada	60	Verruca Vulgaris, palmoplantar warts, filiform and periungual warts	Vitamin D3	3 weeks	4	Mild moderate pain, swelling
Present study	2021	Hyderabad	40	Verruca Vulgaris, palmoplantar warts, filiform warts, periungual warts	Vitamin D3+lignocaine	2weeks	4	Mild p and swelling

Marvin *et al.* [20] observed a good response on treatment of common and palmoplantar warts with higher vitamin D3 dosage. Intralesional therapy with vitamin D3 revealed mild side effects such as local pain, swelling and erythema.
Sonia Raghukumar *et al.* [6] documented a complete response in 54 of 60 (90%), partial response in 4 of 60 (6.66%) and no response in 2 of 60 (3.33%). The average number of injections required to achieve a complete resolution was 3.66. Complete resolution of distant warts was noticed in all patients. Ghada Fathy *et al.* [21] did a study on comparison of intralesional vitamin D3 and candida antigen on multiple recalcitrant warts, showed a good clinical response to vitamin D3 when compared to candida antigen. Various modalities have been observing in the latest decades to reduce warts incidence, may require more focused multifactorial analysis and research works on treatment modalities to curb this disease.

Limitations: Small sample size and lack of control group can be limiting factors for our study.

Conclusion

Vitamin D3 is found to be well tolerated and moderately effective and inexpensive. It is effective both for treated and distant warts, it is a safe and hassle-free procedure with no major side effects. In our study intralesional vitamin D 3 injections were more effective in palmoplantar warts and periungual warts. With its advantages over destructive procedures like low cost, easy availability and minimal down time it's been considered as one of the preferred treatment modalities.

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Conflict of interest: None declared

Ethical approval: The study was approved by the institutional ethics committee.

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