

Original Research Article

Role of intralesional vitamin D3 in cutaneous warts: an interventional study

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ABSTRACT

Background: Cutaneous warts are treated primarily with destructive methods such as cryotherapy or electrocautery. These modalities of treatment may be associated with recurrence and scarring in multiple warts. This study aims to evaluate the efficacy and safety of intralesional vitamin D3 in warts.

Methods: 88 patients with recalcitrant warts of varying sizes and duration were included in the study. About 0.2 to 0.5 ml vitamin D3 solution (600,000 IU, 15 mg/ml) was injected to the base of the wart. A maximum of 5 warts were injected per session at 3-week intervals until resolution or for a maximum of 4 treatments. Patients were followed up for 6 months after the last injection to detect any recurrence.

Results: 88 patients completed the study. Complete response was seen in 63 out of 88 (71.5%), partial response in 24 out of 88 (27.2%), and no response seen in one patient. The average number of injections required to achieve a complete resolution was 3.66. Complete resolution of distant warts was noticed in all the patients.

Conclusions: Intralesional vitamin D3 is a safe, effective, and an inexpensive treatment option for recalcitrant warts.

Keywords: Multiple warts, Vitamin D3, Immunomodulation, Immunotherapy

INTRODUCTION

Verruca vulgaris (viral warts) is a fairly common condition with a plethora of treatment options having variable success rates. Recalcitrant warts are refractory to treatment with often disappointing response and high recurrence rates. Warts are usually treated by traditional destructive modalities like topical keratolytics, electrocoagulation, cryotherapy, or laser therapy.¹⁻⁴ All of these treatment options can be painful, and may be associated with scarring and frequent recurrence. Lately, treatment with intralesional injections has gained momentum due to its effectiveness in clearing warts by enhancing the cell mediated immunity.⁵ In recent years, treatment of warts have included different

immunotherapeutic agents like autogenous vaccine *Candida albicans* antigen, mumps, measles and rubella (MMR) vaccine, BCG vaccine, *Mycobacterium w* vaccine and interferon alpha and gamma injection.⁶⁻⁹ Topical vitamin D has been successfully used for the treatment of warts in some cases.¹⁰⁻¹³ However, intralesional vitamin D3 injection was tried first time by Aktas et al reported encouraging results.¹⁴ Herein, we report the treatment response of intralesional vitamin D3 injections for the treatment of cutaneous warts.

METHODS

The study was conducted out in department of dermatology UPUMS, Saifai, Etawah from July 2018 to

June 2019 (one year). A total of 88 patients were enrolled in the study after inclusion and exclusion criteria were satisfied. Patients with single or multiple viral warts, with no prior treatment with either systemic, topical, intralesional or destructive modalities for at least 6 months prior or those who were recalcitrant to the treatment were primarily selected for the study. Patients of less than 12 or greater than 70 years, pregnant and lactating females, patient with keloidal tendencies, patient having local or systemic infections, immuno-suppressed individuals, patients who have received any other treatment of warts in the past three months before enrolment were excluded from the study. Baseline evaluation were made at first visit, and the demographic data were recorded in a structured questionnaire designed for this study. A graphical wart map was prepared for each patient: site, size, number and type of wart were recorded on it at each visit. Photographs were taken on each visit to support the recorded data.

Method of administration of vitamin D3

About 0.5 ml of vitamin D3 solution (600,000 IU, 15 mg/ml) was injected longitudinal to the wart. A maximum of 4 warts (largest size warts) per session were injected at 3-week interval until resolution or maximum for 4 sessions. Clinical response was documented by decrease in number and size of the lesions at each visit. Complete clearance was considered if all the warts both treated and distant resolved completely. Moderate response if there were 50% to greater than 100% reduction in both size and number of lesions, mild response was considered if response was in between 1% and less than 50%. Patient were evaluated for treatment efficacy and adverse reactions every 2 weeks for first 2 months and monthly thereafter to record for any recurrence for 6 months.

RESULTS

A total of 88 patients received intralesional vitamin D3 injections during a period of one year. Among 88 patients, 56 were males and 32 were females (Figure 1). Age of the patients ranged from 14 to 62 years, with a mean of 22.6 years. 57 (64.7%) patients have verruca vulgaris, among them 36 were males, 25 (28.4%) patients have palmo-plantar warts, 6 (6.8%) patients have filiform warts predominantly over face. The duration of warts ranged from 1 month to 5 years (mean 2.3 years). The dimensions of the warts ranged from 1×2 mm to 22×30 mm. The number of warts ranged from 1 to <20. Out of 88 patients, 6 patients had single wart, 23 patients had 2-5 warts and 59 patients had more than 5 warts. Minimum number of warts is one that was seen in 6 patients, and maximum number of warts was 22, seen in one patient. The study showed that out of 88 patients, 63 (71.5%) showed complete clearance while 24 patients (27.2%) showed mild to moderate clearance, one patient showed no response. The mean number of intralesional vitamin D3 injections required for complete response which was

seen in 63 patients was 5. Representative patients showing complete response are depicted in (Figures 2-4).

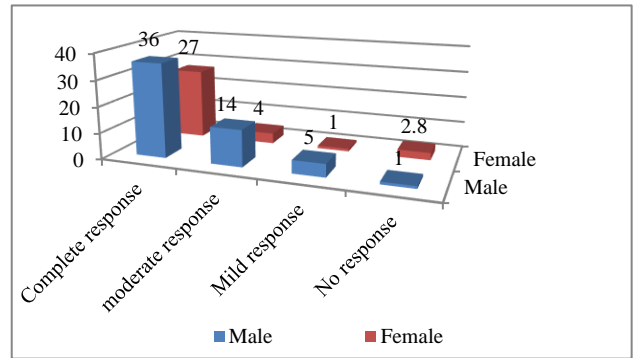


Figure 1: Results after the completion of injection vitamin D3 in both males and females.



Figure 2 (A and B): Pre and post treatment photograph.



Figure 3 (A and B): Pre and post treatment photograph.

Adverse effects were seen in 34 (80%) patients, but all were minor with no life-threatening complications. Pain at the site of injection was the most common adverse effect seen in 12 (13.6%) patients which resolved without any treatment in 2 weeks. Dyspigmentation was seen in three patients. Recurrence was observed in four patients with palmo-plantar warts during 6 month of follow-up period (Figure 5). In four patients having palmo-plantar wart, after four injections all the warts regressed, in one patient's recurrence was seen in three weeks after the last session of injection whereas, in three patient's recurrence

were seen in 3 to 6 weeks after last session of intralesional vitamin D3 injection.

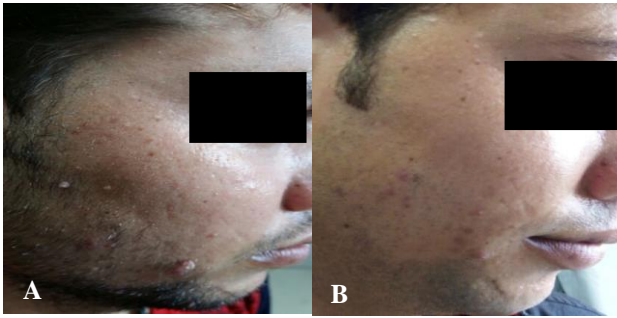


Figure 4 (A and B): Pre and post treatment photograph.

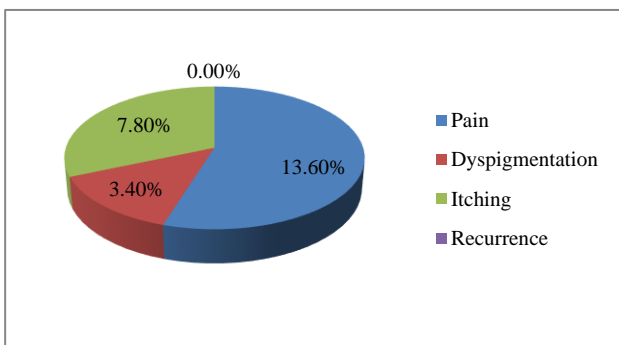


Figure 5: Percentage of patients showing adverse effects after intralesional vitamin D3 injections.

Table 1: Clinical response in various types of warts.

Treatment response	Palmo-plantar warts (n=25)	Verruca vulgaris (n=57)	Filiform warts (n=6)
Complete response (100%)	18	42	03
Moderate response (50% to <100%)	04	12	02
Mild response (1% to <50%)	02	03	01
No response	01	--	--

DISCUSSION

Treatment of cutaneous warts especially recalcitrant palmo-plantar warts is very difficult and it require multidisciplinary modalities like cryotherapy and electrocautery. These modalities are usually associated with pain, scarring and recurrence. Hence, immunotherapy is the best available option in treating warts which includes various antigens and vaccines such as purified protein derivative (PPD), MMR, *C. albicans* and *Mycobacterium w* vaccine.⁸⁻¹⁸ These treatments are considered immunotherapy as they are thought to recognize the HPV virus, leading to clearance of both

treated and untreated warts. Recurrence rate is also low when compared to destructive methods.¹⁹ In this present study, we used intralesional vitamin D3 which was a relatively new treatment option for warts with minimal side effects.

The exact mechanism of intralesional vitamin D3 for the treatment of warts remains unexplained: however, it controls cell proliferation and differentiation and has immunoregulatory activities. Its effects are mediated via the vitamin D receptor (VDR), which is present in keratinocytes, melanocytes, fibroblasts, and immune system cells of the skin leads to the induction of antimicrobial peptide expression.²⁰ Some studies 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.

In several studies topical vitamin D has been used for the treatment of common and anogenital warts. Moscarelli et al successfully treated refractory warts with calcitriol in a renal transplant recipient.¹⁰ Rind et al reported the successful clearance of an anogenital wart in an infant with topical administration of vitamin D.¹¹

Intralesional vitamin D3 has been previously used by Aktas et al on 20 patients having recalcitrant wart showing that 80% patient have complete clearance with no recurrence during follow up. Similar results were obtained by Kavya et al in 2016 on 42 patients, patients received intralesional vitamin D3 at an interval of 2 weeks.²¹ Complete response was seen in 78.5% and recurrence were shown in 2.38% which is in concordance with present study. In this study intralesional vitamin D3 was given to 88 patients with viral wart. Out of 88 (63) i.e. 71.5% experienced complete resolution while twenty-four patients have partial response and one patient failed to show any response. Raghukumar et al noted pain at the site of injection as the main side effects of intralesional vitamin D3 which is similar to our study, while in Kavya et al study main side effect was swelling at the injection site and pigmentary changes (Table 2).^{21,22}

Various other studied conducted on the treatment of warts considering antigens or vaccines as immunotherapy, their response is shown in (Table 3). The response rate achieved in present study was 71.5% in maximum of 4 sessions which was superior to the results achieved with *Bleomycin*, MMR vaccine, *C. Albicans* antigen. However, treatment with PPD (76%) and *Mycobacterium w* vaccine (93%) was superior to that of vitamin D3. but the number of sessions in *Mycobacterium w* vaccine was more i.e., 10 as compared to our study which was 4. Hence, higher response rate reported in the Garg et al study can be attributed to a greater number of sessions.⁸ Furthermore, they reported systemic and local complications such as high-grade fever and redness, swelling and ulcer formation at the injection site. Hence, compared to these adverse effects, we did not experience

any serious systemic and local complications. Only side effects noted was pain at the site of injection, dyspigmentation and itching which needed no

medications hence it is very safe procedure than *Mycobacterium w* vaccine.

Table 2: Comparison of present study with other study conducted on vitamin D3.

Study	No. of patients	Treatment	Interval between sessions	Maximum no. of sessions	Side effects	Results (%)
Aktas et al ¹⁴ 2014	20	Intralesional vitamin D3 + lignocaine	4 weeks	2	Pain at the site of injection	CR=80 R=0
Kavya et al ²¹ 2016	42	Intralesional vitamin D3 + lignocaine	2 weeks	4	Swelling at injection site and pigmentary changes	CR=78.5 R=2.38
Ghamdi et al ¹² 2017	64	Intralesional vitamin D3 + lignocaine	3 weeks	3.66	Pain at the site of injection	CR=90 R=1.4
Present study 2019	88	Intralesional vitamin D3 + lignocaine	3 weeks	4	Pain at the site of injection	CR=71.5 R=4.5

(CR=Complete response, R= Recurrence).

Table 3: Comparing other studies with present study to see response rate of various antigens or vaccine.

Study	Antigen or vaccine	No. of sessions	Clearance rate (%)
Garg et al ⁸	<i>Mycobacterium w</i> vaccine	10	93
Sajoi et al ¹⁵	PPD	4	76
Nofal et al ¹⁷	MMR vaccine	5	53
Majid et al ⁹	<i>Candida</i> vaccine	3	56
Present study	Intralesional vitamin D3	4	71.5

CONCLUSION

Intralesional vitamin D3 injection is an innovative option for warts that are recalcitrant to conventional treatments. It is a simple, well-tolerated treatment method with minimal side effects, that is easy to administer in outpatient clinics. Intralesional vitamin D3 is very effective for verruca-vulgaris both for the treated and distant warts. Less efficacious for palmo-plantar wart. Although our study limitations were its small sample size and lack of randomisation, the results are encouraging. However, the efficacy of this therapy for the treatment of refractory warts requires further evaluation in larger randomized, placebo controlled, clinical trials.

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

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