

## Effectiveness of Intralesional Vitamin D3 in Cutaneous Warts

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**Abstract: Background:** Verruca vulgaris is a common viral infection of the skin caused by human papillomavirus that often causes significant discomfort and embarrassment. Several destructive methods are available for treatment with variable success and may result in scarring, while less aggressive approaches can lead to lesion recurrence. Additionally, these local modalities are not practical for patients with a large number of warts. Much research were performed to evaluate the various immunomodulators intralesionally to treat cutaneous warts. Intralesional vitamin D3 has been reported as a successful treatment of warts.

**Aims:** To evaluate the efficacy of intralesional vitamin D3 treatment for cutaneous warts.

**Materials and Methods:** This study considered 36 patients aged between 18 and 70 years who presented with single or multiple cutaneous warts, varying in size and duration, and who had not received immunosuppression drugs 6 months before starting this study. About 0.2 to 0.5 mL of vitamin D3 solution (600,000 IU; 15 mg/mL) was injected at the base of the wart following a lidocaine (0.2 mL, 20 mg/mL) injection. A maximum of 5 warts would be treated in a session set at 4 weeks for a maximum duration of 4 treatments until resolution. Both pre-and two-month post-intervention standardized photographs were taken. Patients were followed for 6 months after the last injection to see if they had any recurrence. Response was later categorized into complete, partial, or no response. Complete clearance of the injected wart target was recorded in 33.3% of patients in the case group, while only 5% of patients did so in the control group ( $p \leq .001$ ), and that was statistically significant. Therefore, intralesional injection of vitamin D3 may be a plausible and safe intervention for treating common warts. Clinical assessment was by photographic evaluation at baseline, before and after each treatment session, and on completion of treatment.

The results are presented below. A total of 36 patients with cutaneous warts were included in the study. Of the total number of patients, 24 (66.7%) were male and 12 (33.3%) were female. Among the 36 patients, 22 (61.1%) had palmoplantar warts, 10 (27.8%) had common warts (verruca vulgaris), and 4 (11.1%) had filiform warts. The mean age of the patients was  $34.31 \pm 11.33$  years (range, 18 to 58 years). A total of 12 patients (33.3%) exhibited complete clearance of the warts. Out of the total 22 patients with palmoplantar warts, complete clearance was observed in 6 (27.3%). In the group of 4 patients with filiform warts, complete clearance was observed in 3 (75%). In the group of 10 patients with verruca vulgaris, complete clearance was observed in 3 (30%), completing the clearing process at the fourth visit. Thus, of the 36 patients, 12 (33.3%) exhibited a complete response, 8 (22.2%) demonstrated a moderate response, 7 (19.4%) displayed no response, and 9 (25%) were classified as non-responders. Recurrences were observed in six patients (16.7%). Among these, five patients (83.5%) who smoked exhibited a higher recurrence rate. No serious adverse effects were reported.

**Conclusion:** Intralesional injection of vitamin D3 may be considered safe, effective, well-tolerated, easily administrated in outpatient clinics and an inexpensive treatment and safe modality for the treatment of common warts.

**Limitations:** Small study samples and lack of a control group was the main drawbacks in our study.

**Keywords:** Cutaneous wart; immunotherapy; intralesional; cutaneous warts; vitamin D3.

## Introduction

Verruca vulgaris, or warts, are the result of an infection by the human papillomavirus (HPV) and are classified as non-malignant epithelial proliferations of the skin and mucous membranes. It is inevitable that almost all individuals will encounter warts in some form during their lifetime. The virus is transmitted directly from infected individuals or through the use of contaminated materials and surfaces. Although spontaneous resolution occurs in 65%–78% of warts within two years, cosmetic disfigurement, propensity for spread, and poor quality of life dissuade patients from pursuing this course of action. (1, 2) The conventional treatment of warts employs one of two principal therapeutic modalities. The first of these is a conventionally destructive and aggressive method that incorporates electrocoagulation, topical keratolytic agents, cryotherapy, local injection of bleomycin, and laser ablation. However, the efficacy of these approaches is inconsistent, with the majority of patients exhibiting resistant warts. These are often treated with painful procedures that result in scary and recurrent problems. The alternative therapeutic approach is immunotherapy, which is based on the premise that enhanced cell-mediated immunity against human papillomavirus will result in the resolution of warts. (3, 4) This therapeutic modality may be administered topically, intralesionally, or systemically. (5-8) Selecting an appropriate treatment for a specific and unique case is often challenging due to the numerous treatment options available and the varying immune statuses of individual patients. Furthermore, a history of multiple warts or treatment-resistant warts is often associated with defective cell-mediated immune responses. (9) This study by Naglaa et al. demonstrated that patients suffering from viral warts have significantly lower serum vitamin D levels, which is relevant to the role that vitamin D plays in systemic, topical, and intralesional therapy. (10) There are only a few studies in the literature that have demonstrated the efficacy of topical vitamin D3.

## Materials and Methods

This prospective, cross-sectional, randomised study was conducted between November 2020 and November 2021 at the Department of Dermatology and Venereology, Multi-centers (Shirqat General Hospital, Salah Al-Deen, Zafaraniyah General Hospital, Baghdad). The study participants were recruited through a process of volunteer recruitment. The study cohort comprised 36 patients with cutaneous warts. Prior to their participation in the study, all subjects provided written informed consent. The study was approved by the Ethical Committee of the Ministry of Health. A baseline evaluation was conducted at the initial visit, and a structured questionnaire designed for this study was utilized to document demographic information. Photographic documentation was undertaken of all lesions at the baseline visit, with subsequent images taken at monthly intervals until the conclusion of the study and at the end of the follow-up period. A graphical representation of the warts was prepared for each patient, with the location, number, size, and type of wart recorded at each visit. Photographic documentation was undertaken at each visit to provide additional support for the recorded data. The clinical response was documented by measuring the decrease in the number of wart lesions per visit. Complete clearance was defined as the complete resolution of all treated and distant warts. A moderate response was defined as a reduction in the number of lesions by between 50 and 100%. A mild response was considered if the response was between 1% and 50%. If complete clearance occurred before a subject received four injections, the therapy was stopped, and the patient was followed up at six months for recurrence.

## Inclusion Criteria:

The following criteria must be met in order for an individual to be considered for inclusion:

- The subject must be between the ages of 18 and 70 years.

- The patient must have been diagnosed with one or more cutaneous warts by the examining physician at the baseline visit based on the typical diagnostic characteristics.
- The subject provided consent and expressed willingness to participate in the present study.
- Additionally, both recalcitrant and non-recalcitrant warts will be included in the study.

The following criteria will result in exclusion from the study:

### **Method of administration of Vitamin D3 injection**

Vitamin D3 for injection is available in vials containing 600,000 IU of cholecalciferol in 1 ml (15 mg). The selected warts were injected first with 0.2 ml of lignocaine (20 mg/ml); after a few minutes, 0.2 ml of Vitamin D3 (15 mg/ml) was slowly injected into the base of each wart with a 27-gauge syringe. Posttreatment, the patients were advised not to use any topical and oral medications. A maximum of 5 warts was treated in one session. The injections were repeated at four weekly intervals for a maximum of four injections.

### **Statistical analysis**

Statistical analyses were done using SPSS version 23 (Statistical Package for Social Sciences). The P-value of <0.05 was considered statistically significant.

### **Results**

The present study was conducted on a cohort of 36 patients presenting with viral warts. Of the participants, 24 (66.7%) were male and 12 (33.3%) were female. Of the patients, 22 (61.1%) exhibited palmoplantar warts, 10 (27.8%) displayed common warts (*verruca vulgaris*), and 4 (11.1%) presented with filiform warts. The mean age was  $34.31 \pm 11.33$  years. The number of warts per patient ranged from one to nineteen, with an average of  $6.36 \pm 4.34$ . The duration of the warts exhibited considerable variation, with a minimum duration of six months and a maximum duration of 36 months. The mean duration was calculated to be  $18.56 \pm 9.28$  months. Two-thirds of the patients (26) were non-smokers, while four patients (11.1%) smoked less than two packs of cigarettes per day, and six patients (16.7%) smoked more than two packs of cigarettes per day. (Table 1)

Similar observations were noted for the smoking status at the time of presentation. However, no statistically significant correlations were identified between this variable and the age of patients or the number of lesions. The corresponding P-values were 0. The correlation between smoking status and the duration of the disease was significant (P-value = 0.008), with a positive correlation between smoking and disease duration. (Table 2)

The youngest age group (18-28 years) demonstrated a 33.3% complete clearance rate, which increased to 50% in the next age category (29-38 years). Complete clearance was observed in 16.7% of cases in the 39-48 age category, rising to 20% in the 49-58 age category. However, no statistically significant differences were identified across all groups at each visit. (Table 3)

A total of 22 patients presented with palmoplantar warts, of whom 6 (27.3%) achieved complete clearance. Complete clearance was achieved by 3 (75%) of the four patients with filiform warts and by 3 out of 10 (30%) patients with *verruca vulgaris* at the fourth visit. Of the 36 patients with warts, 12 (33.3%) exhibited total clearance (Table 4).

No significant adverse effects were identified. The adverse effects were relatively minor and did not include any life-threatening complications. Pain at the time of injection was observed in nearly all cases while swelling at the site of injection was the second most common adverse effect, occurring in 24 (67%) patients. This had been resolved spontaneously after four to six weeks. Two patients exhibited evidence of dyspigmentation .

Patients were monitored for a period of six months following the administration of the final injection. During this time, six patients (16.7%) experienced a recurrence of their condition. No statistically significant difference was observed between age groups in the number of recurrences (P-value 0.152).

The recurrence rate was 13.6% (3/19) in patients with palmoplantar warts and 30% (3/10) in patients with common warts. No recurrence was observed in patients with filiform warts. (Tables 5 & 6) In a total of six patients, recurrence was noted in four (66.7%) of them: those who were habitual smokers of more than two packs per day, one (16.7%) for each non-smoker and smoker of less than two packs per day. A highly significant difference was observed among the groups (P-value 0.001). (Table -7) No significant difference was observed between recurrence and sex, duration of the disease, and number of lesions (P-values 0.343, 0.240, and 0.082, respectively, Table 5). Between visits for palmoplantar wart and common wart, the paired t-test was highly significant, while no significant differences were observed across all these visits regarding filiform wart. (Table -8)

**Table 1: Summary of Demographic and Clinical Data**

Demographic and Clinical data	N	%
<b>Total patients</b>	<b>36</b>	<b>100%</b>
<b>Gender (m: f) ratio</b>	<b>2:1</b>	
• Male	<b>24</b>	<b>66.7 %</b>
• Female	<b>12</b>	<b>33.3 %</b>
<b>Mean age in years</b>	<b>34.31±11.33</b>	<b>18-58 years</b>
<b>Mean duration in months</b>	<b>18.56±9.28</b>	<b>6-36 months</b>
<b>Mean number of warts</b>	<b>6.36±4.34</b>	<b>1-19</b>
<b>Number of warts</b>		
• Single	<b>5</b>	<b>13.9 %</b>
• Multiple	<b>31</b>	<b>86.1 %</b>
<b>Type of wart</b>		
• Palmoplantar Warts	<b>22</b>	<b>61.1 %</b>
• Filiform wart	<b>4</b>	<b>11.1 %</b>
• Common wart	<b>10</b>	<b>27.8 %</b>
<b>Smoking</b>		
• Nonsmoker	<b>26</b>	<b>72.2 %</b>
• Smoker < 2 packs per day	<b>4</b>	<b>11.1 %</b>
• Smoker > 2 packs per day	<b>6</b>	<b>16.7 %</b>

**Table -2: Descriptive statistics according to smoking Status**

Smoking Status		Age	Duration	No. of Lesions
Nonsmoker	Mean±SD	<b>32.81±10.46</b>	<b>17.08</b>	<b>5.65</b>
	N	<b>26</b>	<b>26</b>	<b>26</b>
Smoker < 2 packs per day	Mean±SD	<b>23.75±2.63</b>	<b>22.75</b>	<b>6.75</b>
	N	<b>4</b>	<b>4</b>	<b>4</b>
Smoker > 2 packs per day	Mean±SD	<b>47.83±5.27</b>	<b>22.17</b>	<b>9.17</b>
	N	<b>6</b>	<b>6</b>	<b>6</b>
<b>P-value</b>		<b>0.090</b>	<b>0.008</b>	<b>0.395</b>

**Table -3: Clearance according to age groups**

Visits	Clearance	Age Group								P-value
		18-28 years		29-38 years		39-48 years		49-58 years		
		N	%	N	%	N	%	N	%	
Visit 2	No	7	46.7%	2	20%	4	66.7%	2	40%	0.495
	Mild	7	46.7%	6	60%	2	33.3%	3	60%	
	Moderate	0	0.0%	0	0.0%	0	0.0%	0	0.0%	
	Complete	1	6.7%	2	20%	0	0.0%	0	0.0%	
	Total	15	100%	10	100%	6	100%	5	100%	
Visit 3	No	6	40 %	1	10%	1	16.7%	1	20%	0.476
	Mild	4	26.7%	2	20%	1	16.7%	3	60%	
	Moderate	3	20%	4	40%	3	50.0%	1	20%	
	Complete	2	13.3%	3	30%	1	16.7%	0	0.0%	
	Total	15	100%	10	100%	6	100%	5	100%	
Visit 4	No	6	40%	1	10%	1	16.7%	1	20%	0.269
	Mild	3	20%	0	0.0%	2	33.3%	2	40%	
	Moderate	1	6.7%	4	40%	2	33.3%	1	20%	
	Complete	5	33.3%	5	50%	1	16.7%	1	20%	
	Total	15	100%	10	100%	6	100%	5	100%	

**Table -4: Clearance according to type of wart.**

Clearance		Type of Wart							
		Palmoplantar Warts		Filiform wart		Common wart		Total	
		N	%	N	%	N	%	N	%
Visit 2 .004	No	11	50.0%	2	50.0%	1	10.0%	14	38.9 %
	Mild	9	40.9%	0	0.0%	9	90.0%	18	50.0 %
	Moderate	0	0.0%	0	0.0%	0	0.0%	0	0.0%
	Complete	2	9.1%	2	50.0%	0	0.0%	4	11.1 %
Visit 3 .000	No	7	31.8%	1	25.0%	0	0.0%	8	22.2 %
	Mild	8	36.4%	0	0.0%	2	20.0%	10	27.8 %
	Moderate	3	13.6%	0	0.0%	8	80.0%	11	30.6 %
	Complete	4	18.2%	3	75.0%	0	0.0%	7	19.4 %
Visit 4 .317	No	7	31.8%	1	25.0%	1	10.0%	9	25.0 %
	Mild	5	22.7%	0	0.0%	2	20.0%	7	19.4 %
	Moderate	4	18.2%	0	0.0%	4	40.0%	8	22.2 %
	Complete	6	27.3%	3	75.0%	3	30.0%	12	33.3 %

**Table -5: Recurrences according to age groups.**

Recurrence	Age Group									
	18-28 years		29-38 years		39-48 years		49-58 years		Total	
	N	%	N	%	N	%	N	%	N	%
No	13	36.1%	10	27.8%	4	11.1%	3	8.3%	30	83.3%
Yes	2	5.6%	0	0.0%	2	5.6%	2	5.6%	6	16.7%
Total	15	41.7%	10	27.8%	6	16.7%	5	13.9%	36	100.0%

P-value 0.152

**Table -6: Recurrences according to type of wart.**

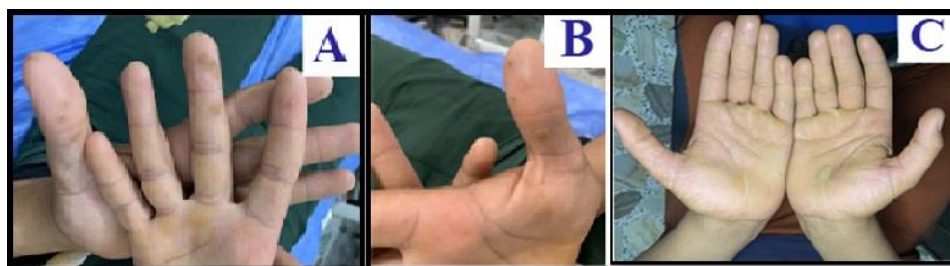
Recurrence	Type of Wart					
	Palmoplantar Warts		Filiform wart		Common wart	
	N	%	N	%	N	%
No	19	86.4%	4	100.0%	7	70.0%
Yes	3	13.6%	0	0.0%	3	30.0%
Total	22	100.0%	4	100.0%	10	100.0%

**Table -7: Recurrences according to smoking status.**

Smoking status	Recurrence					
	No		Yes		Total	
	N	%	N	%	N	%
Nonsmoker	25	83.3%	1	16.7%	26	72.2%
Smoker < 2 packs per day	3	10.0%	1	16.7%	4	11.1%
Smoker > 2 packs per day	2	6.7%	4	66.7%	6	16.7%

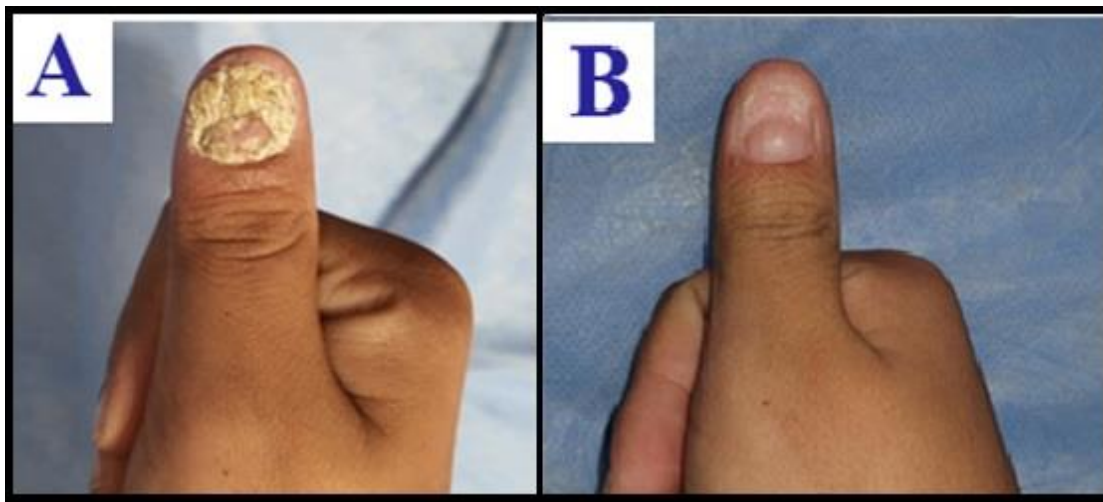
**Table -8: Paired T-test according to type of warts.**

Type of Wart	Visits	Mean	SD	t	df	Sig.
All types	1st - 2nd Visit	1.72	2.05	5.04	35	0.001
	1st - 3rd Visit	2.53	2.12	7.12	35	0.001
	1st - 4th Visit	2.94	2.65	6.67	35	0.001
Palmoplantar Warts	1st - 2nd Visit	1.18	1.59	3.48	21	0.002
	1st - 3rd Visit	2.05	1.89	5.08	21	0.000
	1st - 4th Visit	2.55	2.39	5.01	21	0.000
Filiform wart	1st - 2nd Visit	0.50	0.58	1.73	3	0.182
	1st - 3rd Visit	0.75	0.50	3.00	3	0.058
	1st - 4th Visit	0.75	0.50	3.00	3	0.058
Common wart	1st - 2nd Visit	3.30	2.41	4.38	9	0.002
	1st - 3rd Visit	4.20	1.93	6.87	9	0.001
	1st - 4th Visit	4.50	3.03	4.70	9	0.001

**Figure- 1:** Multiple Refractory Palmar warts before treatment (A & B). Complete clearance after four injections of intralesional Vitamin D3(C).



**Figure- 2:** Cutaneous Planter warts before (A, C & E) and after (B, D &F) treatment for three patients.



**Figure 4:** (A) Periungual wart before treatment. (B) Complete clearance after four injections



**Figure 6:** Hypopigmentation after complete clearance.

## Discussion

Verruca vulgaris is a well-known viral skin disease caused by HPV that can appear at any age, and prognosis cannot be predicted. In some patients, they may spontaneously disappear, whereas others show persistence and progression with spread to other body sites, leading to physical and emotional distress to the patients. There are multiple treatment options of variable success rates. Previously, cutaneous warts were treated by destructive methods like electrocautery, keratolytics, and cryotherapy. These methods were associated with many side effects like scarring, hyperpigmentation, or hypopigmentation. (3, 4, 22)

Nowadays, immunotherapy is a new available treatment option which acts on enhancing cell-mediated immunity against HPV, leading to clearance of both treated and untreated warts. Such therapy may be applied either topically, through intralesional injection, or through systemic administration. Immunotherapy has been tried with various antigens and vaccines such as systemic, topical, and intralesional vitamin D, bleomycin, PPD, MMR, *Candida albicans*, and *Mycobacterium* vaccine. (10-13, 22-27)

Low vitamin D levels may play an etiological role in the development of verruca vulgaris. Naglaa et al. and Coşkun et al. studies revealed low levels of serum vitamin D in patients with warts, suggesting a possible role for vitamin D as a supplement in treating patients with viral warts. Intralesional Vitamin D3 injection was tried for the first time at 2016 by Aktas et al. (13). They used intralesional Vitamin D3 for plantar warts and reported complete clearance in 80% of patients at the end of 8 weeks. Although several studies have reported favorable results with intralesional vitamin D analogs in skin warts, the role of vitamin D insufficiency in the pathogenesis of verruca vulgarism is unknown. (10, 28). This present work showed the efficacy of intralesional Vitamin D3 as a new treatment modality for cutaneous warts.

In our study, the majority (61.1%) of patients had palmoplantar warts, followed by (27.8%) common warts and then (11.1%) filiform warts. In our study, 33.3% of patients showed complete clearance, and 22.2% of patients showed moderate clearance at the end of 4 months. These results are comparable to



studies done by Essam Elden et al. (complete response was 35.5%)<sup>(29)</sup> Ibrahim M et al. and El-Taweel et al. (complete response was 40%).<sup>(30, 31)</sup> Other studies showed a higher complete clearance percentage from 63.3% up to 90%, as shown in **Table- 9**.<sup>(13, 22, 28, 29, 33-38)</sup>

**Table -9: Comparison with various studies**

Study	No. of cases	Interval	Max. sessions	Results
<b>Raghukumar</b> <sup>(32)</sup>	64	3 weeks	4	CR-90%
<b>Muhammad et al.</b> <sup>(33)</sup>	64	4 weeks	2	CR- 85.6%
<b>Aktas et al</b> <sup>(13)</sup>	20	4 weeks	2	CR-80%; R0.0%
<b>Abd El-Magid et al</b> <sup>(34)</sup>	20	-	-	CR- 80%
<b>Naresh et al</b> <sup>(35)</sup>	40	3 weeks	4	CR-80%; R6.6%
<b>Kavya et al</b> <sup>(22)</sup>	62	2 weeks	4	CR-78.5%
<b>Sushmalatha et al.</b> <sup>(36)</sup>	13	3 weeks	4	CR- 76.92%
<b>Khan Farhana</b> <sup>(28)</sup>	10	2 weeks	-	CR- 70%; R- 0.0%
<b>Shaldoum et al.</b> <sup>(37)</sup>	30	3 weeks	6	CR-66.7%; R0.0%
<b>Yousaf et al</b> <sup>(38)</sup>	30	2 weeks	3	CR-63.3%
<b>El-Taweel et al.</b> <sup>(31)</sup>	20	4 weeks	2	CR-40%
<b>Ibrahim et al.</b> <sup>(30)</sup>	30	4 weeks	2	CR-40%
<b>Essam Elden et al</b> <sup>(29)</sup>	62	2 weeks	4	CR- 35.5%
<b>Our study</b>	<b>36</b>	<b>4 weeks</b>	<b>4</b>	<b>CR-33.3%; R16.7%</b>

CR- Complete clearance; R- Recurrence

The clearance rates in our study were different from the previous studies, which can be explained by the changes in the number of patients, type of the wart, and the concentration of vitamin D3.

Among types of warts, the filiform wart was the most common type that responds to intralesional vitamin D with 50% complete clearance at 2<sup>nd</sup> visit and 75% complete clearance at 3<sup>rd</sup> visit, while palmoplantar wart needs four visits to reach 27.3% complete clearance, and common warts need also four visits for 30% complete clearance. Kavya M et al. showed complete clearance in 82.60% of palmoplantar warts and 77.77% of common warts after four sessions with two weekly intervals.<sup>(22)</sup> This may be explained with the small number of patients with filiform warts, and all of them were had single lesions. Our study showed 83.3% complete clearance of warts for patients aged less than 38 years but still statistically not significant. This result agreed with El-Taweel AE et al. study that showed aging may reduce the efficacy of intralesional vitamin D.<sup>(31)</sup>

Smoking was associated with a high duration of lesions and more recurrences after treatments (66.7%). Cigarette smoking may decrease serum levels of vitamin D and reduce its efficacy. However, smoking reduces the efficiency of intralesional vitamin D, and this result is agreed with El-Taweel AE et al study.<sup>(31)</sup>

The precise mechanism of action of vitamin D in wart clearance remains unclear. However, it is hypothesised that injecting HPV-infected tissues creates a robust, non-specific, pro-inflammatory signal that recruits antigen-presenting cells to the site. This action would be followed by the release of several cytokines, including IL-2, IL-8, IL-12, IL-18, tumour necrosis factor- $\alpha$ , and interferon- $\gamma$ , through the VDR-dependent pathway. The enhanced proliferation of peripheral mononuclear cells towards the Th1 cytokine response naturally augments cytotoxic T cells and natural killer cells, which are responsible for destroying HPV-infected cells (22, 29, 35 & 39).

The minor adverse effects observed included pain, swelling, and dyspigmentation. However, there were no major complications requiring intervention. This finding aligns with the safety profile of this procedure, as reported in numerous previous studies (22, 30, 31, 34-38).

## Conclusions

Immunotherapy by intralesional vitamin D3 is a simple, well-tolerated, effective, and cost-benefit modalities for the treatment of warts.

Filiform warts are the most common type that responded to intralesional vitamin D3.

Smoking and older age seemed to decrease the therapeutic response.

Intralesional injection of vitamin D3 may be considered safe, effective, well-tolerated, easily administrated in outpatient clinics, and an inexpensive treatment and safe modality for the treatment of common warts.

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