

Comparison of Intralesional Vitamin D3 Injection, 5% Koh Cream and Their Combination in Treatment of Cutaneous Warts

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ABSTRACT

Background: Warts are a common skin condition that affects people all over the world. This ailment affects 2–20% of students in primary school. A well-known keratolytic agent, potassium hydroxide (KOH), has many dermatological uses. Vitamin D is important in the proliferation and differentiation of keratinocytes.

Objective: The aim of the current work was to compare the efficacy and safety of intralesional vitamin D3 injections and 5% KOH cream separately and in combination with each other in the treatment of warts.

Patients and Methods: This study was carried out at the private outpatient Al- Ahlam Center of Dermatology and Cosmetology in Gharyan, Libya from 1st of Sep to last of Dec 2021. 45 patients with warts were included in the study. They were classified into 3 groups according to method of treatment into Vitamin D3 group, 5% KOH cream group, and combination group.

Results: The mean age of patients was 27.04 ± 11.7 years. 31 patients completed the study. Complete response was seen in 12 patients with vitamin D injection after period of 4 months, 9 patients with 5% KOH cream after period 2-3 months, and 10 patients with combination both treatment after a period of 1 month.

Conclusions: It could be concluded that intralesional vitamin D with 5% KOH cream is safe, effective, and inexpensive treatment option for recalcitrant palmoplantar and periungual warts.

Keywords: Vitamin D3, Palmoplantar, Periungual, KOH, Warts.

INTRODUCTION

The Human Papilloma Virus (HPV) is the most common cause of cutaneous warts, a common condition in dermatology. To date, more than a hundred distinct HPV genotypes have been discovered. With a prevalence of up to 33% in primary school children and up to 22% in the general population, the incidence of disease varies widely among different age groups and demographics^(1,2). Direct or indirect transmission can occur when the epithelial barrier is breached, such as in minor trauma⁽³⁾. As a result of histological examination, the pathognomonic presence of koilocytic cells in the dermal capillaries of the dermis can be identified⁽⁴⁾. In order to determine whether a wart is caused by HPV, the anatomical location or morphology of the wart is examined. Common warts, flat warts, plantar warts, periungual warts, and genital warts are all examples of warts that can be examined (condyloma acuminata)⁽⁵⁾.

Based on clinical observation, genital warts are typically diagnosed. Subclinical genital warts are more common in both men and women than visible genital warts. In cases where lesions are very small or flattened, acetic acid solution (5 percent) for 3 to 5 minutes can be helpful. There may be a need to perform a biopsy and HPV genotype testing to confirm the diagnosis⁽⁶⁾.

As a therapeutic challenge, treating warts has yet to yield a single treatment that has been shown to be effective in every patient⁽⁷⁾. There are a variety of treatment options for treating common warts, each of which must be tailored to the specifics of the patient's case, including the number of warts, size, location, symptoms, personal preference, cost, immune system

condition, and previous treatment options. The most common reason for treatment is the cosmetic discomfort and the risk of spreading the disease to other parts of the body⁽⁸⁾.

Scarring can occur as a result of current wart treatments, which involve physically destroying wart-infected cells, Warts can be treated with electrosurgery (e.g., cryocautery or chemical cautery), carbon dioxide lasers (carbon dioxide laser, bleomycin and photodynamic therapy), oral cimetidine (orally), topical immunotherapy (e.g., contact sensitizers, intralesional injection of antigens), and topical immune response modifiers (topical immunotherapy)⁽⁹⁾.

Recalcitrant warts, repeat warts, extensive warts, and hard-to-treat areas like the periungual and palmoplantar sites can all benefit from immunotherapy⁽¹⁰⁾. Vitamin D3 is an immunotherapeutic agent used to treat warts. It works by inhibiting the expression of tumor necrosis factor (TNF)- α through immunomodulatory effects among others TNF- γ and interleukin-6 through VDR-dependent pathway⁽¹¹⁾.

One of the most commonly used metal bases in medicine, potassium hydroxide (KOH) can be used to diagnose fungal infections and to treat both male genital warts and the molluscum contagiosum infection in children⁽¹²⁾. Keratolytic effects of the drug cause the destruction of virus-infected cells, resulting in the removal of warts. In comparison to other topical methods, this one is much less painful, less scar-forming, and less irritating to the skin. Itching, erythema, and darkening of the skin are possible side effects⁽¹³⁾.

The aim of the present study was to compare the efficacy and safety of intralesional vitamin D3 injections and 5% KOH cream separately and in combination with each other in the treatment of warts.

PATIENTS AND METHODS

This interventional randomized clinical trial study included a total of 45 patients with warts, attending at Al-Ahlam Center for Dermatology and Cosmetology, Gharyan, Libya. This study was conducted between 1st of September to last of December 2021.

Inclusion criteria: Patients diagnosed with warts of variable size and duration, and aged 10 - 60 years.

Exclusion criteria: Pregnant and lactating women, those with a history of vitamin D3 hypersensitivity, those who had past history of tuberculosis, and those who had received wart treatment in the last three months prior to study enrollment.

The included subjects were divided into 3 groups according to method of treatment (15 patients each); **Group 1** (vitamin D3 group), **Group 2** (5% KOH cream group) and, **Group 3** (combination group).

All patients were subjected to:

- History taking including age, sex, and telephone number; patient's complaint; cosmetic problems or pain, history of present condition; onset, duration, course, and history of previous treatment.
- General examination and local examination.
- Dermatological and clinical examination to determine the type, number, and sites of warts.
- The patients were instructed not to use any other treatment modality during this therapy.
- Preparation of 5% KOH cream: Active ingredients: KOH (5 g), water miscible cream 95%. Method: weight and add 5 mg of potassium hydroxide solid pellets mixed well with 95 g water miscible cream for 5 minutes to obtain a homogenized cream and then filled in suitable plastic jar and stored in room temperature in dry place away from humidity.

Treatment steps:

- Vitamin D3 treatment: about 20 – 30 IU vitamin D solution (300000 IU) was injected intralesional. A maximum 10 warts were injected per session with 2 weeks intervals until resolution for a maximum of 8 sessions.

- 5% KOH cream treatment: the cream was applied topically on the lesions.

Resolution:

- Response to treatment was evaluated as follow: Improved: complete disappearance of the warts and return of normal skin markings. No improved: there was no change. Escaped: not complete the treatment period.
- The patients were examined every 2 weeks during the treatment course by assessment of the number of warts and detection of any side effects.
- Photographs were taken for each patient before and after treatment to compare and evaluate the clinical response and side effects of the treatment.

Ethical Consideration:

An approval of the study was obtained from Al-Ahlam Center for Dermatology and Cosmetology, Gharyan, Libya. Every patient signed an informed written consent for acceptance of participation in the study. This work has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for studies involving humans.

Statistic analysis

In order to analyse the data, SPSS version 18 was used (USA). Statistical data is represented as mean standard error of the mean (mean SEM). For parametric data, one-way ANOVA was used to make statistical comparisons between the various groups. The fisher exact (X^2) test was used to compare the frequency and percentage of categorical data. P equals or lower than 0.05 is considered statistically significant.

RESULTS

As shown in table 1, the mean age was 27.04 ± 11.7 with range 10 – 60 years, 42.2% of subjects were male and 57.8% were female. The diagnosis was as following; Periungual (33.3%) was the most prevalent followed by planter warts (26.7%), palmer warts (22.2%), and common warts (17.8%). The site of lesions was 20% in left foot, right foot, and left hand, 28.9% in right hand, 4.4% left hand & left foot, 2.2% left hand & right foot, and 4.4% palmoplantar. The mean number of lesions was 3.1 ± 2.5 with range of 1-10. The mean of duration was 6 ± 5.3 with range of 1-24 months. Size of lesions was 26.7% small, 17.8% moderate, 22.2% large, and 33.3% variable. Family history of warts was 8.9% positive and 91.1% negative.

Table (1): Demographic and description of lesions among the studied subjects:

Variables		Subjects (n=45)
Age/years		27.04 ± 11.7 24 (10-60)
Sex	M	19 (42.2%)
	F	26 (57.8%)
Diagnosis	Common Warts	8 (17.8%)
	Palmer Warts	10 (22.2%)
	Planter Warts	12 (26.7%)
	Periungual warts	15 (33.3%)
Site	Left Foot	9 (20%)
	Right Foot	9 (20%)
	Left Hand	9 (20%)
	Right Hand	13 (28.9%)
	Left Hand + Left Foot	2 (4.4%)
	Left Hand + Right Hand	1 (2.2%)
	Palmoplantar	2 (4.4%)
No of lesions		3.1 ± 2.5 2 (1-10)
Duration/months		6 ± 5.3 4(1-24)
Size of lesions	Small	12 (26.7)
	Moderate	8 (17.8%)
	Large	10 (22.2%)
	variable	15 (33.3%)
Family history of warts	Positive	4 (8.9%)
	negative	41 (91.1%)

Data are represented as mean ± SD or number (%)

Age, sex and number of lesions were not statistically different between groups in the study (Table 2).

Table (2): Age, sex, number of lesions and its duration among the three treated groups:

		Vitamin D (n=15)	5%KOH cream (n=15)	Combination of Both (n=15)	F	P
Age (years)		23.2 ± 7.8	30.3 ± 14.6	27.7 ± 11.3	1.4	0.24
Sex	M	7	4	8	X² = 2.3 , P=0.43	
	F	8	11	7		
No of lesions		2.8 ± 2.08	3.3 ± 3.04	3.2 ± 2.7	0.14	0.86
Duration		7.9 ± 5.6	4.4 ± 3.8	4.8 ± 3.8	2.6	0.08

Data are represented as mean ± SD or number (%). Data were analyzed using one way ANOVA and Fisher Exact test.

For the purposes of diagnosis and description of lesions, there were no significant differences between the two study populations (Table 3).

Table (3): Diagnosis and description of lesions among the three treated groups:

Variables		Vitamin D (n=15)	5%KOH cream (n=15)	Combination of Both (n=15)	X ² , P
Diagnosis	Common Warts	2 (13.2%)	0 (0%)	6 (40%)	X ² = 10.2 , P=0.1
	Palmer Warts	4 (26.)	3 (20.1%)	3 (20.1%)	
	Planter Warts	5 (33.4%)	8 (53.2%)	2 (13.2%)	
	Periungular	4 (26.7)	4 (26.7)	4 (26.7)	
Site	Left Foot	3 (20.1%)	3 (20.1%)	3 (20.1%)	X ² = 12.4 , P=0.3
	Right Foot	3 (20.1%)	5 (33.3%)	1 (6.6%)	
	Left Hand	2 (13.2%)	4 (26.7)	3 (20.1%)	
	Right Hand	5 (33.3%)	2 (13.3%)	6 (40%)	
	Left Hand + Left Foot	0 (0%)	0 (0%)	2 (13.2%)	
	Left Hand + Right Hand	0 (0%)	1 (6.6%)	0 (0%)	
	Palmoplantar	2 (13.3%)	0 (0%)	0 (0%)	
Size of lesions	Small	1 (6.7%)	6 (40%)	5 (33.3%)	X ² = 11.1 , P=0.07
	Moderate	1 (6.7%)	4 (26.7)	3 (20.1%)	
	Large	7 (46.6%)	1 (6.6%)	2 (13.3%)	
	variable	6 (40%)	4 (26.7)	5 (33.3%)	
F\H of warts	Positive	4 (26.7)	0 (0%)	0 (0%)	X ² = 6.4 , P=0.02
	negative	11 (73.3%)	15 (100%)	15 (100%)	

When it came to response time or outcome, there was no discernible difference between the various groups that were examined (Table 4).

Table (4): Duration of treatments and outcome among the three treated groups:

Variables		Vitamin D (n=15)	5%KOH cream (n=15)	Combination of Both (n=15)	X ² , P
Duration of response/weeks		5 ± 2.4	2.3 ± 0.49	1.9 ± 2.3	P<0.001
Outcome	Improved	10 (66.6%)	6 (40%)	9 (60%)	X ² = 3.07, P=0.6
	Not Improved	2 (13.3%)	5 (33.3%)	2 (13.3%)	
	Escaped	3 (20.1%)	4 (26.7)	4 (26.7)	

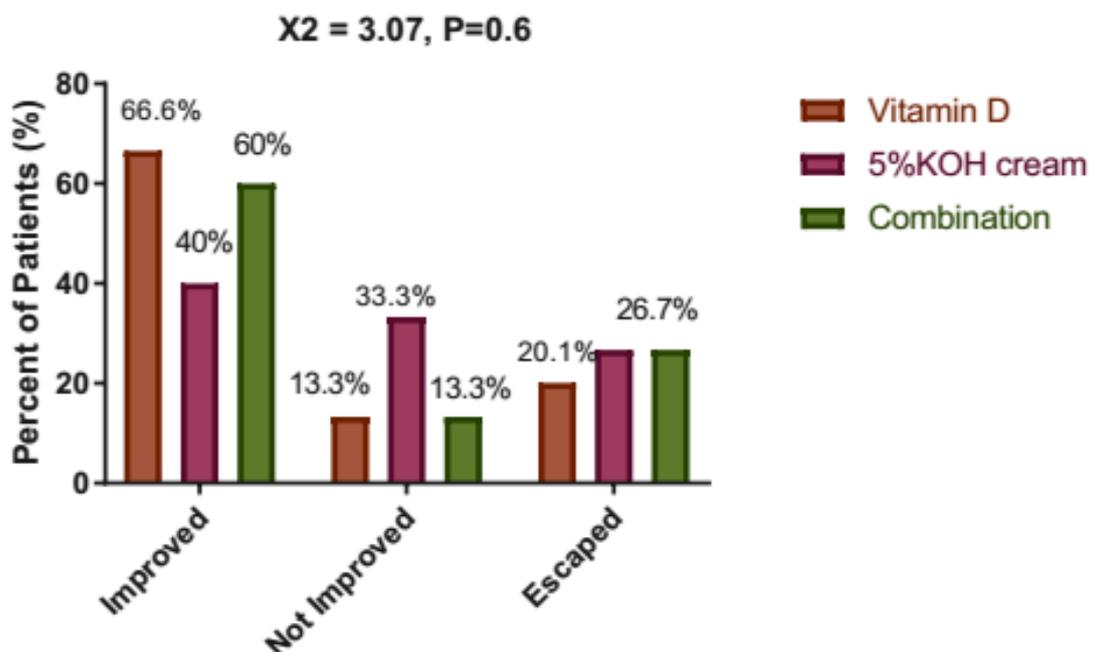


Figure (1): Outcome among the three treated groups.



Figure (2): A case was treated with Vitamin D. (A) before treatment. (B) after treatment.

DISCUSSION

As a therapeutic challenge, treating warts has yet to yield a single treatment that has been shown to be effective in every patient⁽⁷⁾. Immunotherapy is a promising modality for the treatment of resistant and recurrent warts without any disadvantage of scarring and boosts the host's immunity against the causative organism, thus leading to complete resolution and fewer recurrences⁽¹⁴⁾. Antimicrobial peptides are produced by keratinocytes as a result of vitamin D's role in cell proliferation and differentiation⁽¹⁵⁾.

During this study, we compared the efficacy and safety of intralesional vitamin D3 injections and 5 percent KOH cream separately and in combination with each other in the treatment of warts.

In the current study, periungual warts (33.3%) was the most prevalent followed by planter warts (26.7%), palmer warts (22.2%), and common warts (17.8%). The site of lesions was 20% in left foot, right foot and left hand, 28.9% in right hand, 4.4% left hand & left foot, 2.2% left hand & right foot, and 4.4% palmoplantar. The mean number of lesions was 3.1 ± 2.5 with range of 1-10. The mean of duration was 6 ± 5.3 with range of 1-24. Size of lesions was 26.7% small, 17.8% moderate, 22.2% large, and 33.3% variable. Family history of warts was 8.9% positive and 91.1% negative. The prevalence of comorbidities (diabetes mellitus, hypertension, atopy, and others) was negative for all studied groups.

Priya et al.⁽¹¹⁾, demonstrated that plantar warts were most prevalent (29, 46.0%), followed by palmar warts (20, 31.8%) and periungual warts (14, 22.2%). The number of warts varied from 2 to 7 in each patient. **Mohamed et al.**⁽¹⁶⁾, showed that the duration of the lesions ranged from 3 month to 24 months with mean duration 7.65 ± 0.6 months. According to the site of the lesion, 8 patients (12.9%) had lesions in head and neck, 48 patients (77.4%) had lesions in upper limb and 6 patients (9.7%) had lesions in lower limb. **Kandil et al.**⁽¹⁷⁾, demonstrated that their study included 60 patients (28 men and 32 women). They were of different ages, and had different disease durations, side effects, and wart types (common, plane, plantar, and periungual

warts). However, there was a statistically nonsignificant difference between the studied groups in age, sex, complaint, type of wart, and site of the lesion but statistically significant differences in disease duration were found between the two groups studied.

In the present study, age, gender, number of lesions, and time between lesions were not statistically different between the study groups.

In agreement with our study, **Amin et al.**⁽¹⁸⁾, found that regarding age and gender, there were no statistically significant differences between both groups. Also, **Abdel-Azim et al.**⁽¹⁹⁾, showed that there were no statistically significant differences between the study groups regarding age, number and duration of warts. In the current study, duration of response was in vitamin D group 5 ± 2.4 weeks, in 5% KOH cream group 2.3 ± 0.49 weeks, and in combination group 1.9 ± 2.3 weeks. Outcome of treatment was as following; vitamin D group (66.6% improved, 13.3% not improved, and 20.1% escaped), 5% KOH cream group (40% improved, 33.3% not improved, and 26.7% escaped), and combination group (60% improved, 13.3% not improved, and 26.7% escaped).

In agreement with our study, **Priya et al.**⁽¹¹⁾, showed that complete response in vitamin D3 group was observed in majority of patients (88.9%) patients. While **Mohamed et al.**⁽¹⁶⁾, demonstrated that in the vitamin D3-injected lesions, complete improvement was observed in only 35.5%, partial response was observed in 33.9% of patients and no response was observed in 30.6% of patients.

In **Akula et al.**⁽²⁰⁾, the study showed that 14 (70%) of the 20 patients in the intralesional vitamin D3 group had complete clearance, while six (30%) had partial response.

Abdel-Azim et al.⁽¹⁹⁾, found that 56.25% of patients treated with vitamin D showed complete cure both clinically and dermoscopically, 6.25% of patients showed clinical clearance but with dermoscopic remnants of the warts and 9.37% of patients showed a decrease in size of warts more than 50% clinically and dermoscopically 2 weeks after the fourth session. Failure to treatment was reported in 28.13% of patients.

Kandil et al. ⁽¹⁷⁾, demonstrated that a complete response was observed in 75% of patients treated with KOH, a partial response was observed un 20% of patients, while no response was observed in 5% of patient. **Galal et al.** ⁽²¹⁾, found that patients treated with 5% KOH showed a complete response in 56.7% of patients, whereas 23.3% of patients had a partial response and 20.0% of patients had no response. The duration of response was shorter (3.8 weeks) in patients treated with 5% KOH.

In the current study, no serious adverse effects or allergic reactions were reported, and no scars or hyperpigmentations related to injections. The patients complained only of mild pain during injection in vitamin D3 group, which was well tolerated. No further healing was reported during the period of follow-up. None of the healed warts recurred during the 6 months-follow-up period.

Regarding side effects in different studies we found that in **Priya et al.** ⁽¹¹⁾, the most common adverse effect of intralesion vitamin D3 injection was transient pain, which was present in almost all patients and was managed by pre injection with lignocaine. The next most common adverse effect was swelling, found in 25.4% of patients in whom it subsided within a week. None of the patient had any serious/systemic side-effects. In another study, the results regarding comparison of complications demonstrated that pain at the site of injection was the most common complications with intralesional vitamin D3 injection, followed by swelling at the site of injection with recurrence and other complication as eczema, pigmentation and inflammation were observed with vitamin D3 group ⁽¹⁶⁾.

Akula et al. ⁽²⁰⁾, The injection site was found to cause mild pain and swelling, which dissipated on its own. There have been no serious side effects reported.

Kandil et al. ⁽¹⁷⁾, few patients treated with KOH reported side effects such as itching, burning sensation, erythema, and temporary dyspigmentation.

CONCLUSION

It could be concluded that combination of intralesional vitamin D injection with KOH cream is safe, effective, and inexpensive with shorter duration of response as a treatment option for cutaneous warts.

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Author contribution: Authors contributed equally in the study.

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