

ORIGINAL ARTICLE

Efficacy of Intralesional Vitamin D3 Injection in Cutaneous WartsSAMREEN DOST SHAIKH¹, NAEEM AHMED SOOMRO¹, SHUMAILA SHAIKH¹, RAKHI KUMARI², SORATH SOHAIL³, IRFAN AHMED SHAIKH⁴¹Consultant Dermatologist, CMCH Larkana²Senior Registrar Dermatology department, Hamdard University, Karachi³Consultant Dermatologist, JPMC, Karachi⁴Professor of Dermatology, SMBBMU LarkanaCorrespondence to: Samreen Dost Shaikh, Email: drsamreendost@gmail.com, Cell: + 92 323 3648379**ABSTRACT****Background:** Cutaneous warts are common dermatological viral infection caused condition which causes cosmetic problems besides its primary morbidity like pain and discomfort. Intralesional vitamin D3 derivatives therapy is recent and effective modality for treatment of cutaneous warts.**Objective:** To determine the efficacy of intralesional vitamin D3 injection in cutaneous warts in local patients.**Methods and patients:** A descriptive case series study conducted from June to December 24, 2019 at Dermatology OPD, SMBBMU- Larkana. A sample of 65 patients with cutaneous warts, either gender, age 20-50 years, 3 months to 6 months history were included after taking a valid informed/ written consent.Pregnant and lactating women, patients on immunosuppressive therapy, signs of any systemic or local inflammation or infection, history of asthma, allergic skin disorders, meningitis or convulsions, history of hypersensitivity to Vitamin D3 were excluded. The injections of vitamin D3 (vials containing 6,00,000 IU of cholecalciferol in 1 ml = 15 mg) were given at 2 weekly intervals for a maximum of four injections. A standard questionnaire was used to collect demographic and study related data. Data analysis was performed through SPSS Version-21. Descriptive and inferential statistics were calculated. Stratification was done and post stratification chi square test was applied. P-value ≤ 0.05 was considered as significant.**Results:** The mean age of patients was 27.9 ± 5.1 with C.I (26.63-29.16) years. The Mean \pm SD of duration was 4.4 ± 1.9 with C.I (3.92-4.87) months. The Mean \pm SD of number of warts was 14.3 ± 4.2 with C.I (13.25-15.34). Out of 65 patients, 35 (53.8%) were male while 25 (38.5%) patients were belong to urban areas. Primary outcome of this study i.e; the efficacy was $n=54$ (83.1%). Stratified analysis revealed that younger age (20 – 30 years), male gender, urban residence, 3-5 mm size, 2-3 months duration (p value = 0.009) were associated with more efficacy of intralesional vitamin D3 injection in cutaneous warts.**Conclusion:** This study clearly demonstrates that recalcitrant plantar warts can be treated successfully with intralesional vitamin D3 injection. The immunotherapy of injection vitamin D3 has better patient compliance, good therapeutic response without cosmetic disfigurement and capable of preventing recurrences.**Keywords:** Efficacy, Intralesional Vitamin D3, Cutaneous Warts, Treatment, Immunotherapy.**INTRODUCTION**

Environmental changes have resulted in an increase in the occurrence of communicable viral skin infections, the most frequent of which being skin warts or verrucae, which are benign epidermal proliferations of the skin and mucosa that are known as viral cutaneous warts (also known as cutaneous warts).¹ The human papillomavirus (HPV) is the causal organism (HPV). These warts are the third most common skin lesion in the globe, with an incidence rate of up to 7.2 percent. They can occur at any age, but are most frequent in children. Even while warts usually resolve on their own within 2 years in 65-78 percent of cases, most patients seek treatment for them because they are unsightly and occasionally painful, particularly on the soles of the feet.²⁻⁴ Traditional treatments included destructive approaches such as cryotherapy, electrocoagulation, topical salicylic acid, topical 5-fluorouracil, laser surgery, and other similar procedures.⁵ Their prevalent side effects (which include mostly discomfort, a long duration, high cost, and a lower cure rate ranging from 8 to 49 percent) limit their usefulness and reduce their efficacy.^{6,7} Further increased risks of recurrence and transfer from one individual to another through direct contact or through the environment increase the need of searching for and evaluating relatively recent treatment options.^{3,6,8}

Intralesional immunotherapy is one such treatment method that has recently gained popularity as a valuable therapeutic technique. Intralesional antigens such as the measles, mumps, and rubella (MMR) vaccination, skin test antigens (Mumps, Candida, and Trichophyton), and the BCG (Bacillus Calmette-Guerin) vaccine have all been reported to be effective therapy choices for warts of various types in the past.^{5,6,8} Vitamin D is a fat-soluble steroid prohormone with endocrine, paracrine, and intracrine functions that has also been found to be very effective (in the form of Vitamin D3 derivatives) in some studies conducted in western countries.⁹ Vitamin D is a steroid prohormone with endocrine, paracrine, and intracrine functions. Vitamin D derivatives have a variety of impacts on the body, including the stimulation of epidermal keratinocyte differentiation, suppression of hyperkeratosis, stimulation of apoptosis, and anti-inflammatory properties.¹⁰ Moscarelli L and colleagues¹¹ reported that they successfully treated warts in a renal transplant recipient with topical activated vitamin D. Toyota Rind and colleagues¹² reported that topical vitamin D3 treatment of an anogenital wart in an infant resulted in complete elimination of the wart. Henrik H. Aktas et colleagues demonstrated an 80 percent success rate in the treatment of planter cutaneous warts with two intralesional vitamin D3 injections.¹³

In our region of the world, intralesional vitamin D3 injection is a relatively recent therapy option for cutaneous warts. Outpatient clinics can easily give this simple, well-tolerated therapy technique since it is simple and straightforward to deliver. However, because no case specific study has been undertaken, it is necessary to evaluate the efficacy of this therapy for the treatment of cutaneous warts in the general population as well as in the local community. Specifically, the current study sought to assess the efficacy of intralesional vitamin D3 injections in the treatment of cutaneous warts in patients from rural Sindh.

METHODS AND PATIENTS

This descriptive case series study was conducted in a period of six months (June to December 24, 2019) at Dermatology OPD, SMBBMU, after being approved by the Ethical Review Committee (ERC) of SMBBMU- Larkana. A sample of 65 patients with cutaneous warts [calculated on previous documented efficacy of @ 80%¹³] either gender, age 20-50 years, 3 months to 6 months history, were included after taking a valid informed/ written consent after being informed about the objectives and methods of the study. There were several exclusions, including pregnant and breastfeeding women, those on immunosuppressive therapy, those who had a history of allergic skin conditions, those who had convulsions, and those who had a history of hypersensitivity to Vitamin D3. a solid, rough hyperkeratotic papule or nodule with a diameter of 2-4 millimetres and a height of up to 10 millimetres above the skin's surface was characterised as a cutaneous wart.

A standard questionnaire was utilised to gather demographic and medical history data. A 1 ml vial of Vitamin D3 injection contained 6,00,000 IU of cholecalciferol, the active ingredient of the vitamin (15 mg). Warts were injected with Vitamin D3 (7.5 mg/ml) and Lignocaine (20 mg/ml) at the base of each wart, which was then injected with 21-gauge insulin needles. Each patient was given four injections of vitamin D3 at two-week intervals. After four injections, if complete clearance was not obtained, the treatment was terminated. For the first two months, patients were tested every two weeks for treatment efficacy; after that, they were evaluated every month for four months. Immediately following treatment, the patients were instructed to refrain from using any topical or oral medication. At the end of four months of follow-up, the final outcome was measured and labelled.

These variables were collected on pre-designed proforma by the investigator herself and contain the subjects' name(s), age(s), gender(s), and address. Details of warts' locations as well as their size and quantity were also recorded. The number of injections, effectiveness (an outcome variable), and the number of weeks of follow-up were recorded. SPSS Version 21 was used to enter and evaluate the data. The mean and standard deviation (Mean SD) of age, duration of disease, size and number of warts, follow-up weeks, and number of injections received were calculated for each patient. While proportions and percentages of categorical variable i.e., gender, residence, site and efficacy (outcome variable) were expressed.

RESULTS

The mean age of patients was 27.9±5.1 with C.I (26.63-29.16) years. The Mean ± SD of duration was 4.4±1.9 with C.I (3.92-4.87) months. The Mean ± SD of number of warts was 14.3±4.2 with C.I (13.25-15.34) while Mean ± SD of size of warts was 3.7±1.6 with C.I (3.30-4.09) millimeters (Table-1). The mean Mean ± SD of number of injections used was 6.3±2.4 with C.I (5.70-6.89).

Out of 65 patients, 35 (53.8%) were male while 30 (46.2%) were female while 25 (38.5%) patients were belong to urban areas and 40 (61.5%) were from rural areas (Table:2).

Table 1: Baseline demographic characteristics (n= 65)

Characteristics	Minimum	Mean	S.D	Confidence Interval	Maximum
Age of Patient (Years)	20	27.9	5.1	26.63, 29.16	50
Duration of disease (months)	3	4.4	1.9	3.92, 4.87	6
Number of Warts	1	14.3	4.2	13.25, 15.34	60
Size of Warts (mm)	2	3.7	1.6	3.30, 4.09	4
Number of injections	2	6.3	2.4	5.70, 6.89	12

Table 2: Demographic frequencies (n = 65).

Variable/ characteristic	Frequency	Percentage
Gender		
Male	30	46.2
Female	35	53.8
Residence		
Rural	25	38.5
Urban	40	61.5
Side of wart		
Right	29	44.6
Left	36	55.4

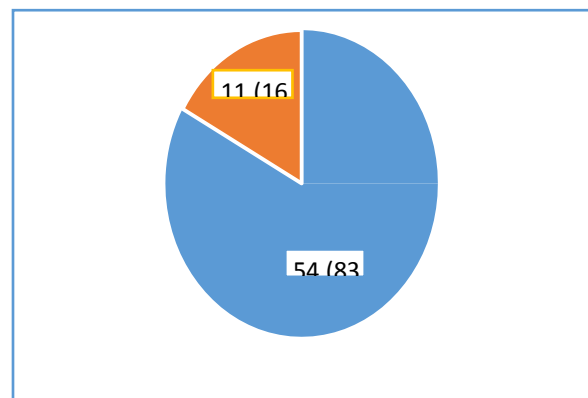


Figure 1: Frequency of efficacy of intralesional vitamin D3 injection in cutaneous warts (n=65)

Primary outcome of this study i-e; the efficacy was found to be in 54 (83.1%). Stratified analysis revealed that younger age (20 – 30 years), male gender, urban residence, 3-5 mm size, 2-3 months duration (p value =

0.009) were associated with more efficacy of intralesional vitamin D3 injection in cutaneous warts (table: 3).

Table: 3. Stratification of different variables with efficacy of intralesional vitamin D3 injection in cutaneous warts (n=65)

Variable	Categories	Efficacy		P value
		Effective	Non-effective	
Age in Years	20 – 30	40 (61.5%)	6 (9.2%)	0.194
	> 30	14 (21.5%)	5 (7.7%)	
Gender	Male	31 (47.7%)	4 (6.2%)	0.194
	Female	23 (35.4%)	7 (10.8%)	
Residence	Urban	34 (52.3%)	6 (9.2%)	0.601
	Rural	20 (30.8%)	5 (7.7%)	
Site of wart	Right	26 (40%)	3 (4.6%)	0.204
	Left	28 (43.1%)	8 (12.3%)	
Size [Millimeters]	3 – 5	37 (56.9%)	7 (10.8%)	0.752
	>5	17 (26.2%)	4 (6.2%)	
Duration [Months]	2 – 3	33 (50.8%)	2 (3.1%)	0.009
	>3	21 (32.3%)	9 (13.8%)	

DISCUSSION

HPV (DNA virus) is responsible for the development of warts, and there are more than 100 different strains. The patient may experience physical and emotional stress from warts that spontaneously dissolve, while others may linger and spread to other body sites, necessitating the use of an appropriate treatment plan. Multiple cutaneous warts, particularly palmoplantar warts, are difficult to cure because they induce morbidity and require multiple sittings with damaging treatments such as cryotherapy and electrocautery. These invasive operations are typically associated with scarring and pigmentation, and they have no effect on warts that are located further away. Some warts are also resistant to these therapies, and the recurrence rate is considerable in the case of some of them.

Immunotherapy is a method of treating warts that relies on the activation of the immune system to deal with the HPV virus and suppress its activity. In addition, it features a new approach of intralesional vitamin D3 derivatives injection, which has been shown to increase the immune system's ability to fight the HPV virus, resulting in the clearing of both treated and untreated warts with a low risk of recurrence. The purpose of the current study was to determine the effectiveness of this new therapy in the treatment of warts. The findings of our study are comparable to those of other national and international studies, which are explored in further detail below.

In our study, the mean age of patients was noted as 27.9±5.1 years. Similarly the studies by Aktaş H, et al,¹³ Naresh M, et al.,¹⁴ Kavya M, et al,⁹ and Raghukumar S,

et al.,¹⁵ noted the mean ages of 28.6, 31, 29 & 23.93 years respectively. Duration of warts by different studies was found between 1.5 to 5 years while the current study duration of disease was 4.4±1.9 months. In present study, the mean number of warts was 14.3±4.2 which other studies recorded between mean values of 4.5 to 6.3. In our study, 65 patients were included, out of which 35 (53.8%) were male while 30 (46.2%) were female patients while other studies had variable presentation of gender which ranges from one third to two thirds of males participants.

The efficacy of intralesional vitamin D3 derivatives administration in current study was found in 54 (83.1%) patients. In the study of Aktaş H, et al.,¹³ efficacy was noted in 16 (80%) patients. Naresh M, et al.,¹⁴ Banoth S, et al.,¹⁶ and Raghukumar S, et al.,¹⁸ noted efficacy in 48 (80%), 12 (46%) and 54 (90%) patients.

However, the actual mechanism of vitamin D's anti-wart activity has yet to be determined; however, it has been shown to regulate cell proliferation and differentiation, as well as have immunoregulatory properties. In order for it to have an effect on the skin, the vitamin D receptor (VDR) must be present in the keratinocytes, melanocytes, fibroblasts, and immune system cells.¹⁷

This study clearly reveals that intralesional vitamin D3 injection can be used to successfully treat persistent plantar warts. During the follow-up period, there was no sign of a return of the warts, indicating that this treatment was safe and effective.

Study Limitations: The cross sectional study design, smaller sample size and conducted at one center therefore; the results of this study may be referred carefully as might not be generalizable to larger populations.

CONCLUSION

It is concluded that the findings of this study supported the idea that intralesional vitamin D3 injection is safe for the treatment of multiple cutaneous warts. The immunotherapy of injection vitamin D3 has better patient compliance, good therapeutic response without cosmetic disfigurement and capable of preventing recurrences.

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