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Original Article

Comparison of efficacy of liquid nitrogen and vitamin D3 in treatment of warts on hands and feet

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Abstract

Objective To compare the efficacy of intralesional vitamin D3 and cryotherapy in treatment of warts of hands and feet.

Methods A total of 100 patients of warts fulfilling the inclusion & exclusion criteria were enrolled in study who presented to Dermatology Department, Lahore General Hospital, Lahore. Patients were divided into two groups (A and B) with random number table leading to 50 patients in each group. Group A patients received liquid nitrogen cryotherapy (-196 ºC) while patients in group B were treated with intralesional vitamin D3 (5mg/ml). Patients in both groups were treated for 3 sessions at every 3 weeks interval. Treatment was labeled as efficacious if there was more than 50% reduction in wart size.

Results Mean age of patients was 23.72±14.10 years. 92% patients of group A showed efficacy while it was 84% in group B. Treatment was found to be efficacious in both groups and there was no statistically significant difference between these treatment modalities.

Conclusion Cryotherapy and intralesional vitamin D3 both are effective in treating palmoplantar warts.

Key words
Cryotherapy, Human Papilloma Virus, liquid nitrogen, warts.

Introduction

Viral Warts of skin are common infection manifested as benign epidermal proliferations. They are caused by Human Papilloma Virus (HPV) affecting 9.5% of children and young adults, commonly under 16 years of age.[1]

They are broadly classified into cutaneous, genital and laryngeal warts and may affect any area of skin although hands and feet are by far the commonest sites. In immunocompetent patients they are not life threatening but they cause discomfort, embarrassment & pain.[2]

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Human papilloma virus is a DNA virus that enters the skin through traumatized areas. Factors favoring its proliferation are use of communal shower, meat handling and in immunosuppressed states. It leads to array of clinical manifestations ranging from plantar or common warts to genital warts to neoplasia of cervix.[3]

Various modes of treatment are being used; most of them are destructive and lead to scarring, such as cryotherapy, curettage, chemical cauterization and electrodessication. Topical and intralesional preparations, homeopathy, Immunotherapy and laser are other options.[4] Cryotherapy with Liquid nitrogen is most widely used method for treating warts. It cures warts by freezing and destroying the tissue containing wart without causing pain or discomfort to the patient.[5]

Immunotherapy is a favorable modality which may lead to resolution of warts without destruction and scarring and in addition also enhances host response against the virus, thus leading to complete resolution, clearing of surrounding lesions and decreased recurrences. Candida antigen, vitamin D3, mumps antigen and BCG vaccine has been used as immunotherapeutic agents to treat various types of warts.[6]

Vitamin D3 is immunotherapeutic agent in treating warts; it heals warts through immunomodulatory effects which involve inhibition of the expression of tumor necrosis factor (TNF)-α, TNF-γ and interleukin-6 through VDR-dependent pathway.[7]

Clinical experience about use of vitamin D3 to treat common warts is limited to few reports published for its use in genital warts and palmoplantar warts. According to these reports, efficacy of vitamin D3 is 78% in treating common warts. In studies so far available, Vitamin D3 has been compared with Candida antigen and Zinc sulphate for treatment of warts.[8] There is no controlled study available in literature to compare it with Cryotherapy.

In our clinical practice, we are using cryotherapy most of the times for treating common warts on hands and feet because it is ablative, may lead to clearance even after single session and more feasible in treating warts in pediatric population.

Rationale of this study was to assess the efficacy of vitamin D3 as a treatment in warts on hands and feet as it is a non ablative method and to compare it with the efficacy of cryotherapy. By determining the effectiveness of vitamin D3 in treatment of warts it will become easier to treat warts even in outpatient department and especially in the patients having multiple warts where cryotherapy is more painful and cannot be done on all lesions. It can also be useful in patients with Raynaud's phenomenon and periungual warts in which cryotherapy may be contraindicated.

Magnitudes produced by this study could be used as a basis for recommending a more widespread use of vitamin D3 in the treatment of viral warts.

Methods

Study was carried out at Department of Dermatology, Lahore General Hospital, Lahore, for 6 months from May 2018 to October 2018, after being approved from the hospital ethical committee. It was a single blind randomized controlled clinical interventional trial of six months on 100 cases of palmoplantar warts which were divided into Group A and group B by simple random sampling method. Patient of both genders and all ages were included. Warts on hands and feet of any type like common, filiform or mosaic, single or multiple in number, of any duration and not taking any treatment of warts for 2 months were selected for inclusion in study. Immunosuppressed patients, patients of chronic skin diseases like eczema or autoimmune disease, diabetes mellitus, cold sensitivity & skin allergies, pregnancy and lactation were not included. Periungual warts and warts which were infected were also excluded from the study.

After enrolling the patients informed consent and photographs were taken before starting the procedure. History and clinical examination was done. Demographic data, duration of warts, site and number of warts lesions, morphological type was recorded at start of study in specified proforma. In group A, patients were treated with cryotherapy with liquid nitrogen at -196 ºC by cryospray using double freeze thaw cycle (freezing for 5-10 seconds followed by thawing

and repeating again). Therapy was given at 3 weekly intervals with maximum of 3 sessions. Patients were monitored on each visit for % reduction in wart size and followed for further 6 weeks after last session to look for any recurrence. Clinical photographs were recorded at each visit to compare with baseline photographs.

In group B, 0.2-0.4ml Vitamin D3 solution (5mg/ml) was injected slowly at the base of wart using 26- gauge syringe after giving local anesthesia by lignocaine (20mg/ml). In case of multiple lesions, main wart was injected and maximum four warts were injected in one session. Patients were advised to avoid any topical or oral medication after the session. Procedure was reperformed at 3 weeks intervals with maximum of 3 sessions.

Efficacy was assessed at the end of study i.e. 3 weeks. Response in both groups was measured as % reduction in size of warts i.e. Excellent response: 75-100% reduction of wart size with reestablishment of skin lines, Good response: 50-74% reduction, Fair response: 25-49% reduction, Poor response: <25% reduction. Treatment was labeled to be effective in patients who showed excellent or good response i.e. ≥50% reduction in warts size; while those showing fair or poor response i.e. less than 50% reduction in wart size were labeled as having no efficacy. If wart lesion disappeared they were further followed for 6 weeks to note any recurrence.

All information was recorded on a predesigned proforma.

Data was entered in SPSS Version 18 for analysis. Frequency and percentages were used for demographic variables like gender and efficacy whereas mean and standard deviation were used for presenting age and duration. Patients were stratified by duration of disease to see its effect on response and relation of site with response was also analyzed. Test of significance, chi-square were applied to compare the efficacy of treatment in both groups, p-values equal to or less than 0.05 were considered to be statistically significant.

Results

Among 100 cases, 58% were females and 42% were males; 28 female and 22 male patients in group A while 30 female and 20 male patients in group B.

Mean age of patients in both groups was 23.04±12.19 with minimum 7 years and maximum 59 years.

According to groups, mean age in group A was 22.44±10.28 and in group B was and 23.72±14.10. Minimum age in group A was 9 years and in group B was 7 years, while maximum age in group A and B was 56 and 59, respectively.

Regarding age and gender, there was no statistically significant difference between both study groups. The range of duration of lesions was from 1 to 9 months with a mean of 2.7 in group A and 3.4 in group B.

Out of 100 cases, 5 patients left the study during follow up. In group A 7 patients (14%) showed cure but warts recurred on follow up while in group B 9 patients (18%) showed recurrence of warts on follow up visit.

The efficacy was evaluated in terms of frequency and percentage and was compared by Chi-square test. Calculated P-value of response between two groups is 0.609. The results are not significant; it means there is no difference in efficacy of both treatments.

Table 1 Clinico-demographic data.

		Groups	
		Group A	*Group B*
Gender	Female	28	30
	Male	22	20
Age Group	1-20 Year	26	26
	21-40 Year	21	17
	41-60 year	3	7
Site (Palm, Soles, Dorsum of hands)	Dorsum of hands	5	11
	Palm	13	16
	Soles	32	23
Number of Warts	Multiple	36	28
	Single	14	22
Duration of Warts (months)	≤6 Months	49	43
	>7 Months	1	7
Type of Wart Common	Common	30	39
	Filiform	14	6
	Mosaic	6	5
Side Effects No/Pain/ Blisters	Blister	3	0
	No	43	42
	Pain	4	8

Table 2 Comparison of efficacy of treatment.

	Group A Frequency (%)	*Group B Frequency (%)*
Cured	46 (92%)	42 (84%)
Not cured	4 (8%)	8 (16%)

Discussion

Warts are not apparently sex dependent, male and female have equal chances to acquire them.[2] Cryotherapy is widely used therapeutic modality to treat warts and it is selected as first line therapy in warts as its success rate is approved in most studies. It eliminates warts by direct damage to viral infected cells and also stimulates immune response due to trauma but procedure may be painful in multiple warts and in case of periungual lesions.[5] Despite various treatment modalities, yet no single method can be labeled as a definitive approved treatment. A search for better option is under progress.

Immunotherapy either topical or intralesional is particularly helpful in treating multiple and refractory warts as it is less painful and immune response may clear distant untreated warts as well, moreover it has no chances of scarring and dyspigmentation which may be a consequence of destructive methods like cryotherapy or electrocautery. Immunotherapy is available with various antigens and vaccines for instance Candida albicans, bleomycin, Measles Mumps Rubella (MMR) and Bacillus Calmette Guerin (BCG) vaccine.[6]

Our study was a part of that effort in which we compared conventionally used ablative method of cryotherapy with intralesional vitamin D3 as immunotherapeutic agents so that the efficacies can be assessed at the same time to treat a very common problem in our population. There is no data available in which comparison of efficacy and safety of both agents is done. In addition, distribution of disease in various demographic features like age, gender, number of lesions and duration was also identified.

The mean age of patients was 23.04 in our study population which correlates with study by Raghukumar *et al.* in which mean age was 23.93 years, whereas a different mean age was seen in a study by Ibrahim *et al.* in which mean age was 12.50 years.[9]

Table 3 Efficacy according to duration of warts.

		Excellent	*Fair*	*Good*	*Poor*	*Total*
Duration of Warts (months)	1 Month	17	1	4	0	22
	2 Month	21	1	6	0	28
	3 Month	15	0	2	1	18
	4 Month	7	0	1	1	9
	5 Month	4	2	2	2	10
	6 Month	2	1	2	0	5
	7 Month	4	1	0	1	6
	8 Month	0	0	0	1	1
	9 Month	1	0	0	0	1
Total		71	6	17	6	100

(% Reduction: 75-100% Excellent, 50-74% Good 25-49% Fair & less than 25% Poor).

Table 4 Response according to site of warts.

Site	*Efficacy*	*Group A n (%)*	*Group B n (%)*	*P-value*
Dorsum of hands	Yes	5 (31.2%)	11 (68.8%)	0.8
	No	13 (45%)	15 (47%)	
Palms	Yes	13 (44.8%)	16 (55.2%)	2.69
	No	4 (7.350)	7 (12.7%)	
Soles	Yes	32 (58.2%)	23 (41.8%)	1.5
	No	4 (36%)	8 (13%)	

According to gender, in group A there were 22 male and 28 female patients. While in group B there were 20 male and 30 female patients. Number of female patients enrolled in our study was higher which correlates with the studies of Khozeimeh *et al.*[10] and Moscarelli L *et al*.[11] It shows that females suffer from warts in greater proportion as compared to male population which could be due to more household related trauma or relatively less immunity than males.

The site of warts which was more commonly seen to be involved in our study was soles of feet which may be due to various factors like habit of walking bare feet, soles are more exposed to trauma and self healing is poor due to thick skin.

In group A and B, the mean duration of warts was 2.7 and 3.4 months, respectively. In the study by Raghukumar,[9] mean duration was found to be 14.12 months.

We also studied the effects of age, duration and site on the response to treatment. Maximum response was seen in warts of 2 to 3 months duration.

Response to treatment modality in our study was assessed by comparing percentage reduction in warts and treatment was labeled to be efficacious if it showed more than 50% reduction in warts. Treatment was found to be efficacious in both groups (84% with vitamin D 3 and 92% with cryotherapy) and results were statistically significant within each group but insignificant when compared with each other, therefore results of both treatment modalities were comparable with each other. Similar results have been observed in clinical trials conducted by Khozeimeh *et al.*[10] and Choi MH *et al.*[12] who reported no statistically significant difference between efficacy of cryotherapy when compared with immunotherapeutic agents.

Deepak *et al.*[13] found vitamin D3 to be efficacious in treating periungual warts within 4-6 weeks when given at 2 week intervals for a maximum of 4 sessions. Shaldoum *et al.*[14] have also reported complete response with vitamin

Table 5 Comparison of efficacy of Vitamin D3 with previous studies

Study	*Conc. of Vitamin D3*	*No. of Patients*	*No. of Sessions*	*Interval between sessions*	*Mean Age*	*Response*	*Follow up*
Raghu Kumar *et al.* [2017]	15mg/ml 600000 IU/ml	64	4	3 weeks	23.93 yrs.	90%	6 months
Aktas *et al.* [2015]	7.5mg/ml 300000 IU/ml	20	2	4 weeks	28.6 yrs.	80%	1 month
Ibrahim *et al.* [2019]	7.5mg/ ml 300000 IU/ml	50	2	1 month	12.50 yrs.	40%	3 months
Our Study [2018]	5mg/ml 20000 IU/ ml	100	3	3 weeks	23.04 yrs.	84 %	3 month

D3 in 60% patients of multiple warts when injected at 3 weeks interval for maximum of six sessions and no response was seen in 6.67% patients.

Raghukumar *et al.*[9] reported vitamin D3 to be more efficacious and safe with complete clearance in 90% of cases, which contrasts with our study which might be explained by the fact that maximum number of treatment sessions were four and a higher concentration of vitamin D3 (15g/ml) was used in their study.

Table 5 shows comparison of previous studies on vitamin D3 in treating warts with our study. Difference in response in our study may be due to the dose of vitamin D3 which was 5mg/ml in our study while in previous studies were 15mg/ml and further implies about different immune response in our population required to clear warts.

Different side effects were seen in both treatment groups but these were transient like pain during injecting vitamin D3 intralesionally in 7 cases. Haemorrhagic blisters at the site of cryotherapy in 4 cases. Similar side effects were observed in studies done by Wafa M *et al.*[17] and Khozeimeh F *et al.*[10] Therefore we observed that both the treatments were safe.

Conclusion

Our study shows that both cryotherapy and intralesional vitamin D3 are effective in treating warts on hands and feet and there is no statistically significant difference in their efficacies. Vitamin D3 can be used as first line therapy because it is readily available option especially in resource limited centers. More studies are required with inclusion of genital and periungual warts to see the role of Vitamin D3 in treating such worrisome conditions in our population.

Limitation

Periungual warts were excluded from study as these couldn't be treated by cryotherapy but it is easy to treat them with vitamin D3 whose efficacy thus couldn't be studied in such cases.

Serum vitamin D3 level was not checked before or after study.

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