Comparison of Efficacy of Cryotherapy Versus Intralesional Vitamin D3 in the Treatment Of Plantar Warts

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Abstract

Objective: To compare the efficacy of cryotherapy versus intralesional vitamin D3 in plantar warts.

Method: A Randomized controlled trial conducted from 30th July 2020 -29th January 2021 in the Department of Dermatology, Services Hospital, Lahore. 110 patients of both genders with age ranging from 18-60 years suffering from plantar warts (for more than 4 weeks) participated. Those allergic to xylocaine and Vitamin D3, pregnant females, immunocompromised, having bleeding disorders, Raynaud's phenomenon or cold urticaria were excluded. Participants were randomly divided in two groups. Group A patients was treated with cryotherapy and Group B was treated with intralesional Vitamin D3 for 4 sessions 2 weeks apart. Patients were followed at each treatment session every 2 weekly and then in OPD every month for 4 months for treatment response. Efficacy was assessed as complete cure of the lesion.

Results: Mean age of patients in group A was 34.36 ±12.06 years and in group B was 31.93 ±10.99 years with 81 (73.64%) patients between 18 to 40 years. Male patients were 76 (69.09%) and 34 (30.91%) were females. Efficacy of Group A was 56.36% while Group B showed 87.27% (p-value = 0.0001).

Conclusion: This study concluded that intralesional vitamin D3 is more effective than cryotherapy in the treatment of plantar warts.

Keywords: Plantar warts, intralesional vitamin D3, cryotherapy

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Introduction

Verrucae plantaris (plantar warts) are common cutaneous lesions of the plantar aspect of the foot that are caused by the human papillomavirus (HPV). There are more than 100 serotypes of HPV which cause different types of warts including common, plane, palmo-plantar, perianal and anogenital warts.[1] HPV virus is resistant to heat and drying, survives for longer periods at low temperatures and very contagious. Verruca vulgaris are the most common variety representing 70% of all cutaneous warts, common in school going children. Plantar warts, caused by HPV type 1, 2, 4 and 27, are hyperkeratotic papules having roughened surface and smooth collar of thickened horn occurring at pressure points of feet. In children may regress spontaneously but in adults become persistent.[2]

Plantar warts treatment depend on symptoms, patient preferences and cost.[1,2] Salicylic acid, cryotherapy, retinoic acid, podophyllin, topical 5-fluorouracil, Candida antigen, BCG, MMR vaccine interferon and imiquimod have been used for treatment but treatment failure and recurrence is common and treatment side effects are common cause of patient's dissatisfaction.[1] Therefore there has always been a quest for simple, safe and cost-effective treatment option in such patients.[2]

Cryotherapy freeze wart at -196°C leading to local inflammatory response.[2,3] It may result in hypopigmentation and pain.[1] Intralesional vitamin D3 upregulate vitamin D receptors resulting in production of antimicrobial peptides and cytokines thereby regulating cellular proliferation and differentiation. The most common side

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effect is pain at site of injection.[3,4]

Naresh et al.[3] (2019) reported the intralesional injection of vitamin D3 was associated with complete cure of lesion in 88.9% of Indian patients with plantar warts. In two other Indian studies, Singh et al. 4(2018) and Kavya et al.[5] (2017) reported the frequency of complete cure to be 72.5% and 82.6% respectively after intralesional injection of vitamin D3 while Aktaş et al.[6] (2016) reported it to be 80.0% in Turkish patients. While assessing the efficacy of cryotherapy, Tahir et al.[7] (2018) reported complete cure of lesion in 66.7% of Iraqi patients with plantar warts. Much lower frequency of complete cure has been observed by Bruggink et al.[8] (2015) and Cengiz et al.[9] (2016) who reported it to be 39.1% and 6.7% in Netherlands and Turkey respectively.

In the light of this review, intralesional vitamin D3 (72.5%[4] – 88.9%[3]) appears to be associated with higher frequency of complete cure than conventional practice of cryotherapy (6.7%[9] - 66.7%[7]) in patients with plantar warts. However, the evidence is currently limited to studies assessing the treatment response of these two treatment modalities individually and that can be biased due to differences in the population studied and skills of the treating dermatologist.

To the best of our knowledge, there is no single trial comparing these two therapeutic agents directly minimizing the selection bias. Therefore, we conducted this research to compare these two therapeutic options and the results will enable selection of more appropriate treatment option for patients with plantar warts in future practice.

Material and Methods

It was a randomized controlled trial conducted in the Department of Dermatology, Services Hospital, Lahore, 30th July 2020 to 29th January 2021. After approval from Hospital Ethical Review Board, total 110 patients (55 patients in each group) of either gender with age in the range of 18-60 years suffering from plantar warts (for more than 4 weeks) as per operational definition were enrolled through non-probability, consecutive sampling from outpatient department of dermatology. Plantar Warts: A single or cluster of skin lesions which is elevated, hard, rough, flesh-colored granular with pink base on clinical examination on plantar surface of foot mostly at pressure points of heel and metatarsal heads for more than 4 weeks. Patients suffering from warts in the preceding 6 months period only were included, after signing written informed consent to participate in the study. Patients who have taken any treatment during last four weeks, allergic to xylocaine or injection vitamin D, suffering from bleeding disorder (INR >2.0), having erythema around the wart or superadded infection were excluded. Pregnant and lactating mothers, patients with immunodeficient condition or taking immunosuppressive drugs, hypersensitive to cold such as Raynaud's phenomenon and cold urticaria, peripheral vascular disease, angina pectoris or other severe cardiac disease were also excluded.All the participants were than explained the details. Written informed consent and detailed history was taken from each patient along with measuring the size of lesions and photographs of lesions. These patients were then randomly divided into following two treatment groups using lottery method Group-A: Cryotherapy (n=55) in the group A, patients were treated with liquid nitrogen for 4 sessions 2 weeks apart. Liquid nitrogen was applied with cryogun in two freeze thaw cycles, each of 15 seconds duration, till freezing reaches 2 to 3 mm beyond the lesion in each thaw cycle. Group B: Intralesional vitamin D3 (N=55) in group B patients were treated with vitamin D, using aseptic technique 0.2ml of xylocaine plain 2% (20mg/ml) was injected by 30-gauge needle using insulin syringe at the base of the wart. Five minutes after injection the base of the wart was infiltrated with 0.6ml of vitamin-D3 200000 IU (Inj. Indrop-D 5mg/ml) by 30-gauge needle using insulin syringe. A maximum of 4 warts per session were injected at the base of wart. As in the group A, 4 sessions were delivered with a gap of 2 weeks. Patients were examined at each treatment session every 2 weeks for 2 months and then were followed in OPD every month for 4 months and to assess for treatment response. Efficacy was assessed as per operational definition. The efficacy was defined as ability of intralesional vitamin D3 or cryotherapy to result in complete clearance while moderate response is 50 to 99% resolution in size and number of lesions and mild response is 1 to 49% resolution in size and number of lesions. All the pre and post-treatment clinical examination was performed by a consultant dermatologist to eliminate bias. Confounding variables were controlled by exclusion. All the collected data were entered and analyzed through SPSS version 17. Numerical variables i.e., age, duration of disease and size of lesion at presentation were presented by mean ± SD. Categorical variables i.e. gender and efficacy were presented as frequency and percentage. Chi-square test was applied for comparison of efficacy between the groups taking p-value

≤0.05 as significant. Data were stratified for age, gender, duration of disease and size of lesion at presentation to address effect modifiers. Following stratification, chi-square test was re-applied for comparison of frequency of complete cure between the groups taking p-value ≤ 0.05 as significant.

Results

Age range in our study was from 18-60 years with mean age of 32.59 ±11.64 years. The mean age of patients in group A was 34.36 ±12.06 years and in group B was 31.93 ±10.99 years. Total 81 patients (73.64%) were between 18 to 40 years of age. Out of 110 patients, 76 (69.09%) were men and 34 (30.91%) were women with ratio of 2.2:1 as shown in figure I. Mean duration of disease was 7.77 ±2.54 weeks. Efficacy of Group A (Cryotherapy) was seen in 31 (56.36%) patients while in Group B (intralesional vitamin D3) was seen in 48 (87.27%) patients as shown in Figure II (p-value = 0.0001). Stratification of efficacy with respect to age groups and gender has shown in Table I & II respectively. Stratification of efficacy with respect to duration of disease shown in Table III.

Figure1: *Distribution of Patients according to Gender*

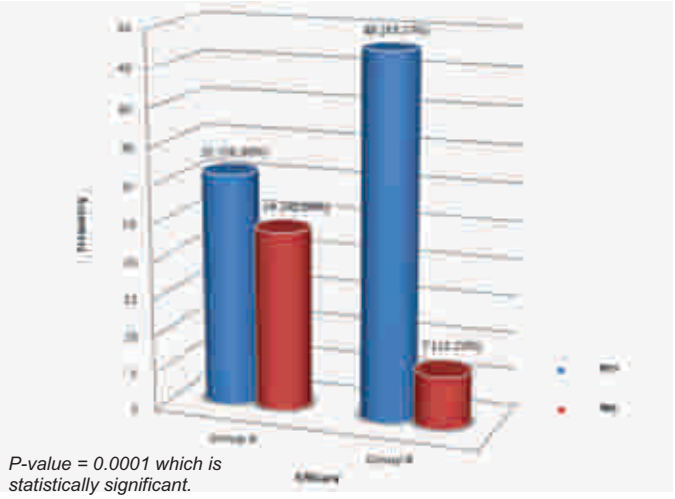

Figure II: *Comparison of the Efficacy of Cryotherapy Versus Intralesional Vitamin D3 in Plantar Warts*

Table 1: *Stratification of efficacy with respect to age groups*

Age of patients (years)	Group A (n=55)		Group B (n=55)		P-value
	Efficacy		Efficacy		
	yes	No	Yes	No	
18-40	23	18	33	07	**0.010**
41-60	08	06	15	00	**0.004**

Table 2: *Stratification of efficacy with respect to gender.*

Gender	Group A (n=55)		Group B (n=55)		P-value
	Efficacy		Efficacy		
	Yes	No	yes	No	
Male	24	13	36	03	**0.003**
Female	07	11	12	04	**0.034**

Table 2: *Stratification of efficacy with respect to gender.*

Duration of disease (weeks)	Group A (n=55)		Group B (n=55)		P-value
	Efficacy		Efficacy		
	Yes	No	yes	No	
≤8 weeks	19	16	36	03	**0.0001**
>8 weeks	12	08	12	04	**0.343**

Discussion

Warts are common cutaneous viral infections caused by the human papilloma virus (HPV), which has more than 100 strains; some of them are known to be premalignant. Warts occur more commonly in children and adolescents. May spontaneously disappear in a few but in majority persist and may spread to other body parts causing considerable physical and emotional distress.[10] Among treatment options are the conventional destructive and aggressive method, including chemical cautery, cryotherapy, electrocauterization, surgical excision, and laser ablation and non ablative is immunotherapy, which activates immune system to fight with the virus and suppress its activity. [11]

Topical vitamin D has been utilised in several studies for the treatment of common and anogenital warts. For example, Moscarelli et al[12] applied topical vitamin D in refractory warts in renal transplant patients. Rind et al[13] successfully used topical vitamin D in the clearance of anogenital wart in an infant. In both case reports, the effect of vitamin D on warts postulated to regulate epidermal cell proliferation and differentiation. In addition, Toll-like receptor activation of human macrophages upregulates the expression of VDR and vitamin D 1-hydroxylase genes, leading to release of antimicrobial peptides.[12,13] In a study of 17 patients with referatory warts, topical application of maxacalcitol ointment three times daily, cured warts within 2 weeks to 6

months.[14] Three immunocompromised patients with refractory warts were treated with topical vitamin D3 via a half-day occlusive dressing technique.[15]

This study is a comparison of cryotherapy versus intralesional vitamin D3 in the treatment of plantar warts. Mean patient age in our study cases was 32.59 ±11.64. Our study results have reported that majority of our study cases i.e., 81 (73.64%) belonged to age group of 18–40 years of age. Raghu Kumar et al[16] also reported viral warts being predominating 18–40 years age group which is similar to our study results. A study conducted by Moscarelli et al[12] reported 24.3 years mean age of the patients with warts which is less than our study results.

Out of these 110 patients, 76 (69.09%) were males and 34 (30.91%) were females with male to female ratio of 2.2:1. Such male gender preponderance has also been reported by Moscarelli et al[12] who reported 69% male gender predominance which is similar to our study results. While a study conducted Raghu Kumar et al[16] reported 56% female gender preponderance which is different from our study results. Mean duration of disease was 7.77 ±2.54 weeks. Raghu Kumar et al[16] and Moscarelli et al[12] reported very high duration of illness, the reason for this difference is due to our inclusion criteria as we only included warts having duration less than 3 months.

Efficacy of Group A (intralesional vitamin D3) was seen in 31 (56.36%) patients while in Group B (cryotherapy) was seen in 48 (87.27%) patients (p-value = 0.0001). Naresh et al.[3] (2019) reported the intralesional injection of vitamin D3 was associated with complete cure of lesion in 88.9% of Indian patients with plantar warts. In two other Indian studies, Singh et al.[4] (2018) and Kavya et al.[5] (2017) reported the frequency of complete cure to be 72.5% and 82.6% respectively after intralesional injection of vitamin D3 while Aktaş et al.[6] (2016) reported it to be 80.0% in Turkish such patients. While assessing the efficacy of cryotherapy, Tahir et al.[7] (2018) reported complete cure of lesion in 66.7% of Iraqi patients with plantar warts. Much lower frequency of complete cure has been observed by Bruggink et al.[8] (2015) and Cengiz et al.[9] (2016) who reported it to be 39.1% and 6.7% in Netherlands and Turkey respectively.

A trial done by Raghu Kumar et al, on 64 patients having warts showed that 90% of patients had complete clearance and 6.66% of the patients showed partial response when given intralesional vitamin D3.[16] Moscarelli et al applied topical vitamin D3 on referatory warts in renal transplant patients with good results.[17] Rind et al observed successful clearance of an anogenital wart in an infant after topically applying maxacalcitol.[18]

The vitamin D works through vitamin D receptors (VDRs) and vitamin D receptor activators (VDRAs) are immunomodulatory in function by regulating cell turnover. Toll-like receptor (TLR) activation of human macrophages upregulated expression of vitamin D receptor and vitamin D-1-hydroxylase genes resulting production of the antimicrobial peptide by infected cells as a part of innate immunity.[19] Isotretinoin when combined with calcitriol successfully cleared HPV-associated precancerous and cancerous skin lesions.[20]

Conclusion

The present study concluded that intralesional vitamin D3 can be used for treating plantar warts as its efficacy was higher than cryotherapy.

Conflict of interest: none

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Authors Contribution

HA, SA: Conceptualization of Project
HA: Data Collection
SD, AC : Literature Search
SS: Drafting, Revision
HE: Writing of Manuscript