Original Article

Efficacy and Safety of Intralesional Vitamin D3 Injection in Recalcitrant Periungual Warts: A Randomized Controlled Trial

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Abstract

Introduction: Although the treatment of recalcitrant warts is often disappointing due to its high recurrence rates, the intralesional injections of Vitamin D3 (as an immunotherapeutic molecule) may regulate epidermal cell proliferation.

Objective: To evaluate whether intralesional vitamin D3 immunotherapy is efficient and secure in treating the recalcitrant periungual warts.

Materials and Methods: This randomized controlled therapeutic trial was performed in the Department of Dermatology and Venereology of Combined Military Hospital, Dhaka from July 2018 to December 2019. A total of 64 participants' having different sizes and duration of recalcitrant periungual warts were included. Half of them were injected with about 0.2ml vitamin D3 solution (600,000 IU, 15 mg/ml) at the base of the wart (Group-A) and the remaining participants were subjected to cryotherapy (Group-B). A follow-up period of 6 months following the last session was performed to detect any recurrence.

Results: The mean age of participants in Group A and B were 25.9±12.6 and 26.4±12.4 years, respectively (78.1% male in Group-A and 62.5% in Group B). The size and duration of warts between the two groups were not statistically significant ($p>0.05$). The treatment outcome in Group-A varied from excellent 19(59.4%) to significant 8(25.0%), moderate 3(9.4%), mild (3.1%), and no response 1(3.1%), whereas in Group-B, the results were as follows: excellent 13(40.6%), significant 3(9.4%), moderate 9(28.1%), mild 7(21.9%). The efficacy was significantly higher in Group-A when compared to Group-B ($p <0.05$). Furthermore, the burning sensation, blister, erythema, hypopigmentation, depigmentation and skin atrophy were significantly higher in Group-B compared to Group-A. The recurrence of warts were 12.5% and 34.4% in Group-A and B respectively.

Conclusion: Vitamin D3 injection is more effective and secure than cryotherapy in the treatment of periungual warts.

Key-words: Periungual warts, Vitamin D_3 injection, Cryotherapy.

Introduction

Warts or verrucae of skin and mucosa is a benign epidermal proliferation caused by Human Papillomavirus (HPV)[1], appeared as a horny ring of hyperkeratosis, and therefore its elimination a still a challenge[2]. Among them, cutaneous warts are clinically present as verruca plana, verruca vulgaris, verruca palmaris and plantaris, periungual warts, and genital warts. Furthermore, it is raveled that among the HPV, the most common types of cutaneous warts are caused by HPV[3] 1, 2, 3, 4, 7, 10, 27 and 57. Moreover, 65%–78% of warts develop without apparent external influence and patients usually seek treatment when it causes cosmetically disfigure, the tendency to koebnerize, and pain or in a stage is transmitted to others. This makes adequate and timely treatment important[1,4]. The previous study also indicated that periungual warts are difficult to manage because of their location, and it causes psychological distress and embarrassment to the patients in the case of recalcitrant warts and is said therapeutic challenge for the dermatologist[3].

Regarding the treatment option, conventional treatments with variable responses have been reported[4]. This includes topical keratolytics, electrocoagulation, cryotherapy and laser therapy[5-8]. However, they often results in pain, scarring and frequent recurrences. In addition, they are not suitable in the case of destructive modalities (e.g. multiple and refractory warts) due to their limitation in the treatment of distant ones. Therefore, to overcome these shortcomings, the use of immunotherapy is expected during the last few years[9] and antigen such as measles, mumps, rubella (MMR); tuberculin purified protein derivative (PPD); *Mycobacterium* vaccine and *Candida* antigen have been tried in many previous studies[10-13].

Immunotherapy shows a potential modality for the treatment of resistant and recurrent warts without producing any scarring. It also boosts the host's immunity against the causative organism to reduce the chance of recurrences[3]. On the other hand, Vitamin D minimized the production and demarcation of keratinocytes, and it enhances the cell-mediated immunity to clear the warts[9]. Furthermore, when applied topically, it regulates the epidermal cell proliferation as well as the formation of antimicrobial peptides[2]. However, a limited number of studies have been performed to evaluate the safe treatment of warts by topical Vitamin D3 derivatives[14,15]. Aktas et al treated the plantar warts by using the direct injection of Vitamin D3 injection and found encouraging results[16]. Therefore, in the present study, cutaneous warts were subjected to the direct injection of Vitamin D3 and compared its effectiveness to that of cryotherapy, an established method of destructive therapy.

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Materials and Methods

This randomized controlled therapeutic trial was performed in the Department of Dermatology and Venereology of Combined Military Hospital, Dhaka from July 2018 to December 2019. The inclusion criteria consist of participants who had periungual warts but not received any topical modalities for at least 6 months. The exclusion criteria were as follows: participants whose age is <12 and >70 years, expecting and lactating females, immunosuppressant (including HIV), and history of hypersensitivity to Vitamin D3. The participant's history and clinical features were used for the diagnosis of Periungual warts. At first, the pre-operative condition of the warts, and demographic data for each participant was recorded using a structured questionnaire. Furthermore, the location, number, size and type of wart were recorded. A total of 64 participants were enrolled in this study and randomized by lottery method into Group-A and Group-B of 32 in each group.

Participants of Group-A received Vitamin D3 injection where a vial contain 6,00,000 IU of cholecalciferol in 1 ml (15 mg); warts were injected with 0.2 ml of lignocaine (20 mg/ml), and wait for few minutes. The base of each wart was subjected to 0.2 ml of Vitamin D3 (15 mg/ml) injection by using a 27-gauge insulin syringe. In each session, a maximum of 5 warts were treated where therapy were repeated in every 3 weeks but it was limited to four injections. Furthermore, it was stopped after achieving a complete clearance of the warts. During the first 2 months, the treatment efficacy and any adverse reactions were observed whereas the recurrence was varied for 6 months. Participants were advised not to use any topical and oral medications. Moreover, the size of warty lesions were also verified at each visit.

Participants of Group-B were subjected to cryotherapy where liquid nitrogen at -195.6 °C was used as cryogen. It is applied with a spray gun by using nozzles of suitable sizes for each patient and a maximum of 4 treatments was given in every 3 weeks. During the application, the spray gun was kept 1-2 cm far the warts and it was continued until the ice-ball spread from the center to the edge of the wart and 1 mm around the margin. Post-operative follow-up was performed every 4 weeks and continued for 6 months following completion of the last treatment given. Baseline evaluation and the size of warts were recorded during the first visit. The outcome of the treatment was graded as no response, mild response (1-25% reduction in the size of lesions), moderate response (26-50% reduction in the size of lesions), significant response (51-75% reduction in the size of lesions) and excellent response (76%-100% reduction in the size of lesions).

Results

The mean age of Group-A and B participants were 25.9±12.6 (range: 5 to 55 years), and 26.4±12.4 years (range: 9 to 60 years), respectively, and they were not statistically significant (p>0.05). Furthermore, in Group-A, the age range of 50.0% of the participants was 21-40 years, whereas, among Group-B, 53.1% was 21-40 years. Table-II shows that out of 32 participants, 78.1% were male and 21.9% are female in Group-A. Among 32 participants in Group-B, 62.5% were male and the rest 37.5% were female. The difference between the two groups was not statistically significant (p>0.05) (Table-I). The mean size of warts (largest) in Group-A was 6.5±4.7 and 6.4±4.2 in Group-B. Moreover, the size of warts and duration were not statistically significant (p>0.05) between the two groups (Table-II).

Table-III showed the outcome and recurrence between the two groups. It was revealed that the treatment response was excellent in 19(59.4%) participants followed by significant 8(25.0%), moderate 3(9.4%), mild (3.1%), and no response 1(3.1%) in Group-A. On the other hand, the response achieved in Group-B was excellent 13(40.6%) followed by significant 3(9.4%), moderate 9(28.1%), mild 7(21.9%) in Group-B. Furthermore, concerning excellent, Group-A revealed significantly ($p < 0.05$) higher (84.4%) clinical outcomes compared to Group-B.

Figure-1 shows that burning sensation, blister, hypopigmentation, depigmentation and skin atrophy were significantly higher in Group-B compared to Group-A and erosion and hyper-pigmentation were higher in Group-A. Hypopigmentation, dyspigmentation and skin atrophy were found in Group-B but were absent in Group-A. Figure-2 shows that the observed persistent side effects were skin atrophy (31.3%), dyspigmentation (15.6%), hypopigmentation (12.5%) which were found in Group-B but only hyperpigmentation (12.5%) was observed in Group-A. Recurrence of warts was 12.5% in Group-A and 34.4% in patients in Group-B and a significantly ($p < 0.05$) higher percentage of recurrence was found in Group-B in comparison to Group-A (Table-III).

Table-I: Age and sex distribution of the patients

Characteristics		Group-A (n=32)	Group-B (n=32)	Statistics
Age (years)	≤20	12(37.5)	11(34.4)	χ^2 =0.078 df = 2 p > 0.5
	21-40	16(50.0)	17(53.1)	
	41-60	4(12.5)	4(12.5)	
	Mean± SD	25.9±12.6	26.4±12.4	p > 0.5
Sex	Male	25(78.1)	20(62.5)	χ^2 =1.871 df = 1 p > 0.5
	Female	7(21.9)	12(37.5)	

Note: Percentage in parenthesis

Table-II: Distribution of two groups by size of warts and duration of warts

Size and Duration of warts		Group-A (n=32)	Group-B (n=32)	t-test's p value
Largest warts (mm)	Mean ± SD	6.5±4.7	6.4±4.2	> 0.05
	Range	1.5-20.0	2.0 -20.0	
Smallest warts (mm)	Mean ± SD	0.9±0.5	1.1±0.6	> 0.05
	Range	0.5-2.0	0.5-2.0	
Duration of warts (months)	Mean ± SD	9.5±5.02	9.4±6.2	> 0.05
	Range	2.0-24.0	1.0-24.0	

Table-III: Final outcome and recurrence between two groups

Outcome / Recurrence		Group A (n=32)	Group B (n=32)	Statistics
Final outcome	No response	1(3.1)	0(0.0)	χ^2 =11.353 df = 4 p < 0.5
	Mild	1(3.1)	7(21.9)	
	Moderate	3(9.4)	9(28.1)	
	Significant	8(25.0)	3(9.4)	
	Excellent	19(59.4)	13(40.6)	
Recurrence	Yes	4(12.5)	11(34.4)	χ^2 =4.267 df = 1 p < 0.5
	No	28(87.5)	21(65.6)	

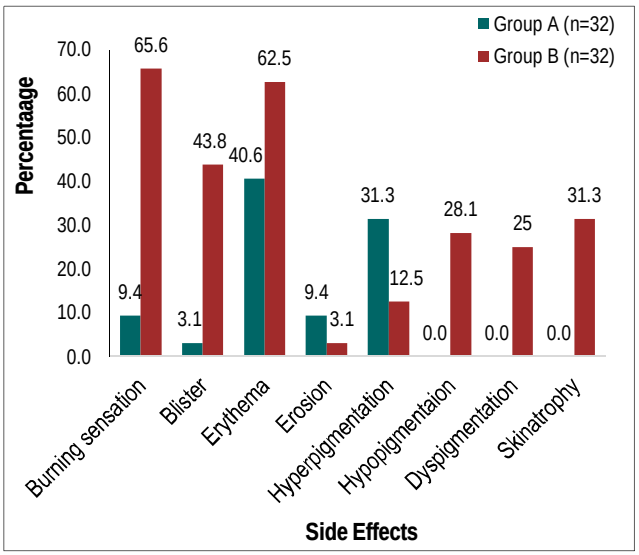

Figure-1: Bar diagram showing the side effects of the patients

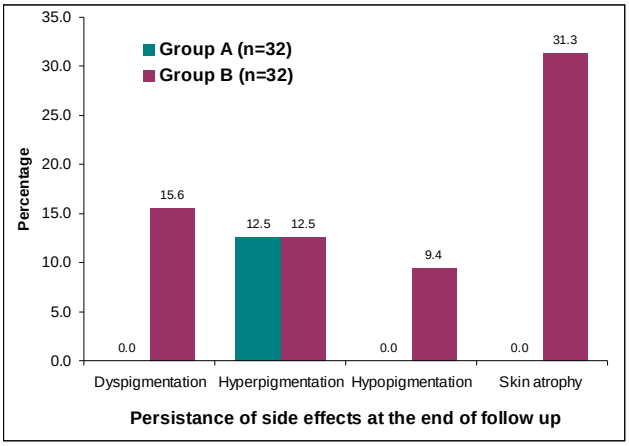

Figure-2: Bar diagram showing the persistence of side effects

Discussion

The findings of the present study are similar to the study of Priya A et al, Kavya M et al, Raghukumar S et al and Wafaa M et al[2,3,17,18]. Priya A et al conducted a study among patients at Aligarh, India in the year of 2018 who had palmoplantar and periungual warts for more than 6 months. The warts were non-responsive to at least two conventional treatment modalities following an intralesional injection of 0.2-0.5 ml of vitamin D3 (15 mg/ml), every 2 weeks. Among the 63 patients, 42 (66.7%) were men (age range: 12 to 49 years; mean duration of the disease: 1.5±1.2 years). The treatment outcome varied from complete response in 56 (88.9%) participants followed by 4 (6.3%) moderate and 3 (4.8%) mild. Complete clearances were observed in periungual warts (92.9%), then palmar warts (90.0%) and plantar warts (86.2%). Among the adverse side-effect, transient pain was prominent but it was managed by pre-injection with lignocaine. Other effects include swelling in 16 (25.4%) patients and it was subsided within a week. There were no other prominent side effects. Furthermore, at 6-month follow-up, 2 (3.2%) patients presented with recurrence (1 each of plantar and palmar warts). They recommended that immunotherapy with vitamin D3 was an effective and safe tool for the treatment of recalcitrant palmoplantar and periungual warts[3].

Kavya M et al conducted a study from August 2015 to November 2016 using 42 patients with cutaneous warts. A total of 27 males and 15 females were included in the study (age: 12 to 66 years, duration of warts: from 1 month to 96 months). The site of warts among the patient was as follows: twenty-three had palmoplantar warts, one had filiform warts over the face and 18 had verruca Vulgaris. Furthermore, multiple non-contiguous sites were involved in 16 patients (38.1%). Treatment and evaluation was performed in a similar manner of our present study. The results indicated that 19 (82.6%) of 23 patients having palmoplantar warts and 14 (77.8%) with verruca vulgaris were completely eliminated. However, six patients (14.3%) i.e., three each in the palmoplantar and verruca vulgaris group showed a moderate response. An improvement of 1 to <50% was achieved in one of each subtype

of warts. Minor adverse effects were seen in 34 (80%) patients but it was resolved without any treatment. Dyspigmentation was seen in one patient[17].

Raghukumar S et al performed a study with sixty-four patients having recalcitrant warts of varying sizes and duration and found that complete response was seen in 54 of 60(90%), partial response in 4 of 60(6.7%) and no response in 2 of 60(3.3%) with minimum side effects. They recommended that direct injection with vitamin D3 is a safe and effective treatment option for recalcitrant warts[18]. Another study by Wafaa et al[2] verified the response of Vitamin D3 versus zinc sulfate for the treatment of plantar warts among forty patients. In Vitamin D3 group, patients received intralesional injection of 0.3 ml vitamin D3 (100,000 IU (2.5 mg/ml) while zinc group patients received intralesional 2% zinc sulfate. They found that eighty percent of Vitamin D3 treated patients and 70% of zinc sulfate patients showed complete response[2]. This is also supported by Asghariazar R et al who reported that 60% positive response was achieved in the 5-FU group in comparison to 26.7% positive response in the cryotherapy group, $p < 0.05$. Asghariazar et al demonstrated that having scars was the only effect in the 5-FU group that was equal with the cryotherapy group[19].

Conclusion

Vitamin D3 injection is more effective than cryotherapy in the treatment of periungual warts and side effects and recurrence rate are more in cryotherapy group than Vitamin D3 injection group. A prospective multicentre evaluation with a larger sample size and a longer study period with long time follow-up are recommended.

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