

Original Article**A Prospective Clinical Study for Safety and Efficacy of Intralesional Tuberculin Purified Protein Derivative in Treatment of Palmoplantar Verruca**

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Article Received: 28th February, 2022; Accepted: 10th June, 2022; Published: 30th June, 2022DOI: <https://doi.org/10.3126/jonmc.v11i1.45720>**Abstract****Background**

Multiple treatment options are available for verruca, however none is completely effective. Conventional modalities such as salicylic acid, cryotherapy have inconsistent treatment efficacies. Newer modalities such as immunotherapy, bleomycin and lasers have shown higher clearance rates of warts in recent studies. Immunotherapy is an innovative approach to treat warts which relies on the principle of enhancement of cell-mediated immunity. This study was done to evaluate the efficacy of immunotherapy with Tuberculin Purified Protein Derivative injection in palmoplantar verruca in our context.

Materials and Methods

This is an open labelled, prospective interventional study. Patients with palmoplantar verruca enrolled in the study were injected with purified protein derivative intralesionally by an insulin syringe at a dose of 10 IU (0.1 mL) in the largest wart every 2 weeks until all lesions disappeared or for a maximum of six sessions. They were followed up for 3 months after final treatment session.


Results

A total of 54 patients, 34 males and 20 females, were enrolled in the study. Commonest distribution of palmoplantar verruca was in plantar distribution (48.1%). Among them, 12 (22.2%) patients had periungual warts. Complete clearance of warts without any scarring was seen in 66.7% (36) patients with palmoplantar verruca at the end of 6th session whereas 33.3% (18) patients did not respond. Adverse effects noted were erythema, edema and pain at injection site.

Conclusion

Intralesional injection of purified protein derivative is an effective and inexpensive treatment option for palmo-plantar verruca with good outcome.

Keywords: Immunotherapy, PPD, Verruca

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Introduction

Warts are benign tumors of the skin and mucosa caused by Human papilloma viruses (HPVs) leading to a slow and focal expansion of squamous epithelial cells [1]. The incidence of verrucae range from 0.84% to 4.7% different countries worldwide [2]. The disease process can be self-limiting; however, the course is unpredictable. Treatment is aimed to prevent further spread, decrease infectivity and for cosmetic concern [3]. Purified protein derivative of tuberculin bacilli has been used to boost cell mediated immunity in patient with warts [4]. The results current locally destructive treatments may be satisfactory but these modalities are associated with frequent recurrences along with significant scarring and dyspigmentation [5]. Immunotherapy is an innovative approach to treat warts which relies on the principle of enhancement of cell-mediated immunity [6]. A variable response has been observed with the use of antigens such as the measles, mumps, and rubella (MMR) vaccine; *Candida albicans*; *Bacillus Calmette–Guérin* (BCG), and *Mycobacterium indicus pranii* injected intralesionally [5]. Despite multiple treatment modalities, efficacy of any treatment isn't significantly superior to others. PPD injection is an innovative treatment modality, which has shown excellent clearance rates in previous studies, especially in recalcitrant and palmoplantar warts. The aim of this study was to evaluate the efficacy of immunotherapy with PPD injection in patients with palmoplantar warts. It would also delineate any adverse events associated with this treatment modality.

Materials and Methods

This open labelled, prospective interventional study was conducted in the Department of Dermatology of Dhulikhel Hospital from June 2019 to March 2020. The study was conducted after acquiring approval from the institutional Review Committee of Kathmandu University School of Medical Sciences/Dhulikhel Hospital (IRC-KUSMS). Written consent was obtained after the patient was explained about the study, regarding disease, treatment modality, follows up and advantages and disadvantages of procedure. Patient visiting the outpatient department of Dermatology during that time frame with new onset palmoplantar verruca and those recalcitrant to other modalities of treatment were included in the study. Patients with active infection or systemic illnesses, those on immuno-

suppressive drugs, and patient not giving consent were not included in the study. Prevalence of verruca has been seen upto 4.7% [2]. Using formula $(CI)^2 P(1-P)/(ME)^2$ sample size was calculated with Confidence Interval of 1.96, 5% margin of error. The sample size was calculated to be 68. Total number of patients included in the study was 61. Prospective purposive sampling method was used. A detailed history and examination was done to determine palmoplantar verruca, the number of lesions and any comorbidities. Photograph of the lesion were taken prior to treatment and on each follow up. Tuberculin purified protein derivative was injected intralesionally by an insulin syringe at a dose of 10 IU (0.1 mL) in the largest wart or the dose was divided in upto 10 lesions if multiple warts were present. It was then injected into the same lesions every 2 weeks until all lesions disappeared or for a maximum of six treatments. The size of warts at the injected site and that of other lesions were noted and distant warts were observed at follow-up visits. Patients were followed up for at least 3 months after the last treatment to look for recurrence of warts or the development of new warts. Only topical antibiotic was given post injection for duration of 3 days. No other adjuvant therapy was given during the treatment.

The response to treatment was evaluated by observing all the warts on injected and non-injected sites. The response was graded as Responder: Total clearance of the lesions, and Non-responder: No or partial clearance of the lesions. Data was entered in Microsoft excel and analysed by SPSS version 20. For categorical variables, frequencies were calculated.

Results

Out of a total of 61 patients with single or multiple palmoplantar warts that were included, 7 patients did not comply with the protocol or were lost to follow up and were thus excluded from the study. Among 54 patients remaining for complete analysis, warts were assessed for clearance. The patients in this study were between 14 to 55 years of age, and their mean age was 23.4 years. Maximum number of patients were in the age group of 11-20 years i.e. 26 (48.1%) followed by 21 (38.8%) patients in the age group of 21-30 years. The duration of the existing lesions ranged from about 2 months to 50 months. There were 34 males and 20 females and male: female ratio was 1.7:1 showing male predominance. Regarding the number of warts, 32 (59.2%)



patients had less than 10 warts, and remaining 22 (40.7%) patients had more than 10 warts at the time of presentation. Commonest presentation of palmoplantar verruca was in plantar distribution presenting in 26 patients followed by palmar distribution in 22 patients and only 6 cases with both palmo-plantar involvement. Among the cases 12 (22.2%) patients had periungual warts.

Following treatment 66.7 % of patients had complete resolution of lesions after 6 sessions. However 33.3 % patients did not show response to the treatment. The treatment was well tolerated by patients except for immediate pain due to injection. Few patients reported injection site erythema with swelling requiring oral analgesics. During the follow up period 4 patients had recurrence. In patients receiving immunotherapy who responded healing of lesions occurred without much scarring.

Table 1: Age wise distribution of patients

S. No	Age Distribution (Years)	Number of patients	Percentage (%)
1	11-20	26	48.1%
2	21-30	21	38.8%
3	31-40	5	9.3%
4	>40	2	3.7%

Table 2: Frequency of responders

	Frequency	Percentage
Responders	36	66.7%
Non responders	18	33.3%

Table 3: Response rate as per session of injection PPD.

Number of sessions	Responded patients	Cumulative response (%)
1	1	2.8%
2	5	13.9%
3	6	16.7%
4	11	30.5%
5	8	22.2%
6	5	13.9%



Figure 1: Palmar verruca at presentation and total clearance after 5th injection of PPD.



Figure 2: Periungual verruca before treatment and clearance after 6th session of PPD.



Figure 3: Palmar verruca at presentation (a), after 2nd session of PPD (b), and following 3rd session (c).

Discussion

Cutaneous viral warts are one of the common conditions presenting to the Dermatology OPD [1]. Although the spontaneous resolution rate for warts is 65–78%, the cosmetic disfigurement, tendency to spread and associated poor quality of life warrants quick intervention [7]. PPD or tuberculin stimulates the cell-mediated immunity nonspecifically by activating Th1 cells, NK cells, and cytokine production. An increase in IL-12 as a process in boosting the cell-mediated immunity contributes to the mechanism of action [7,8]. With immunotherapy, warts have been found to regress without any scarring and hence it is considered useful for plantar, facial and genital lesions [6]. Injection of antigen to which the patient was previously sensitized stimulates the elicitation phase of the immune response by enhancing the ability of the immune system to recognize human papilloma virus antigens. The immunostimulation is generalized which helps in clearing distant warts as well [9]. Intradermal injection of PPD results in stimulation of sensitized T cells and results in delayed hypersensitivity reaction, which begins at 5 – 6 hours and becomes maximum at 48–72 hours after the administration of tuberculin PPD [10]. Use of PPD has been proven to be safe among the children and pregnant women as well because of the fact that PPD does not contain any viable organisms [5].

In our study maximum numbers of cases were in the age groups 11-20 years (48.1%) followed by 21-30 years (38.8%). In a study conducted by Ranjit A and colleague [1], maximum frequency distribution of cases was in the age group 21-30

years (42%) which was similar with our findings. The highest frequency observed in these age groups might suggest their aesthetic concern as well as greater environmental exposure to HPV [1]. In this study, the frequency distribution of palmoplantar verruca had male predominance (63%) which was similar to the findings of other study [1]. It may be due to more outdoor work related in males and lack of awareness regarding need to seek medical help in females. The clearance rate of palmoplantar warts, after 6 sessions of treatment was 66.7% in our study. The result of our study was comparable to a study by S. Wananukul et al [11], in which 67% cure rate was observed. In contrast to our study, KerureAS [9] and colleagues observed higher cure rates of 94.4% (84 patients).

Common side effects after administration of PPD include pain, pruritus and discomfort at injection site. Development of ulcer or necrosis may rarely occur at the site of injection [10]. In our study we encountered 2 cases of local site reaction leading to intense swelling, pain and edema requiring discontinuation of therapy. Conservative management was done promptly. All other patients tolerated the therapy very well. Similarly side effects were minimum as pain was observed by only 3 patients (5.8%) and swelling or erythema in 10 patients (19.6%) in a study conducted by Jaiswal et al [12]. There are many agents used for immunotherapy which show significant results in terms of safety and efficacy. There may be concern regarding tendency for spontaneous resolution in warts resulting in a false increase in treatment response to injection PPD [7]. However, few studies have shown that there is significantly increased rate of clearance of warts with PPD injection when compared with injection of normal saline thus signifying that clearance of wart is due to immunity stimulation rather than due to effect of injection alone [5].

According to a study done by Khozeimeh et al [13], the patients showed a significant therapeutic response to immunotherapy compared to cryotherapy. Moreover, a significant difference was observed between the time-elapsd before treatment and the therapeutic response between both groups ($P = 0.041$). 76.7% of patients were completely cured with immunotherapy, while only 56.7% responded to cryotherapy. A comparative study done to see the result of Pulsed dye laser versus Nd-Yag in plantar verruca showed the cure rate was 73.9% with PDL with no significant difference ($p = 0.87$) from Nd:YAG (78.3%) [14]. This response rate is comparable to immunotherapy hence making it a treatment option with mild complications. Similarly a study showed

overall clearance rate of 75% in electrosurgery versus 73.3% in cryotherapy patients. However, pain, delayed wound healing and scarring were observed significantly in more patients treated with electrosurgery than cryotherapy [15].

In our study the higher clearance rate with injection PPD may be due to high prevalence of tuberculosis and compulsory Bacillus Calmette–Guérin (BCG) vaccination in our population. The higher prevalence of tuberculosis infection in developing countries may make it easy to induce a positive cell mediated immunity response with injection PPD. The limitation of our study was small sample size and absence of control group. More trials with larger number of patients need to be undertaken to prove the efficacy and exact dosing of PPD for the treatment of warts.

Conclusion

Palmoplantar verruca is a long standing disease with slight male predominance. Immunotherapy is a novel approach that helps resolution of palmoplantar warts without much scarring. Injection PPD is easily available, inexpensive and easy to administer with minimal side effects. However, local site reactions can cause severe pain and edema which needs prompt management. Therefore, intralesional immunotherapy using PPD could prove to be one of the treatment modalities for palmoplantar verruca.

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Conflict of interest: None

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