Original Research Article

Efficacy of tuberculin purified protein derivative (PPD) immunotherapy in the treatment of plane warts on face

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Abstract

Background: Viral warts are caused by Human Papillomavirus (HPV). Immunotherapy is one of the recent treatment modality with variable success rate. We undertook prospective study to evaluate the efficacy and safety of immunotherapy using tuberculin PPD for treatment of plane warts on face. **Material and Method:** A total of 40 patients were enrolled in the study each having more than 15 lesions on face. Each patient received 2 tuberculin units (TU) of PPD intra-lesionally not exceeding a maximum of 10 TU during each session. A total of 4 sessions were given at 2 weekly interval and patients were followed up to 6 months after the last dose. Clinical assessment was done by photographic measurements at baseline, before each treatment session, 1 and 6 months after completion of treatment. **Result:** Twenty-six patients (65.75%) showed complete clearance after 4 sessions, 10 (25%) patients showed partial clearance and 4 patients (10%) showed no improvement. Recurrence was seen in 10% patients. Erythema and pain at site of injection were the common adverse effects. **Conclusion:** Tuberculin PPD immunotherapy was found to be effective and safe treatment modality for plane warts with minimal side effects.

Key Word: Immunotherapy, Purified protein derivative, Viral Wart

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INTRODUCTION

Warts are caused by human papillomaviruses (HPVs)which infect keratinocytes. Local destruction of thewarts is a commonly employed treatment modalitywhich may be performed by chemical, electriccauterization, carbon dioxide laser andcryotherapy. All these modalities have a potential to causedyspigmentation and/or scarring and may be associatedwith frequent recurrences. The rate of clearance is influenced by many factors such as HPV serotype, host immune status, extent and duration of warts.[1]The role of immunity is documented by the appearance and persistence of warts in immunosuppressed, spontaneous regression of the majority of warts is related to cellular immunity.[2] The body's immune response to HPV infection is a multifactorial. It includes a reduction in epidermal Langerhans cells,[3,4] expression of human leukocyte antigen HLA-DR+ by keratinocytes, and intraepithelial up-regulation of intracellular adhesion molecule-1 (ICAM-1) and lymphocyte function–associated antigen-1.[5] A decrease in epidermal Langerhan's cells, an increase in dermal Langerhan's cells, CD4+ and CD8+ cellular infiltrates, and HLA-DR+ cells in the dermis are all seen with plain warts. Spontaneous regression is known to occur in warts due to the development of cell-mediated immunity (CMI) to the virus and such lesions demonstrate prominent lymphocytic infiltration in the dermis.[6,7] An immune response is essential for clearance of warts.[6,8,9] Immunotherapy is an innovative approach to treat warts which relies on the principle of enhancement of cell-mediated immunity. Immunotherapy for warts has been

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performed using diphenylcyclopropenone, squaric acid dibutyl ester (SADBE), imiquimod, tuberculin jelly, interferon alpha and gamma (IFN-gamma), skin test antigens like Candida,[6,7] mumps,[8,9] Trichophytin[8] and tuberculin. The objective of this study was to evaluate the efficacy, possible adverse effect anad reoccurrence rate of intra-lesional purified protein derivative (PPD) immunotherapy in treatment of plane watrs on face.

METHOD

The study was done in Department of Dermatology of National Institute of Medical Sciences and Research Institute, Jaipur. Patient more than 15 years of age with > 15 lesions of plain warts on face who were untreated or were off treatment for at least 4 weeks were included prospectively between September 2016 and September 2017. Those who declined to participate, pregnant women, positive history of keloid tendency, patients on immunosuppressive drugs and patients with active systemic illness or infection were excluded. After informed consent from the patient (or parent if the patient was a minor), 2 TU of PPD was injected into each lesion. In case of multiple lesions, a maximum of 10 TU of PPD was injected during each session. A total of four sessions were planned at an interval of 2 weeks irrespective of whether they had had a complete response. Patients reporting late for a session were continued on the regimen provided they were late by less than a week. Every patient was asked to complete the schedule of four sessions even if their lesions cleared earlier. Those patients who had complete resolution before four sessions were given 2 TU of PPD on the site of cleared lesions. Clinical response was assessed and photographs were taken during each visit. Patients were followed up at 1 month after the last dose. After 6 months, all the patients were called telephonically to enquire about any recurrence and 26 patients who returned for follow up were examined. No other systemic or topical anti-wart medications were allowed to be used simultaneously. 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:
  - Partial clearance- decrease in number > 30 %, as assessed by clinicial and photographic evaluation.
  - No improvement- no decrease in number of warts

RESULT

A total of 40 patients were available for analysis which included 24 males and 16 females age between 15-40 years with a mean (SD) age of 25.3 years (8.45). The number of lesions ranged from 15 to 40 with average of 25.85 lesions. Duration of disease ranged from minimum 6 months and maximum of 24 months with mean duration of disease of 7.05 months. Bilateral warts were present in 30 (75%) patients. Twenty six (65%) patients showed complete clearance after four sessions [Figures 1a and b, 2a and b,], while 10(25%) patients were Partial-responders [figure 3a and b]. The response rate of various types of warts is shown in Table 1. Mean age of responders and non-responders were 24.1 years and 27.1 years respectively which was statistically non-significant (p-0.48).Mean duration of lesion in responders and non-responders were 7.5 and 7.1 statistically non-significant (p-0.927). PPD injection was well tolerated. The most commonly observed side effects were mild redness and swelling and pain at the injection site seen in 5 patients which lasted for 4–7 days. Constitutional symptoms including low grade fever and body ache developed in one patient who had received 10 TU PPD and required analgesics for 3 days. No scarring or pigmentary change was observed in any patient. Two patient developed recurrence during the follow-up period.

Table 1: Number Of Sessions And Response Rate

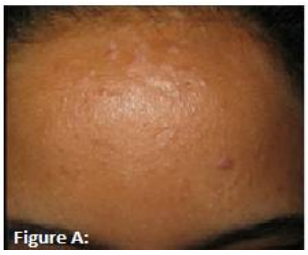
Visit	Complete clearance	Cumulative response	Partial response	No Response
First visit	0	0	0	0
Second visit- 2 weeks	3	3(7.5%)	0	0
Third visit- 4 weeks	4	7(17.5%)	2	0
Fourth visit- 6 weeks	7	14(35%)	3	4
1 month	10	24(60%)	2	4
6 month	2	26(65%)	3	4

Table 2: Response rate of various antigens/vaccines

Study	Antigen/ vaccine	Number of sessions given	Duration between twosessions(week/s)	Clearance rate (%)
Eassa *et al*.[8]	PPD	12	1	47
Wananukul *et al*.[9]	PPD	6	2	93
Johnson *et al*.[5]	Mumps/Candida	3	3	74
Present study	PPD	4	2	65
Gupta *et al*[10]	Mycobacterium w vaccine	10	1	89
Nofal and Nofal[11]	MMR	5	2	85

PPD: Purified protein derivative, MMR: Mumps, measles, and rubella

Figure 1



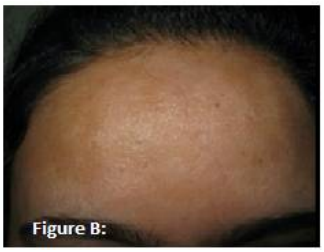


Figure 1

Figure 1: verruca plana (a) before treatment and (b) complete clearance after treatment; **Figure 2:** Female patient with plain warts on forehead (a) before treatment (b) after treatment; **Figure 3:** Patient of verruca plana (a) before treatment and (b) partial clearance after treatment

DISCUSSION

Local tissue destruction is a commonly employed method in the treatment of warts. However, it is not practical for facial lesions because of associated scarring or pigmentation.[6]None of the destructive methods available are precise enough to destroy only the epidermis and hence scarring is almost inevitable with the use of these modalities. With immunotherapy, warts have been found to regress without any scarring and hence it is considered useful for facial lesions.[11-13] In addition, the recurrence rate following immunotherapy is minimal as compared to destructive therapies.[6,12-14] Cell-mediated immunity plays a protective role against viral, fungal and mycobacterial infection. Warts are known to clear spontaneously and a Cochrane review found a cure rate of 22% in the placebo arm.[6,9] Hence, to stimulate cell mediated immunity viral, fungal or mycobacterial antigens and vaccines have been used.[10,11,13-16] Because of the high prevalence of tuberculosis infection in developing countries like India, it is easy to induce a positive cell mediated immunity response with PPD, which was the reason for selecting PPD for immune stimulation in our study. Injection of PPD stimulates cell mediated immunity non-specifically through activation of Th1 cytokines, natural killer cells and cytotoxic T cells and is found to be effective against all types of warts such as verruca plana irrespective of the serotype of HPV.[12,13,17]It was observed that immunotherapy injections lead to significantly greater clearance of warts than normal saline injections indicating that it is the specific effect of cell mediated immunity stimulation and not the effect of injection alone.[15,16] In a study of 233 patients, the response rate to immunotherapy was found to be unrelated to age and gender of the patient, type of warts and HLA typing.[16] It is believed that injection of PPD not only stimulates the local immunity but also leads to circulation of activated T cells in the body leading to clearance of injected as well as non-injected, distant warts.[12,13,17] The risk of hypersensitivity is very rare occurring in less than 1/million doses.[18]The maximum reported safe dose of PPD is 88 TU. No linear correlation has been observed

between tuberculin dose and skin reaction.[19]The largest dose used in our study was 10 TU in one patient who experienced constitutional symptoms which were easily managed with anti-inflammatory drugs. There are variations in various studies regarding the dose, the interval between sessions and the number of sessions [Table 2] and further studies are needed to develop a standard protocol. We decided to use an interval of 2 weeks as the usual time taken for local induration to resolve after the Mantoux test is[5,10] days. Table 2 compares the response rate of various antigens/ vaccines used in previous studies with the present study. In our study 26 (65%) patients had complete clearance of warts in only 4 sessions. The higher and quicker response rate may be due to the use of intralesional injections in multiple lesions and the higher quantity of PPD injected which was not done in earlier studies. The present study and other studies reveal that intralesional injections given on multiple lesions and over a number of sittings gives better and faster results.[12-16] In this study, the response obtained with using PPD was 65%. Kus *et al* [20] found that the result of treatment of common wart especially periungual wart was around 29.4%. It seems that the cure rate is different from that obtained by Kus *et al* due to small number of the patients or short duration of treatment in Kus *et al* study. Lahti and Hannuksela[21] used tuberculin (PPD) as topical jelly in treatment of common warts, 8 out of 14 patients (57%) showed complete disappearance of their warts. The disappearance of warts usually occurred in the 3rd or 4th month. The major disadvantage of topical tuberculin jelly is the long duration of treatment as the disappearance of warts occurred after 3-4 months of treatment. PPD injection is better than topical tuberculin (PPD) in spite of its tolerable pain due to its short duration of therapy and the strength of the tuberculin reactivity was correlated with the disappearance of the warts. Purified protein derivative immunotherapy was well tolerated by our patients. In our study, only 2 patients developed recurrence during the follow-up period similar to that observed in another study.[13]The limitations of our study include absence of a control group and Mantoux test not having been done and hence we could not correlate the response rate with Mantouxpositivity. This study suggests that intralesional immunotherapy with tuberculin PPD may be a useful treatment of plane warts on face with minimum side effects and no associated scarring or pigmentation. It is widely available, cheap and easy to use.

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