Original Research Article

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Intralesional immunotherapy with purified protein derivative antigen in the treatment of multiple cutaneous warts: an open label study in an urban teaching hospital

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ABSTRACT

Background: Viral warts caused by human papilloma virus are a group of oncogenic viruses that result in verrucous growths on the skin and mucosae. Intralesional immunotherapy has been tried in recent years with success with the use of a variety of antigens to non-specifically stimulate the cell mediated immune response. Similarly, we undertook a study to evaluate the efficacy and safety of tuberculin purified protein derivative as an immunotherapeutic modality. **Methods:** A total of 25 patients were included in the study. Each patient was injected with 2.5 TU of tuberculin PPD (0.04 ml) intralesionally into most of the warts at 2 weekly intervals for a maximum of six sessions. It is an interventional study with follow-up upto 6 months. Descriptive analysis was done with use of SPSS version 23 tool. Complete resolution of warts was considered as the clinical end point. Response was graded as excellent response (>80% resolution), good response (50-80%), fair response (20-50%) and no response (<20%).

Results: Out of the 25 patients, 14 patients showed excellent response (56%), 4 patients showed good response (16%), 5 patients showed fair response (20%) and 2 patients did not show any response (8%). Over 22 patients (88%) showed features of pain, erythema and inflammation at the injection site, whereas 3 patients (12%) developed itching at the site. The 'faces' pain rating scale was used to measure pain tolerance. An overall response rate (fair/good/excellent) was given by 23 out of the 25 patients (92%), which proved satisfactory.

Conclusions: Intralesional immunotherapy with PPD effectively cures warts which are present locally and also at distant sites. It is safe, economic and efficacious.

Keywords: Intralesional, Tuberculin PPD, Cell mediated immunity, Human papilloma virus

INTRODUCTION

Human papilloma virus (HPV) causes cutaneous and mucosal warts which manifest in the form of verrucous growths. Out of the various layers of the epidermis, though stratum basale is primarily infected with the virus, stratum spinosum and stratum granulosum bear the brunt of viral replication as they are mature keratinocytes.

There are a wide range of factors that predispose an individual to develop viral warts. Idiopathic aetiologies also do play a role, but the common factors include trauma in the form of nail biting, scratching, using swimming pools, colposcope, fumes generated by laser, electrocautery and cryotherapy.¹

Treatment of warts has proved to be quite distressing from the patient's and well as dermatologist's

perspective. But point of concern lies in recurrence and incomplete cure after treatment. Dermatologists have tried numerous surgical treatment methods as well, but there again lies the problem of patient compliance and expenditure in refractory cases.

Immunotherapy has gained relevance and importance in the recent past as a promising treatment modality for typically multiple and recalcitrant warts. Immunotherapy can be used either in the form of topical, intralesional or systemic route. Out of the intralesional modalities, Purified protein derivative finds a significant role. Other intralesional therapies include bleomycin, interferon, *Candida albicans* antigen, measles-mumps-rubella (MMR) vaccine, lipid garlic extract (LGE), bacillus calmette guérin (BCG) vaccine and mycobacteriumindicuspranii vaccine.^{2,3}

A nonspecific immunological response is activated by the Th1 cytokines which further stimulate the natural killer cells and cytotoxic T cells leading to a delayed form of hypersensitivity response that augments host immune status. This is the basis for lesion clearance at not only the injection site but also at distant sites. ^{4,5} We have tried to make use of purified protein derivative in context of Indian population for the management of multiple warts as this treatment modality is easily available and most importantly cost effective.

METHODS

The study was conducted at Sree Balaji medical college and hospital between April 2016 and March 2017 after prior approval from institutional ethics committee. Total of 25 patients with cutaneous warts were included in the study. A well-informed consent was taken prior to patient inclusion in the study. We used tuberculin purified protein derivative (PPD) as immunotherapeutic agent in our study to demonstrate its safety and effectiveness in patients in ages between 18 and 60. Inclusion criteria included new patients of either sex in the above mentioned age group with common warts (verruca vulgaris) >1 in number and not on any systemic or topical therapy. Exclusion criteria included non-consenting patients, patients with other types of warts, pregnant and lactating females, patients on immunosuppressive treatment, patients with keloids and patients with immunocompromised status.

All patients were clinically examined for number of warts, duration, site and symptomatology. 0.04 ml of 5 TU/0.1 ml strength PPD was injected intralesionally into all warts if less than 5 in number or majority of warts if more than 5 in number with the help of insulin syringe in every patient at regular interval of 2 weeks for a maximum of 6 injections. Patients were followed up fortnightly to assess clinical improvement and after completion of treatment and further follow ups were done every month for 6 months. It is an interventional study. Descriptive analysis was done with use of SPSS tool

version 23. The improvement was compared with the help of clinical photographs taken at baseline, at 6 and 12 weeks of completion of treatment. The response was concluded as excellent (>80% clearance), good (50-80% clearance), fair (20-50% clearance) and no response (<20% clearance). We stopped giving PPD, if either the patient got complete clearance of the lesion or did not respond even after 6 visits (12 weeks), but all the patients were followed up for duration of 6 months.

RESULTS

All 25 patients either completed the entire course of treatment of twice weekly injection of intralesional PPD for 6 sessions or till they achieved complete cure. Of all patients 17 patients were males and 8 were females. An age- group wise and sex wise distribution is mentioned in (Table 1).

Table 1: Age group and sex wise distribution of the study group.

No. of warts	No. of patients	Male	Females
18-40	17	12	5
41-60	8	5	3

We had included patients in the age group of 18-60 years. 17 patients were in the age group of 18 to 40 years and 8 patients were in the age- group of 41 to 60 years. The duration of warts in the patients is mentioned in (Table 2). 12 out of 25 patients (48%) had warts from <6 months duration, 8 patients (32%) had warts from 6 to 12 months, whereas 5 patients (20%) had warts for >1 year.

Table 2: Duration of the warts with respect to the age group.

Duration of warts	Age group (years)				
Duration of warts	<40	>40			
<6 months	10	2			
6 to 12 months	6	2			
>1 year	1	4			

Two patients had <2 warts whereas 7 patients had >10 warts. A distribution chart showing the number of patients with respect to wart count has been mentioned in (Table 3).

Table 3: Number of warts with respect to the patient age groups.

No. of warts	No. of patien	ts
110. 01 Walts	<40 years	>40 years
<2	2	0
2-5	2	2
6-10	9	3
>10	4	3

Result before and after treatment is demonstrated in (Figure 1-3). Excellent response (>80% clearance) was noted in 1 patient as early as 2 weeks. There was a steady increase in the response shown by other patients over the course of treatment. By the end of 12 weeks, 14 patients had shown excellent response (56%), 4 patients showed good response (16%) and 5 patients gave a fair response (20%), whereas 2 patients showed no response at all (8%). A detailed clinical response grading with respect to the age group and number of visits has been given in (Table 4).



Figure 1: (A) Before and (B) after treatment photographs of warts over the dorsum of hands.



Figure 2: A) Before and B) after treatment photographs of subungual warts seen on the left thumb.

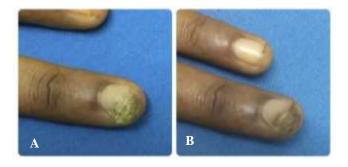


Figure 3: A) before and B) after treatment photographs of subungual warts seen on the ring finger.

Table 4: Clinical response grading with respect to age group during each visit.

Clinical response	No response (<20% clearance)		Fair response (20%-50% clearance)		Good re (50%-8	esponse 0% clearance)	Excellent response (>80% clearance)		
Age group (years)	<40	>40	<40	>40	<40	>40	<40	>40	
Week 2	3	8	11	0	2	0	1	0	
Week 4	2	6	11	2	3	0	1	0	
Week 6	3	5	8	3	4	0	2	0	
Week 8	4	4	6	3	5	1	2	0	
Week 10	2	2	2	4	3	1	10	1	
Week 12	0	2	1	4	4	0	12	2	

Table 5: Pain rating scale during each visit.

Pain scale (out of 22 patients)	0		1		2		3		4		5	
Age group (years)	<40	>40	<40	>40	<40	>40	<40	>40	<40	>40	<40	>40
2 weeks	0	0	1	0	3	2	8	4	3	1	0	0
4 weeks	0	0	2	0	4	2	8	4	1	1	0	0
6 weeks	1	0	2	1	1	2	11	4	0	0	0	0
8 weeks	1	1	3	3	10	1	1	2	0	0	0	0
10 weeks	6	3	7	3	2	1	0	0	0	0	0	0
12 weeks	13	5	2	2	0	0	0	0	0	0	0	0

During the entire course of treatment, we assessed the pain severity of patients by using the 'faces' pain rating scale (PRS). Figure 4 depicts the image of this scale. Pain was a predicted outcome due to the requirement of multiple intralesional injections at each sitting. The

proposed mechanism of action of PPD via developing an immunological response itself can cause resultant pain and inflammation. 22 patients (88%) complained of pain, erythema and inflammation at the site of injection. But over the course of time, patients showed better

tolerability and compliance to treatment. At the start of treatment 4 patients had a PRS of 4 (18.18%), 12 patients had a PRS of 3 (54.54%), 5 patients had a PRS of 2 (22.72%) and 1 patient had a PRS of 1 (4.54%). (Table 5) shows the distribution of PRS with age-wise and two-weekly follow-up among the 22 patients that complained of pain. 3 patients complained of non-specific pruritus at the injection site which self resolved with time.

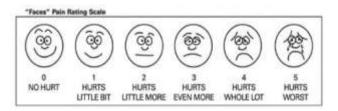


Figure 4: 'FACES' pain rating scale.

DISCUSSION

HPV are a large group of DNA viruses resulting in several dermatoses including verruca vulgaris (common wart), palmoplantar warts, verruca plana, Butcher's warts, Epidermodysplasia verruciformis, focal epithelial hyperplasia (Heck's disease) etc., The common HPV types known for the causation of verruca vulgaris are 1, 2, 27, 57 and rarely types 4, 29, 41, 60, 63, 65.

Recurrent viral warts are troublesome to the patient and even to the treating physician as they are recalcitrant to conventional modes of therapy. Cryotherapy is a widely used local destructive therapeutic modality but, recurrent and multiple warts are troublesome. A definite role of host immunity has been suggested for persistence of warts. Immunodeficient status of the individual has been often linked with multiplicity and chronicity of warts. But an impaired cell mediated immune response in even a healthy individual can be a cause of delayed cure.

Chemical cauterisations with use of trichloroacetic acid, monochloroacetic acid, surgical excision, radiofrequency, electrocauterization, laser ablation have been used in clinical practice. But the tendency of these lesions to recur causes an impaired patient compliance and piles up the overall therapeutic cost. Repeated aggressive therapies lead to a significant impact on quality of life of patients. Several topical treatment modalities have also been tried with varying results. Many novel approaches have hence been developed for the management of this distressing dermatoses.⁸

Immunotherapy has shown promising results in treatment refractory cases. It can be administered either solitarily or in combination with other topical/surgical therapeutic procedures. Immunotherapy is a mode of biological therapy that helps to either boost or suppress immunity in the manner required to give necessary clinical results. Patients of multiple and recalcitrant viral warts are ideal candidates for immunotherapy. Immunotherapy as a

treatment modality has been used not only in the treatment of warts but also in the management of atopic dermatitis, alopecia areata and lentigomaligna. 9-11

Use of topical immunotherapy in recalcitrant warts traces way back to 1970s.Immunotherapeutic agents in the treatment of viral warts can be classified as topical agents, intralesional agents and systemic agents.Injection of purified protein derivative (live attenuated *Mycobacterium tuberculosis* antigen) intralesionally, causes stimulation of the cell mediated immune response as discussed earlier.

It has been found to be useful in genital as well as extragenital warts. A study conducted by Eassa et al. shows the efficacy and safety of using PPD for treatment of anogenital warts in pregnant females. Overall, 85% response rate was found with 47.5% cases showing complete clearance.⁴ This closely matches the 56% excellent response in our study.

Kaimal et al conducted an open labelled uncontrolled trial for the use of PPD in cryotherapy resistant warts and the results were encouraging.⁵ Their study outcomes also matches our observations. Jaiswal et al., report clearance in over 68.6% patients.¹² It was also put forth in this study that periungual and palmar warts give much betterresults which resembles our observation. Nimbalkar et al also reproduces similar results (62.2% response) in their study.¹³

An open labelled study conducted by Saoji et al shows the varying types of adverse effects that may occur following these injections most commonly erythema and swelling at injection site in 23.63% cases. ¹⁴ Our study reported a high incidence (88%) of these local side effects in the first sitting which gradually settled with subsequent sittings.

Limitations

In this study, sample size was small and results were not compared with a control group. Larger studies with the use of other immunotherapies and PPD have to be performed to determine further efficacy.

CONCLUSION

In conclusion we would like to state, BCG vaccination and high prevalence of tuberculosis in India is the cause of adequate and early sensitisation of Indians to the PPD antigen which forms a strong foundation to the use of PPD for the treatment of recalcitrant warts. Hence it is an encouraging cheaper and excellent treatment alternative for warts.

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Ethical approval: The study was approved by the

 $institutional\ ethics\ committee$

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