J Nepal Health Res Counc 2022 Oct-Dec;20(57): 881-5

Efficacy and Safety of Intralesional Immunotherapy with Tuberculin Purified Protein Derivative among Cutaneous Wart Patients

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ABSTRACT

Background: Cutaneous warts are common skin problems caused by Human Papilloma Virus. Conventional therapies are mostly ablative and limited by recurrences and side effects. Immunotherapy using bacterial, fungal, and viral antigens is an emerging and safer technique to treat warts at local and distant sites. The objective of this study was to measure the efficacy and safety of intralesional immunotherapy with tuberculin purified protein derivative among cutaneous wart patients in the dermatology department of a tertiary care centre.

Methods: A cross sectional, time series design, was conducted between October 2019 and September 2020 among 77 patients of cutaneous warts attending Dermatology out-patient department using convenience sampling. Percentage response was evaluated for patients treated with tuberculin purified protein derivative for eight weeks at an interval of two weeks into complete response (100% clearance), partial response (50-99% clearance), no response (0-49% clearance). Side effects were also recorded. Statistical Package for the Social Sciences version 20.0 was used for data analysis.

Results: Out of 77 patients, complete response (100%) was seen in 53.2% patients, partial response (50-99%) in 14.3% and no response (0-49%) was seen in 32.5%. Side effects noted were pain and erythema (19.50%), blisters (2.60%) and flu like symptoms (1.30%).

Conclusions: Intralesional PPD is an effective and safer therapeutic option for the treatment of cutaneous warts.

Keywords: Immunotherapy; intralesional injections; purified protein derivative of tuberculin; warts

INTRODUCTION

Cutaneous warts are benign proliferations of the skin caused by the human papillomavirus (HPV).[1] Cutaneous wart account for 7-12% of Dermatology outpatient visits.[2] Viral warts are notorious for being contagious, recurrent, and recalcitrant. Spontaneous remission of warts occurs in two-thirds of children within two years while in adults, it may take up to several years. Treatment is challenging with frequent failures and recurrences especially when they are numerous or present over inaccessible areas.[3]

Conventional modalities of treatments are usually destructive and limited by frequent recurrences and side effects (scarring and pain).[4] Immunotherapy using Purified Protein Derivative (PPD), Measles Mump Rubella (MMR), Bacillus Calmette Guerin (BCG), and Candida antigen is a novel and non-invasive modality of treatment for cutaneous warts.[5]

This study aims to measure the safety and efficacy of tuberculin PPD for the treatment of cutaneous warts in a tertiary care center in Nepal.

METHODS

A cross sectional, was conducted in the outpatient department of Dermatology at Kathmandu Medical College Teaching Hospital (KMCTH) between October 2019 and September 2020. Data was collected using a predesigned proforma. Informed written consent was taken from the patient and ethical clearance was taken from the institutional review board, KMCTH (Reference number: 1207201913).

Considering the proportion of complete response of PPD in cutaneous warts to be 72% in previous studies and Standard error of 10%, the sample size was calculated as 77.

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Considering 20% drop out rate final sample size was calculated as 92.

Inclusion criteria were i) age between 13 and 65 years and ii) Cutaneous warts. Exclusion criteria were i) mucosal warts, ii) other treatment modalities in the past two weeks, iii) active tuberculosis, iv) acute febrile illness, v) immunocompromised status, vi) generalized dermatitis and vii) hypersensitivity to purified protein derivative. Convenience sampling technique was used.

Tuberculin purified protein derivative 0.1ml (10U/0.1ml; beacon diagnostic Pvt. Ltd; code no I 02; Mfg.Lic.No. G/433) was injected over the mother wart or the largest lesion at intervals of two weeks for a total of eight weeks. The overall response was evaluated by a registered Dermatologist subjectively by photographic comparison with previous pictures. The response was categorized based on the percentage of clearance of lesions: complete response (100% clearance), partial response (50-99% clearance), no response (0-49% clearance). Side effects of treatment were also recorded.

Data analysis was done using Statistical Package for the Social Sciences (SPSS)version 20.

RESULTS

Out of 92 patients treated with intralesional immunotherapy, 77 patients' completed the study. Complete response was seen in 41 (53.24%) patients, partial response in 11 (14.30%) patients and no response in 25 (32.50%) patients (Figure 1).

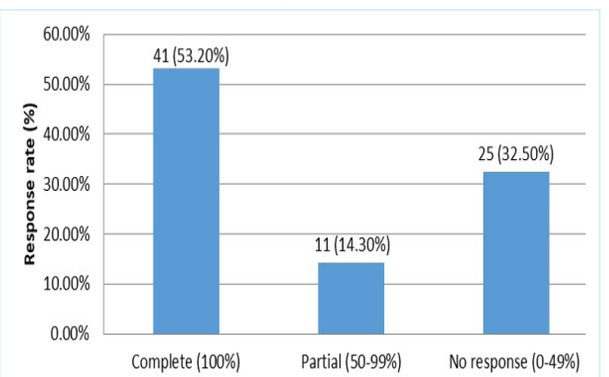

Figure 1. Response to treatment (n= 77).

Overall, 18 (23.4%) patients developed side effects. Most common side effect was pain and erythema in 15 (19.50%) followed by blisters in 2 (2.60%)(Figure 2).

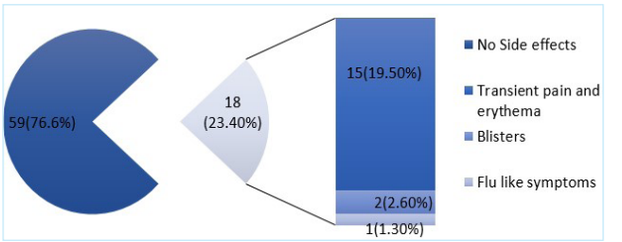

Figure 2. Side effects of tuberculin purified protein derivative (n= 77).

Out of the total 92 patients treated with intralesional immunotherapy,52 (56.52%) were male and 40 (43.47%) were females. The age range was 13 to 52 years (mean=22.4± 7.5). Almost half 57 (55.43%) of the patients were of the age group 20-29 years followed by 34 (32.60%) in 12-19 years age group (Figure 3)

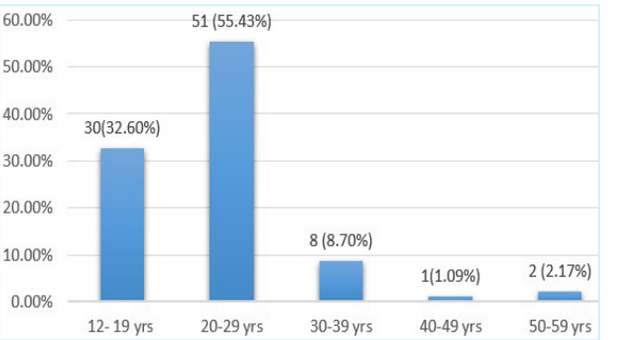

Figure 3. Age distribution of cutaneous warts (n=92)

Figure 4. Slightly more than half of the lesions were on the extremities 48(52.17%) followed by palms and soles 37 (33.94%)

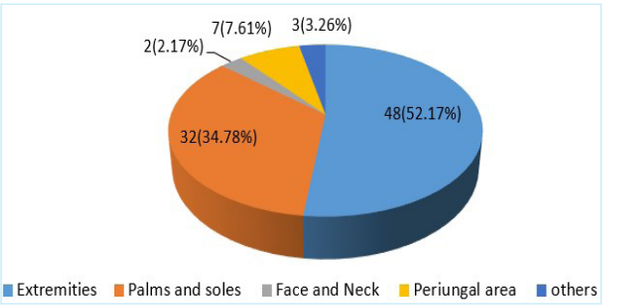

Figure 4. Site of Warts (n=92)

The duration of the lesions ranged from 1 month to 12 years (mean=25.7 months, SD=27.74).

Almost half 42 (54.5%) of the patients had 1-5 lesions.

The minimum and maximum number of lesions were 1 and 100 respectively. Median number of lesions was 5±18.87.

The smallest lesion was 12mm^2 and the largest was 300mm^2 (mean size =91.83 mm^2 ± 52.99)

The Majority of the patients 71 (77.30%) did not receive previous treatment. Of Those who received treatment, the most common modalities of treatment were corn tape 10 (10.87%) and salicylic acid 5 (5.43%) (figure 5).

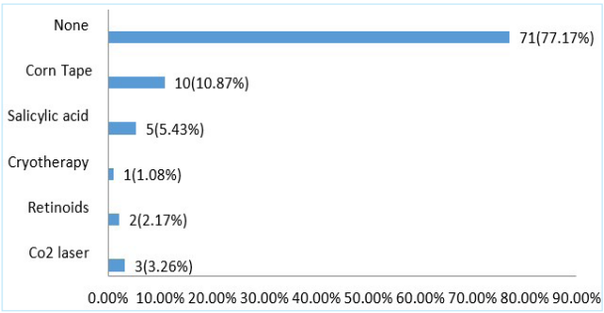

Figure 5. Previous Treatment modalities of warts (n=92).

DISCUSSION

Our study showed a complete response rate of 53.24%. This is comparable to other studies where the complete response rate ranged between 29-76%.[6] An interventional, randomized, placebo-controlled, parallel-group study done in Ismailia, Egypt among 40 patients showed complete clearance of target lesion in 12 (60%) vs. distant untreated warts in five (25%) vs. no response in target and distant wart in the placebo group.[7] In this study, PPD dose was given weekly for six weeks to patients who already had a BCG vaccine during childhood. Dosing (0.1-0.3ml) was based on the reading of the Mantoux test, and the response was measured separately at the injection site and distant site. The higher efficacy seen in this study might be due to testing of preexisting immunity by Mantoux test or inclusion of patients who had a prior history of BCG vaccination during childhood. The duration and frequency of administration are also different from our study. Doing more sessions might be another reason for higher efficacy seen.

Saoji V, et al. performed a study in the university hospitals in Maharashtra, India among 55 patients.[5] Complete clearance was seen in 42 (76%) after four sessions. In this study, an injection was applied to all the lesions. 2.5U in each up to a maximum of 25 tuberculin units (TU) at a maximum of 10 sites. It was injected every two weeks for a total of eight weeks irrespective of the clearance status. Mantoux test was not done to see the pre-existing immunity because of the practical difficulties in reading after 48-72 hours and neither was the response measured categorically at lesional and nonlesional sites. The higher dose used and injection at all the lesions might explain the higher efficacy seen in this study compared to ours.

A study was done by Shaheen M, et al. to compare the efficacy of PPD vs placebo and PPD vs MMR.[8] Thirty patients with multiple warts were included (10 treated with PPD, 10 with MMR, and 10 with normal saline (control). Pre-existing immunity was tested using the respective antigens and only the responders were included. Dosing was based on the measurement of induration. The injection was given every three weeks until clearance or a maximum of three treatments. The clinical response of target and distant warts was evaluated. It showed that six (60%) of the patients receiving PPD had complete clearance at distant and lesional sites compared to placebo. The better results seen in the above studies could be due to higher dosage of PPD used, longer duration of treatment, dosing based on Mantoux test, and injection into each lesion compared to injection of a single lesion in our study. We also did not check the preexisting immunity looking at the BCG scar which might also be a reason for not mounting adequate cell-mediated immunity to clear the virus.

A study done by Kus S, et al. in 13 patients in Israel showed that only six (29.4%) had complete clearance. This low response might be attributed to the inclusion of only recalcitrant warts in this study.[9] Another study done in 42 patients by Wananukul S, et al in Thailand for palmoplantar and periungual wart showed 39 (67%) had complete resolution of the lesion.[10] In this study 0.1ml PPD was given every two weeks for a total of eight weeks like in our study.The higher efficacy seen in this study might be because of a better selection of patients with preexisting immunity to the injected tuberculin antigen.

The use of PPD has been compared with other antigens such as candida antigen, MMR, and BCG vaccine. In one review complete resolution using candida antigen was between 43-100% and using PPD was between 29-76%.[6] In a study by Shaheen M, et al. MMR vaccine was shown to have 40% and 80% complete response rate for distant and target warts respectively compared to PPD which had 60% complete response for distant and target warts.[9] Na C, et al used measles mumps rubella vaccine (MMR) as intralesional antigen to treat cutaneous warts with

a response of 51.5% in local warts and 46.7% in distant warts.[11] A network meta-analysis has shown that PPD (OR 39.56), MMR (OR 17.46), and interferon-ß (OR 15.55) had significant superior efficacy ($p<0.05$) for complete recovery at the primary site compared to placebo while at distant sites autoinoculation (OR 79.95), PPD (OR 42.95) and MMR (OR 15.39) were found to have significantly superior efficacy ($p<0.05$) for complete recovery.[12]

The notable side effects in our study were transient pain and erythema 15 (19.5%), blisters two (2.6%), and flu-like symptoms one (1.3%). These side effects were transient and subsided within a few days with rest and anti-inflammatories and were comparable to the other studies done by Saoji V, et al.[5] (pain and erythema- 23% and flu-like symptoms- 1.8%) and Abd- Elazeim F, et al.[7] (pain and erythema-15% and no flu-like symptom), however blistering was more common in our study two (2.6%) compared to theirs 0%. No or minimal side effects were noted in the study done by Shaheen M, et al.[8] Kus S[9] and Wananukul S.[10]

Intralesional immunotherapy have shown to be an efficacious treatment by inducing a non-specific inflammatory response against HPV infected cells with a predominant TH_1 cytokine profile which helps to clear not only the local but also warts at a distant site.[7,13] Purified protein derivative is safe, standardized, inexpensive, and widely used antigen in immunotherapy.[5,9,10,14] 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.

Lack of placebo group, dosing of PPD without mantoux test and no measurement of treatment response seperately at target and distant lesions are few limitations of our study.

CONCLUSIONS

Intralesional PPD is an effective and safer therapeutic option for the treatment of cutaneous warts.

CONFLICT OF INTEREST

The authors declare no conflict of interest

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