Efficacy of Intralesional Purified Protein Derivative (PPD) in the Treatment of Cutaneous Warts

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ABSTRACT

Introduction: Warts caused by human papilloma virus are common problem. Various methods of treatment are available including immunological methods. In this study we aim to measure the efficacy of immunologic treatment of cutaneous warts with intralesional injection of purified protein derivative.

Materials and Methods: All the patients presenting to the Out-patient Department of Dermatology and willing to participate for the treatment of warts and not falling under the exclusion criteria were included as study cases. Each of them were given the injection into the largest lesion every fortnightly for total 3 injections. Length, breadth, number of lesions and any local changes at the site of injection were recorded in each visit.

Results: There was significant decrease in number of warts and length as well as breadth of the largest wart at the time of final assessment. Minimal and minor adverse events were noted during assessments post injection.

Conclusion: Intralesional immunotherapy with purified protein derivative is a safe, effective and tolerable therapeutic modality for the treatment of common warts at low cost.

Keywords: cutaneous warts, immunotherapy, purified protein derivative

INTRODUCTION

Warts are common problem worldwide. They are non-cancerous (benign) skin growths caused by Human Papilloma Viruses (HPV) which develop on different parts of the body and can take on various forms. They are contagious. Warts can affect people at any age, but they are most common among children and young people. Warts appear in various forms on different sites of the body and include common warts (Verruca vulgaris), plane or flat warts (Verruca plana), plantar warts, coalesced mosaic warts, filiform warts, periungual warts, anogenital warts (venereal warts or condyloma acuminata), oral warts, respiratory papillomas.[1]

Warts are caused by infection of keratinocytes (the predominant cell type in the epidermis) by HPV. The development of epidermal thickening and hyperkeratinization occurs following infection at the basal layer and clonal proliferation occur which eventually results in a visible wart, weeks or even months later. HPV can spread from one individual to another by direct contact or via the

environment.[2] HPV, of which there are over 100 types, probably infects the skin via areas of minimal trauma. Risk factors include use of communal showers, occupational handling of meat, and immunosuppression.[3]

Purified Protein Derivative (PPD) is widely used for Mantoux test, a nonspecific test for screening for latent tuberculosis.[4] Besides topical salicylic acid, cryotherapy and curettage which are inexpensive, other treatment options are expensive. Other treatments include: special ointments and solutions like 5-fluorouracil, aciclovir, imiquimod and zinc; Injections using different kinds of medicines including Bleomycin, 5-fluorouracil and interferons; Laser surgery including pulsed dye laser treatment, Erbium YAG laser and carbondioxide laser. Photodynamic therapy is also used.[5-6]

Procedure for intralesional injection is an easy procedure where the treating physician can inject drugs into the lesion. The procedure can be conducted in the Out Patient Department (OPD) within a few minutes. It has been seen that injecting PPD or other antigens like Measles, Mumps, Rubella (MMR) vaccine into a single wart can be effective in curing multiple warts over the body parts by a probable immune mediated mechanism.[5,7-8] So, it can be justified that this simple procedure of intralesional injection can be a simple, convenient, cost effective procedure that can be undertaken in busy tertiary centres especially when the warts are multiple.

The objective of the study is to assess the efficacy of intralesional injection of 2.5 Tuberculin Unit (TU) injection of PPD into the largest wart in decreasing the size and numbers of injected as well as distant warts.

MATERIALS AND METHODS

Ethical clearance for the study was obtained from Institutional Review Committee of Pokhara Academy of Health sciences. All the patients above the age of five years presenting to the Dermatology Out Patient Department during the study period from 1ST May 2018 to 30th April 2019 at Western Regional Hospital, Pokhara, Nepal, for the treatment of warts, providing consent to participate and not falling under exclusion criteria were included. The consent for the paediatric age group patients were obtained from accompanying guardian.

Patients with low immune status, patients under immunosupressive treatments, anogenital and oral warts, pregnant and lactating women, patients with keloidal tendency of the skin, patients with fever or signs of any systemic or local inflammation or infection or patients who have received any other treatment of warts in the past 3 months were excluded. Patients with a history of tuberculosis infection or disease as well as those with known allergic reaction to PPD injection were also excluded.

At presentation, injection PPD manufactured by Arkray Healthcare Pvt Ltd , Gujarat, India, at dose of 2.5 TU was injected into the largest wart with insulin syringe, the number of warts were counted and the length and breadth of the largest wart was measured. The longest diameter was recorded as length and the diameter perpendicular to the axis of length was recorded as the breadth. The patients were reviewed every fortnight for three more visits (total 4 visits). In each visit the above measurements were repeated, the injection was repeated into the largest wart at the time for up to the total of three injections. Cases were enquired for any adverse effects in the past 2 weeks and the injection site was examined for any changes. Data was analyzed for decrease in the length and breadth of the largest wart and number of the warts.

RESULTS

There were total 199 participants enrolled in the study. Out of 199 (male= 174, female= 75) only 111 (55.77%) (male=68, female= 43) completed the all four visits. There was no drop-out in the first follow up whereas 22.11% dropout was found in the second follow-up visit and 44.22% dropout was found in the third follow up.

The age of the participants was ranging from 5 to 74 years with mean± S.D 22.33±11.17.

The most common type of wart in our study was Verruca Vulgaris (VV) 90 (81.1%) followed by palmer and or planter wart 13 (11.7%), VV + periungal wart 4 (3.6%), Verruca plana 2 (1.8%), VV + Verruca plana + filiform wart 1 (0.9%) and VV + palmer and or planter wart 1 (0.9%) (Table 1).

Table 1. Type of Wart present (N= 111)

Type of Wart	No. of Patients	Percentage (%)
Verruca Vulgaris (common wart)	90	81.1
Palmer and/or Planter wart	13	11.7
Verruca vulgaris + Periungal wart	4	3.6
Verruca plana	2	1.8
Verruca Vulgaris + Verruca plana + Filiform wart	1	0.9
Verruca Vulgaris + Palmer and /or Planter wart	1	0.9

The mean length of wart was decreased from 0.92± 0.72cm at baseline to 0.48±0.56 cm at third follow up which was statistically significant. The mean breadth of wart was found to be 0.64 ± 0.52 at the baseline which decreased significantly to 0.34 ± 0.36 at third follow up. The mean number of warts decreased from 15.32±10.69 to 8.25±8.404 at the third follow up which was statistically significant (Table 2).

Table 2: Comparison of warts at baseline and follow-up visits.

Variables	Mean± S.D	F value	P® value
Length at baseline	0.92 ±0.72	19.91	<0.001
Length at first follow-up	0.80 ± 0.69		
Length at second follow-up	0.67 ± 071		
Length at third follow-up	0.48 ± 0.56		
Breadth at baseline	0.64 ± 0.52		<0.001
Breadth at first follow-up	0.56 ± 0.50		
Breadth at second follow-up	0.48 ± 0.50		
Breadth at third follow-up	0.34 ± 0.36		
Number of warts at baseline	15.32±10.69	22.03	<0.001
Number of warts at first follow-up	12.83±9.264		
Number of warts at second follow-up	10.39±8.577		
Number of warts at third follow-up	8.25±8.404		

There was significant decrease in wart length at first, second and third follow up visits (Table 2).

Table 2. Pairwise comparison of Length using Post hoc tests

Group	Mean difference	Standard error	Confidence interval		P value
			Lower bound	Upper bound	
Baseline-first follow up	0.121	0.031	0.037	0.204	0.001
Baseline-second follow up	0.244	0.040	0.136	0.353	<0.001
Baseline-Third follow up	0.436	0.060	0.275	0.597	<0.001
First-second follow up	0.123	0.021	0.066	0.181	<0.001
First-third follow up	0.315	0.050	0.181	0.450	<0.001
Second-third follow up	0.192	0.045	0.071	0.312	<0.001

There was significant reduction in wart breadth at first, second and third follow up visits (Table 3).

Table 3. Pairwise comparison of Breadth using Post hoc tests

Group	Mean difference	Standard error	Confidence interval		P value
			Lower bound	Upper bound	
Baseline-first follow up	0.086	0.021	0.030	0.142	<0.001
Baseline-second follow up	0.161	0.029	0.083	0.239	<0.001
Baseline-third follow up	0.301	0.043	0.185	0.417	<0.001
First-second follow up	0.075	0.018	0.026	0.123	<0.001
First-third follow up	0.215	0.037	0.115	0.314	<0.001
Second-third follow up	0.140	0.031	0.056	0.224	<0.001

Number of warts more than 20 at baseline were found in 42 individuals which was decreased to 30, 24 and 19 individuals in the first follow up, second follow up and third follow up visit respectively. There was significant decrease in number of warts at each different visits (Table 4).

Table 4. Pairwise comparison of Number of warts using Post hoc tests

Group	Mean difference	Standard error	Confidence interval		P value
			Lower bound	Upper bound	
Baseline-first follow up	2.486	0.428	1.335	3.638	<0.001
Baseline-second follow up	4.928	0.680	3.100	6.756	<0.001
Baseline-Third follow up	7.063	0.865	4.739	9.387	<0.001
First-second follow up	2.441	0.440	1.258	3.625	<0.001
First-third follow up	4.577	0.679	2.753	6.401	<0.001
Second-third follow up	2.135	0.442	0.948	3.323	<0.001

Adverse reactions reported in 13 patients were hypopigmentation, swelling, pain, pruritus, headache and burning sensation.

The complete clearance rate of warts was 0.9% (1 case) at the first follow up, 9.0% (10 cases) at the second follow up and 21.6% (24) at the third follow up.

DISCUSSION

In our study, intralesional injection of tuberculin was significantly affective in decreasing the length, breadth and the number of warts. The result is lower than that in the study by Nimbalker et al [9] In the study a total of 62.2% patients showed complete clearance at injected and distant warts. But in their study they had the final assessment done at 3 weeks after the completion of six biweekly injections.

Our findings are of lower response rate compared to results from studies by many other authors.[10-12]

Choudhary D et al. in their study found clearance rate of 78.8% which was more than our findings. In their study injection PPD was injected at 2 weeks interval for 5 sessions and the final assessment was done 6 months after the last injection. [13] Very short interval (2 weeks) between the final injection and the final assessment and less number of injections (3 compared to 5) may be the reason of low clearance rate in our study. In the study only mild side effects like erythema, pain and oedema at the site of injection were observed which are similar to our study.

In a similar study by Jaiswal et al. from Uttar Pradesh, India, where each patients were given injection PPD 5 TU at weekly interval for 6 weeks and final assessment done at 6 weeks of completion of the injection sessions, the clearance rate for different types of warts were 47% for VV and 100% for periungal and plantar warts.[14] There were large number of cases of VV (81.1%) and less number of cases of Palmer and or Planter warts (11.7%) and

periungal warts(3.6%) in our study. The findings suggest that palmer/planter and periungal warts may be more responsive to immunotherapy with PPD than VV and larger percentage of VV cases may be a reason behind the low clearance rate in our study.

In another study Ghaly et al injected 0.1 TU of PPD into planter warts and found 30% clearance after 3 sessions.[15] In our study the clearance rate after 3 sessions was 21.6% but the dose (2.5 TU) was more than their study. This may imply that lesser dose of tuberculin may be as affective in immunotherapy of warts.

In our study number of warts more than 20 at baseline were found in 42 individuals which with each follow up visit. Large number of warts at baseline may be a reason behind low clearance rate in our study. The response to treatment was also significant in these cases with large number of warts.

In a study by Atef H et al, they applied six treatments of 5 TU of PPD at 2 weeks interval. After all sessions, the reduction in wart size was a mean of 55.55 ± 42.65. 35% of patients had complete wart clearance, 20% had a moderate response, and 40% had an inadequate response, 5% showed marked response.[16] These findings are similar to our study.

Limitations: The limitation of our study was that we had a short post injection assessment interval (2 weeks after the third injection) because of our shorter study period and we had no controls.

CONCLUSION

Intralesional immunotherapy with PPD is a safe, effective and tolerable therapeutic modality for the treatment of common warts at low cost. It is suggested that studies with larger sample sizes and longer follow up periods with balanced controls are conducted before reaching a definite conclusion.

Conflict of the study: None

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