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RESEARCH ARTICLE

Efficacy of Intralesional Purified Protein Derivative (PPD) in Refractory Warts: A Randomized Placebo-Controlled Study

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Abstract

Introductıon: This study aimed to evaluate the efficacy and safety of intralesional Purified Protein Derivative (PPD) in patients with recalcitrant warts in a randomized, double-blind, placebo-controlled setting.

Methods: A total of 55 patients with treatment-resistant warts were enrolled between July 2003 and February 2005. Participants were randomized into two groups: one received intralesional PPD injections, and the other received placebo (saline) at two-week intervals for a total of four sessions. Only one target lesion per patient was injected. Baseline and post-treatment wart dimensions were recorded, and patients were followed for two months after treatment completion. Clinical response was categorized as complete, partial, minimal, stable, or progressive. Adverse effects were monitored throughout the study.

Results: Forty-five patients completed the treatment and follow-up period. Both groups showed statistically significant reductions in target wart size (PPD: from 34.86 ± 30.58 mm² to 13.55 ± 21.71 mm², $p<0.001$; Placebo: from 48.65 ± 62.08 mm² to 23.96 ± 21.45 mm², $p<0.05$). Complete or ≥50% regression was observed in 68.2% of the PPD group and 50.8% of the placebo group; however, the difference between groups was not statistically significant ($p>0.05$). No serious adverse effects were reported, and minor local reactions occurred in only two patients in the PPD group.

Conclusion: Intralesional PPD is a safe and potentially effective therapeutic option for recalcitrant warts. Although clinical improvements were observed, its efficacy did not significantly differ from placebo in this trial.

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Introduction

Warts (verrucae) are common dermatological conditions caused by human papillomavirus (HPV) infections, which are transmitted through direct or indirect contact.[1,2] HPV can infect both keratinized and non-keratinized stratified squamous epithelium and may affect almost any region of the body.[3] However, lesions most commonly appear on acral areas.[4] Although warts are most frequently observed between the ages of 12 and 16, they can occur at any age and often present as chronic and recurrent lesions.[5]

Warts are a frequent concern in dermatological practice due to their persistence and resistance to treatment.[6] Patients often seek medical care for cosmetic, functional, or social reasons. The therapeutic approach is influenced by various factors including the patient's age, immune status, duration and extent of lesions, and willingness to undergo treatment.[7, 8] While spontaneous regression is possible and mediated by both humoral and cellular immune responses, it is often unpredictable and may take months or years.

Several treatment modalities are available for warts, including keratolytics, caustic and cytotoxic topical agents, cryotherapy, electrosurgery, surgical excision, and immunotherapy.[9-11] However, none of these options has proven to be entirely safe and consistently effective. An ideal treatment for HPV infection should not only eliminate visible lesions but also eradicate the virus and prevent recurrence.[12, 13] In addition, such a treatment should be safe, easily applicable, time-efficient, and cost-effective. To date, no single therapy fulfills all these criteria.

In recent years, the intralesional administration of antigens such as Candida albicans and mumps has shown promise, with studies reporting wart clearance rates of up to 70% through the induction of a cellular immune response.[14, 15] Given the high rate of tuberculin positivity in the Turkish population, intralesional injection of Purified Protein Derivative (PPD) has also been explored as an immunotherapeutic option. In an open-label study conducted in our clinic involving patients with warts resistant to conventional treatments, approximately 60% showed clinical improvement following intralesional PPD administration. These results are comparable to the success rates reported with traditional therapeutic approaches.

Based on these observations, the present study aims to evaluate the efficacy of intralesional PPD in the treatment of recalcitrant warts through a prospective, randomized, double-blind, placebo-controlled clinical trial.

Material and Methods

Study Design and Ethical Approval

A prospective, randomized, double-blind, placebo-controlled clinical trial was designed to evaluate the efficacy of intralesional PPD in the treatment of recalcitrant warts. The study protocol was approved by the Marmara University School of Medicine Research Ethics Committee (approval date: May 2, 2003; approval number: Mar-YÇ-2003-0050). All patients were informed about the study, and written informed consent was obtained from both the patients and the investigators.

Patient Selection

Participants were recruited from the dermatology outpatient clinic of Marmara University. Eligible patients were aged 12 years or older, had at least one wart resistant to a prior conventional therapy, had not received any wart-directed treatment in the past month, and demonstrated a PPD induration of ≥5 mm following intradermal testing. Patients were excluded if they had active tuberculosis infection, were pregnant or breastfeeding, had received topical or systemic wart treatments within the previous four weeks, had a history of immunosuppression or autoimmune disease, were using immunomodulatory drugs, were receiving additional wart treatments concurrently, had lesions located exclusively on the face, or showed a PPD induration <5 mm or >15 mm in the presence of BCG vaccination, or <5 mm without BCG vaccination.

Between July 2003 and February 2005, a total of 55 patients were enrolled in the study, with 24 patients assigned to the PPD group and 31 patients to the placebo group. All participants had previously failed to respond to at least one conventional treatment, including topical 5-fluorouracil (5-FU), topical acids, cauterization, cryotherapy, or surgical excision. Of these patients, 10 discontinued follow-up voluntarily. In the PPD group, 2 patients dropped out after the first injection, 4 after the second, and 2 after the third. In the placebo group, 2 patients discontinued after the second injection. All dropouts were contacted by telephone, and it was determined that the primary reason for withdrawal was the inability to attend follow-up visits at the required intervals due to personal or logistical constraints. No patient discontinued treatment due to adverse effects. A total of 45 patients successfully completed the 2-month treatment period and the 2-month follow-up and were included in the final statistical analysis.

Treatment Protocol

Participants who met the inclusion criteria were randomly assigned to either the treatment (PPD) group or the placebo group using a random number table by a physician who was not a researcher in the study and had no knowledge of the treatment protocol. The study results were also recorded in the file by the same healthcare professional. All patients (Those who have not previously received the BCG vaccine) received a standardized intradermal PPD injection into the volar forearm using a 26-gauge insulin syringe, and the PPD induration was measured after 48 hours. Only those with an induration diameter ≥5 mm were included in the treatment phase. The PPD solution used in this study (PPD Test Tuberculin Tween 80, BB-NCIPD Ltd, Sofia, Bulgaria) was supplied by the Istanbul Provincial Health Directorate and stored at +4°C.

In each patient, the size and location of all warts were documented. A single target wart was selected for treatment, and intralesional injection was administered only to this lesion using a 26-gauge insulin syringe. This approach was based on the hypothesis that immune stimulation from a single lesion could affect distant warts as well. Patients in the treatment group received intralesional PPD, while those in the placebo group received normal saline. Injections were performed by physicians not involved in the evaluation of treatment response, in order to maintain blinding. The injection volume was determined according to the size of the lesion, with 0.1 mL administered for every 0.5 cm² of wart surface area.

To minimize pain during the procedure, EMLA cream was applied before each injection. For lesions on the hands and feet where EMLA was insufficient, cold anesthesia was used. All patients received a total of four injections at two-week intervals. Clinical photographs were obtained at baseline and after completion of therapy. If complete clearance of the target lesion was observed and maintained, treatment was discontinued. Patients were re-evaluated two days after each injection for local and systemic side effects. Those experiencing pain or swelling were treated with paracetamol. Patients who missed two consecutive treatment sessions or experienced a grade 3 or higher adverse event were withdrawn from the study. Following completion of the treatment protocol, patients were monitored with monthly follow-up visits for two additional months. Patients who did not respond to treatment were offered alternative therapies.

Clinical Evaluation and Follow-up

Clinical efficacy was assessed by measuring the size of the target wart and other lesions at baseline, during each treatment visit, and two months after treatment completion. Treatment response was categorized as follows: complete response was defined as 100% resolution of the target wart; partial response as ≥50% reduction in size; minimal response as <50% reduction; stable disease as no change in wart size; and disease progression as an increase in target lesion size or the appearance of new warts. In addition, clearance of distant, non-treated lesions was also recorded.

Adverse effects were evaluated two days after each injection. Patients were specifically asked about the presence of pain, swelling, vesicle formation, itching, or necrosis at the injection site. Each symptom was scored on a 0–3 scale (0 = none, 1 = mild, 2 = moderate, 3 = severe), and the cumulative score was recorded as the overall adverse effect severity.

Statistical Analysis

Statistical analyses were performed using SPSS software. The distribution of gender and the number of warts between the two groups were compared using the chi-square test. Independent samples t-tests were used to assess differences in mean age, disease duration, PPD induration size, and the number of BCG scars between groups. Within-group comparisons of the mean target wart size at baseline, post-treatment, and post-follow-up were performed using paired samples t-tests. In the PPD group, the relationship between the percentage change in target wart size and PPD induration was evaluated using ANOVA and t-tests. The percentage change in wart size from baseline to post-treatment and from baseline to follow-up was also compared between the two groups using independent samples t-tests. Additionally, the number of patients in each response category was compared between groups using the chi-square test. Correlation analyses were used to assess the relationship between treatment response and variables such as PPD induration, number of BCG scars, patient age, and disease duration. A p-value of less than 0.05 was considered statistically significant.

Results

Baseline Characteristics

When comparing baseline characteristics between the two groups, no statistically significant differences were observed regarding sex distribution, age, duration of disease, number of BCG scars, number of warts, or PPD induration ($p > 0.05$). In the PPD group, 4 patients were under 18 years of age, while this number was 6 in the placebo group. The majority of patients completing the study presented with common warts located on the hands or feet, including some with subungual or periungual involvement. Additionally, four patients had filiform warts in the head and neck region, and one patient had a flat wart on the face (Table 1).

Table 1. Baseline characteristics and wart burden of patients.

Variables	PPD n = 22	Placebo n = 23	*p*
Age, years (mean [min–max])	23.0 ± 9.7	28.1 ± 13.0	0.144
Gender, n (%)			0.550
Female	14 (63.6)	12 (52.2)	
Male	8 (36.4)	11 (47.8)	
Disease duration, years (mean)	3.01 ± 2.9	3.7 ± 3.2	0.516
PPD induration, mm (mean)	12.6 ± 4.8	11.9 ± 5.4	0.354
Number of BCG scars (mean)	1.6 ± 1.0	1.5 ± 1.0	0.786
Total number of warts, n			0.450
Single wart (target wart)	4 (18.2)	2 (8.7)	
2–10 warts	15 (68.2)	15 (65.2)	
>10 warts	3 (13.6)	6 (26.1)	

Abbreviations: PPD, purified protein derivative; BCG, Bacillus Calmette–Guérin.

Clinical Outcomes

In the treatment group, therapy was discontinued for 6 patients after complete resolution of the target wart following the second or third injection, and these patients entered the follow-up phase. In the placebo group, 2 patients experienced complete clearance of all lesions, including the target wart, after the second injection and were similarly transitioned to follow-up.

In the PPD group, the mean size of the target wart decreased significantly from 34.86 ± 30.58 mm² at baseline to 13.55 ± 21.71 mm² at the end of treatment ($p < 0.001$). At the two-month post-treatment follow-up, a slight increase to 15.86 ± 28.28 mm² was observed. In the placebo group, the mean target wart size decreased from 48.65 ± 62.08 mm² to 23.96 ± 21.45 mm² ($p < 0.05$) at the end of treatment, and further to 22.57 ± 25.68 mm² at the two-month follow-up. These reductions were statistically significant within both groups, indicating that both PPD and placebo were associated with a measurable decrease in wart size.

However, no statistically significant correlation was found between treatment response (defined as the percentage change in target wart size) and PPD induration, BCG scar count, disease duration, or patient age in either group ($p > 0.05$). In the PPD group, the mean percentage reduction in wart size did not significantly differ among patients with <50% response, ≥50% response, or complete clearance ($p > 0.05$). Patients with PPD induration of 5–9 mm (n=3) had a mean response of 78.5 ± 30.34%, while those with induration of 10–15 mm (n=19) had a mean response of 68.39 ± 35.08%, again with no statistically significant difference ($p > 0.05$).

The mean percentage reduction in wart size after two months of treatment was 61.15 ± 34.00% in the PPD group and 50.76 ± 56.54% in the placebo group. At the end of the two-month follow-up, these values were 54.50 ± 49.60% and 53.62 ± 58.86%, respectively. The between-group differences at both time points were not statistically significant ($p > 0.05$).

When patients were categorized based on percentage change in wart size, chi-square analysis revealed no significant difference between the two groups ($p > 0.05$). A complete response or ≥50% reduction in target wart size was observed in 68.2% of the PPD group and 47.8% of the placebo group; however, this difference was not statistically significant ($p > 0.05$) (Table 2).

Table 2. Distribution of percentage change in wart size at the end of follow-up in the PPD and placebo groups.

Percentage change in wart size	PPD n = 22	Placebo n = 23	*p*
<50% reduction	7 (31.8)	12 (52.2)	
≥50% reduction	9 (40.9)	10 (43.5)	0.085
100% clearance	6 (27.3)	1 (4.3)	

PPD, purified protein derivative.

Response in Non-Target (Distant) Warts

Treatment responses of non-target, distant warts are presented in Tables 3 and 4. Among patients with multiple warts, regression of distant warts was observed in 2 of 18 patients (11.1%) in the PPD group, compared to 7 of 20 patients (35.0%) in the placebo group.

Table 3. Total number of warts in the PPD group at baseline, end of treatment, and end of follow-up.

Patients no	Baseline warts	End of treatment warts	End of treatment Notes	End of follow-up warts
1	3	3	—	3
7	5	4	Target wart cleared after the 3rd injection.	4
8	4	3	Target wart and 2 additional warts cleared; however, a new wart developed.	3
16	9	9	—	9
17	11	11	Target wart cleared after the 3rd injection; a new wart developed.	11
20	9	10	—	11
21	3	3	Target wart cleared by end of follow-up.	2
22	6	7	Target wart cleared after the 3rd injection; 2 new warts developed after the 1st injection.	6
30	2	3	—	0
32	1	1	—	1
33	2	2	Target wart cleared by end of follow-up.	1
37	1	0	Target wart cleared after the 3rd injection.	1
38	10	10	—	10
41	7	7	—	7
42	1	1	—	0
44	18	23	—	6
45	7	7	—	8
48	1	1	—	1
50	6	6	Target wart cleared after the 3rd injection; a new wart developed.	7
51	5	5	—	5
53	13	12	Target wart cleared after the 2nd injection.	13
54	2	1	Target wart cleared after the 2nd injection.	1
Total (n=22)	126	129		110

Table 4. Total number of warts in the placebo group at baseline, end of treatment, and end of follow-up.

Patients no	Baseline warts	End of treatment warts	End of treatment Notes	End of follow-up warts
4	2	0	Both warts cleared after the 2nd injection.	0
9	8	8	—	8
10	10	10	—	10
11	12	1	All warts except the target wart cleared after the 2nd injection.	1
14	7	7	—	7
18	17	21	One non-target wart cleared.	21
19	22	0	All warts cleared after the 2nd injection.	0
25	6	6	—	5
27	9	10	A new wart developed after the 3rd injection.	10
28	11	10	—	10
29	1	2	A new wart developed after the 2nd injection.	1
31	2	2	—	2
34	5	5	—	7
35	4	5	—	5
36	7	7	—	7
39	5	3	—	0
40	2	2	—	2
43	20	20	—	20
46	2	2	—	2
47	11	8	Two new warts developed after the 2nd injection; five warts cleared after the 3rd injection.	0
49	4	4	—	4
52	1	1	—	1
55	1	1	—	1
Total (n=23)	169	135		124

When the relationship between the total number of warts and percentage response in the target wart was analyzed, it was observed that patients with a ≥50% response in the PPD group were mostly those with 2–10 warts at baseline (Table 5). In the placebo group, patients with <50% response were also predominantly those with 2–10 warts at baseline (Table 5).

Table 5. Relationship between baseline total wart count and treatment response of the target wart at the end of follow-up in the PPD and placebo groups.

Baseline total number of warts	PPD			Placebo		
	100% clearance	≥50% reduction	<50% reduction	100% clearance	≥50% reduction	<50% reduction
Single wart, n (%)	1 (25.0)	-	3 (75.0)	-	3 (100.0)	-
2–10 warts, n (%)	4 (26.7)	7 (46.7)	4 (26.7)	1 (7.1)	4 (28.6)	9 (64.3)
>10 warts, n (%)	1 (33.3)	2 (66.7)	-	-	3 (50.0)	3 (50.0)

Data are presented as n (%); percentages are calculated within each baseline wart-count category for each treatment group. Abbreviations: PPD, purified protein derivative.

Adverse Events

A total of 29 adverse event evaluations were conducted across all 55 patients, two days following each injection. Overall, the treatment was well tolerated in both groups. Adverse effects were observed in only two patients (Patients 37 and 42), both of whom received PPD and had only a single lesion. These patients experienced mild erythema and edema, which resolved within a few days and occurred only after the first injection. Notably, both patients achieved complete resolution of their warts. No systemic side effects were reported in any participant during the study.

Discussion

In this randomized, double blind, placebo controlled study, we evaluated the efficacy of intralesional PPD immunotherapy for the treatment of warts resistant to conventional approaches. Despite extensive research into various therapeutic modalities, an ideal treatment that consistently yields complete and durable remission of warts has not yet been identified. Indeed, wart management remains challenging for clinicians due in part to the heterogeneous nature of the disease, the intrinsic variability in host immune responses, and the limited number of robust, well designed randomized clinical trials.

Traditional wart therapies such as cryotherapy, electrosurgery, laser ablation, topical acids, and surgical excision are widely used and have demonstrated varying degrees of efficacy.[9, 16, 17] However, these methods are often associated with disadvantages including pain, scarring, high cost, and variable effectiveness, particularly in recalcitrant cases. Furthermore, even when treated lesions resolve, new lesions frequently emerge, complicating long term disease control. The present study sought to address these limitations by investigating an immunotherapeutic strategy based on intralesional antigen stimulation.

Immunotherapy for cutaneous warts relies on enhancing the host's immune response to HPV.[8,18] The rationale for such strategies is supported by observations that spontaneous regression of warts is frequently associated with activation of both humoral and cellular immune mechanisms.[19] Immunotherapeutic approaches have included topical sensitizers such as dinitrochlorobenzene (DNCB), diphenylcyclopropenone (DPCP), and squaric acid dibutyl ester (SADBE), as well as systemic agents such as cimetidine.[20] Despite some promising reports, the clinical adoption of these agents has been limited due to safety concerns, logistical challenges in administration, and inconsistent evidence of efficacy. For example, DNCB has been associated with mutagenicity, while DPCP and SADBE have been linked to significant local and systemic reactions, including erythema multiforme–like responses and dyschromia.[21] Cimetidine's immunomodulatory effects observed in early non controlled studies were not consistently reproduced in placebo controlled trials, and its use is not recommended in adults.[22] Together, these limitations illustrate the need for safer, more effective, and more easily administered immunotherapeutic options.

Intralesional antigens such as Candida, mumps, and tuberculin have been investigated over the past two decades, with several studies reporting encouraging outcomes. Phillips et al. demonstrated wart clearance in approximately 72% of cases treated with intralesional Candida antigen, and other trials showed superior responses with antigen inoculation compared with cryotherapy.[23] In some reports, non targeted distant warts also resolved, suggesting a systemic immune activation following local antigen stimulation.[14] A similar open label study using intralesional tuberculin reported a 60% treatment success rate in a small cohort of patients with recalcitrant warts. These findings provided the impetus for the present, more rigorously designed trial.[24]

In our study, both the PPD and placebo groups experienced statistically significant reductions in mean target wart size at the end of treatment and at two month follow up. The average percentage reduction in wart size following PPD treatment was 61.15 ± 34.00%, with complete clearance or >50% reduction observed in 68.2% of patients. Although these outcomes were numerically higher than those in the placebo group (mean reduction 50.76 ± 56.54% and 50.8% achieving ≥50% reduction), the differences between groups did not reach statistical significance. The response observed in the placebo group may be explained by several non-specific mechanisms previously described in the literature. Intralesional injection itself can induce local tissue injury and a mechanical needling effect, leading to the formation of an inflammatory microenvironment that enhances antigen presentation and triggers cell-mediated immune responses. In addition, local cytokine release and activation of innate immune cells following injection may contribute to the clearance of HPV-infected keratinocytes. Considering the natural course of warts, spontaneous regression is a well-recognized phenomenon, particularly in the context of immune system activation. Therefore, the reduction in lesion size observed in the placebo group is more likely attributable to non-specific immune stimulation and local immune responses induced by mechanical trauma rather than a specific therapeutic effect. Nevertheless, the more robust and sustained response observed in the BCG-treated group supports the contribution of a specific immunomodulatory effect to the overall clinical outcome.

First, the high response rate in the placebo group warrants consideration. Literature reviews of multiple controlled trials encompassing traditional wart therapies report an average placebo response rate of approximately 30% (range 0–73%).[25] In the present study, the placebo group's response rate was higher than the reported pooled average, yet still within the boundaries of previously observed outcomes. The elevated placebo response may be attributable to the mode of administration; intralesional injection itself can trigger a non specific inflammatory response that may accelerate wart regression independent of antigen specificity. However, prior studies examining needle based interventions without active antigen did not consistently demonstrate such pronounced placebo responses,[26] suggesting that procedural factors alone may not fully account for these results.

Another finding of interest was the relatively modest clearance of distant, non targeted warts. While earlier studies with Candida and mumps antigens reported distant wart resolution rates as high as 78%.[15] the present trial observed distal regression in only 11.1% of PPD treated patients and 35.0% of those receiving placebo. The differential response may reflect variations in host immune priming, antigen specificity, or methodological differences such as the number, frequency, or quantity of injections.

The lack of correlation between PPD induration diameter and clinical response is also noteworthy. Although some earlier studies with tuberculin antigen suggested a possible association between stronger skin test reactivity and treatment outcome,[27] this relationship was not observed in the present cohort. Similar findings have been reported in other investigations, indicating that baseline immune reactivity as measured by induration may not reliably predict therapeutic benefit from antigen based immunotherapy.

Safety is a critical consideration in any therapeutic approach, and intralesional antigen administration in this study was generally well tolerated. Only two patients in the PPD group experienced mild erythema and edema, both of which resolved without intervention and did not necessitate discontinuation of therapy. This favorable safety profile contrasts with the relatively higher incidence of local and systemic side effects reported in some Candida and mumps antigen studies, including blistering, flu like symptoms, and treatment discontinuation in a minority of subjects.

From a clinical perspective, the findings of this study underscore the complexity of wart immunotherapy. Although PPD induced significant reductions in wart size and achieved high rates of clinical response, the absence of a statistically significant difference compared with placebo highlights the challenge of demonstrating clear superiority over non specific immune stimulation in controlled settings. It remains possible that refining antigen selection, dosing regimens, or combining immunotherapy with other modalities could enhance therapeutic efficacy.

The present study also emphasizes the importance of standardized protocols in immunotherapy trials. Variability in antigen types, injection intervals, dose determination, and lesion selection criteria across different studies complicates direct comparisons and synthesis of results. For example, while some protocols adjust antigen dosage based on lesion size or skin test induration, others employ fixed doses irrespective of individual characteristics.[28] In this trial, antigen volume was tailored to lesion surface area, which may influence outcomes relative to alternative dosing strategies.

Limitations of this study include the relatively small sample size and the short duration of follow up, which may limit the ability to detect late recurrences or differences that emerge with longer observation. Additionally, the study was conducted in a population with high baseline tuberculin reactivity, which may affect generalizability to populations with different epidemiologic backgrounds.

In conclusion, intralesional PPD immunotherapy demonstrated clinically meaningful reductions in wart size and achieved substantial response rates among patients with recalcitrant lesions. However, its outcomes were not statistically superior to placebo in this controlled setting. The safety profile was favorable, suggesting that PPD immunotherapy remains a viable option in selected cases. Future research should focus on optimization of antigen based strategies, including combination approaches, identification of predictive biomarkers of response, and exploration of mechanisms underlying non specific immune activation observed with intralesional interventions. Such efforts may ultimately contribute to the development of more effective and targeted immunotherapeutic treatments for chronic and treatment resistant warts.

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