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Intralesional Injection of Purified Protein Derivative in the Treatment of Viral Warts: A Pilot Study

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ABSTRACT

Background: Human papilloma virus (HPV) could contribute to warts and prevalence of warts is estimated to be from 7 to 10 percent of population. Immunity system could recognize bacterial, fungal as well as viral antigens. Researchers got benefit of this through development of antigen immunotherapy intralesional management. Purified protein derivative (PPD) is an intralesional immune-treatment for warts that has shown promising results.

Objective: To determine whether intralesional PPD is effective and safe in common warts management.

Patients and methods: The study involved twenty patients. History taking, general exam, and complete dermatological exam were performed on each patient to determine the type and number of warts, as well as the size and location of each wart in every patient. Without any pre-sensitization, all patients were then given PPD injection of 0.1 ml into the largest wart every two weeks for a maximum of six treatment sessions, or until the wart was completely cleared. The effectiveness of the treatment was determined by the size and number of warts. PPD injections were also evaluated for patient satisfaction and side effects. There was a follow-up evaluation for wart recurrence six months after the end of the treatment.

Results: After 1/3 sessions, the mean of wart size reduction was 11.25 ± 14.67 whereas after 2/3 sessions the mean was 29.80 ± 28.72. After all sessions, the wart size reduction ranged from 0 – 100 with 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.

Conclusion: Common warts can be treated with intralesional immunotherapy using PPD, which is a safe, effective, and tolerable treatment modality.

Keywords: Human papilloma virus, Wart, PPD, Immunotherapy.

INTRODUCTION

Human papilloma virus (HPV) infection can cause warts on the skin and mucous membranes. It affects about 7–10% of the population [(1)]. It is presented in different clinical forms including common wart (Verruca vulgaris), wart on the sole of the foot, plantar wart (Verruca plantaris), flat wart (Verruca plana) and genital wart (Condyloma acuminate). On the hands of children and young adults, common warts are hyperkeratotic papillomas that can occur anywhere on the skin or mucous membrane surface [(2)].

Warts have been treated with a variety of destructive and immunotherapeutic methods. Some of the destructive therapies include the use of medical agents such as trichloroacetic acid, salicylic acid, and formaldehyde or the surgical use of cryosurgery, surgical excision, and electrocautery or laser ablation. All of these treatments have the potential to cause dyspigmentation and/or scarring, as well as recurrences. They can also be used to treat multiple warts and facial warts to a limited extent. Diphencyprone is an example of a contact sensitizer and imiquimod is an example of an immunomodulatory agent [(3)].

Virus-induced cell-mediated immunity (CMI) has been shown to cause warts to spontaneously regress. In recent years intralesional immunotherapy using antigens like tuberculin, mumps, and candidin have gained good popularity [(4)].

Immunity system could recognize bacterial, fungal as well as viral antigens.

Researchers got benefit of this through development of antigen immunotherapy intralesional management. As a result of the delayed-type hypersensitivity reaction, the immune system is better able to recognise, clear, and prevent HPV infection in both treated and untreated lesions and thus to prevent recurrence [(5)]. Functional host immunity is very important for successful intralesional antigen immunotherapy [(6)].

There has been promising efficacy in the treatment of warts using a purified protein derivative (PPD). As an extract of Mycobacterium tuberculosis, PPD can be used to test for tuberculin protein, either through previous vaccination or exposure to the environment. Immunity is stimulated by PPD injection in an unspecific manner by activation of cytokines and natural killer cells as well as T lymphocytes. Regardless of the HPV serotype, it is effective against all types of warts, including verruca vulgaris, verruca plana, and planter warts [(7)].

In addition to its efficacy and safety profile, this therapeutic approach has the following main advantages: low cost, simple and easy application and only one wart per application [(8)]. In addition, there are no side effects such as scarring, pigmentary changes, and movement restrictions [(9)]. The aim of this work was to determine whether intralesional PPD is effective and safe in common warts management.

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PATIENTS AND METHODS

This pilot study included twenty patients that were recruited from the Outpatient Dermatology, Venereology, and Andrology Clinic, Zagazig University Hospitals. The patients were subjected to intralesional PPD treatment. Patients with multiple common warts between the ages of 18 and 65 were included in the study. Patients with a history of TB infection or disease as well as those with an allergic reaction to PPD injection and patients who had received any other treatment for their warts in the last month before enrolling were excluded.

History taking, general examination and dermatological examination were all performed on each patient to determine wart size, location and type. All lesions were photographed before starting treatment and at each follow-up session. This was done to document the progress of the treatment. No other wart treatment was allowed during the study period. We injected PPD directly into all patients, without pre-sensitization (brought from vacsera vaccination center) at a dose of 0.1 ml (5 tuberculin units) until complete clearance or up to six treatment sessions with insulin syringe injected into the largest wart at 2-week intervals.

Decrease of wart size and number, including treated and untreated warts, and return to normal skin marking were used to evaluate treatment response, with photographic comparisons at baseline and at each visit.

We graded the response using the following system: (1) Complete response, respondents who had improved by 100% (return to normal skin marking and disappearance of all wart lesions). (2) A marked response is one in which the number and/or apparent volume and size of respondents had decreased by 76-99%. (3) Moderate response, respondents with a partial response showed 25 to 75% improvement. (4) No or minimal response, less than 25% reduction in the size, volume, and number of all warts [(10)].

There were three different levels of satisfaction with each treatment: poor, fair, and excellent at the end of each treatment. Each time a PPD injection was administered, the immediate and long-term adverse effects of the injection were assessed. In order to detect any recurrence of warts, a follow-up evaluation was performed every month for six months after the treatment ended.

Ethical considerations:

Approval was obtained from Institution Review Board (IRB), Zagazig University (approval number 5703).

Each patient signed a written informed consent before being enrolled in the study and after being informed of the study's nature. This work has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for studies involving humans.

Statistical analysis

The collected data were coded, processed and analyzed using the SPSS (Statistical Package for Social Sciences) version 22 for Windows® (IBM SPSS Inc, Chicago, IL, USA). Qualitative data were represented as frequencies and relative percentages.

Chi square test (χ^2) was used to calculate difference between two or more groups of qualitative variables. Quantitative data were expressed as mean ± SD (Standard deviation). Shapiro-Walk test was used to determine whether the data were normal. Independent samples t-test was used to compare between two independent groups of normally distributed variables (parametric data). P value ≤ 0.05 was considered significant.

RESULTS

Patients' ages ranged between 19 and 60 years old with a mean age of 31.10 ± 11.73 years. 75% were females and 25% were males. The percentage of patients with skin type III was 70% while type IV was 30%. Concerning previous wart infection, 35% of the patients (7) were previously infected and cryotherapy was the most common treatment modality used (85.7%) followed by immunotherapy (14.3%). The response rate for the previous treatment was inadequate in 57.1%, moderate in 42.9% and no complete response was achieved with such treatments. According to clinical data, hand was the most involved site (95%) and cosmetic disfigurement was the most common clinical symptom (70%). 100% of the patients had common warts and the disease duration ranged from 5 – 36 months (Table 1).

Table (2) showed that the number of warts ranged between 3 and 20 warts with a mean of 6.95 ± 4.54. As regards the number of sessions, it ranged between 4 and 6 sessions with a mean of 5.65 ± 0.74. Regarding the complications, pain was reported in 18 patients (90%), myalgias in 13 patients (65%), fever in 11 patients (55%), erythema in 9 patients (45%), edema in 4 patients (20%) and skin pigmentation in 4 patients (20%). After all sessions, the number of warts ranged between 0 and 12 warts with a mean of 3.55 ± 3.70 (Table 3).

After 1/3 sessions, the mean of wart size reduction was 11.25 ± 14.67, whereas after 2/3 sessions the mean was 29.80 ± 28.72. After all sessions, the wart size reduction ranged from 0 to100 with a mean of 55.55 ± 42.65 (Table 4).

Seven patients (35%) showed complete resolution after the treatment modality, marked response in one patient (5%), moderate response in 4 patients (20%) and inadequate response in 8 patients (40%). Time to complete response (TCR), which is defined as the period the patients took to achieve complete remission, took 8-18 weeks with a mean of 1.42 ± 4.11 (Table 5).

Figure (1) showed an example of the complete response of the patient after six sessions. Excellent satisfaction was noticed in 7 patients (35%), fair satisfaction in 4 patients (20%) and poor satisfaction in

9 patients (45%). patients in the study group showed no recurrence of lesion, but one patient (5%) showed recurrence of lesion in other site.

Table (1): Clinical criteria of the patients

Clinical data	(N=20)	
	No.	%
Symptoms		
Cosmetic disfigurement	12	70%
Fear of spread	8	30%
Disease duration (months)		
Mean ± SD	18.45 ± 11.12	
Median	15	
Lesion duration (months)		
Mean ± SD	17.42 ± 11.41	
Median	12	
Type of wart		
Common	20	100%
Common + Planter	0	0%
Site of wart		
Neck	1	5%
Hand	19	95%
Leg	0	0%
Feet	0	0%

Table (2): Baseline evaluation of the patients

Baseline evaluation	(N=20)
Number of warts	
Mean ± SD	6.95 ± 4.54
Median	5
Size of largest wart (mm)	
Mean ± SD	6.10 ± 2.10
Median	5.50

Table (3): post-treatment evaluation of the patients after all sessions

Post-treatment evaluation	(N=20)
Number of warts	
Mean ± SD	3.55 ± 3.70
Median	2.50
Size of largest wart (mm	
Mean ± SD	2.90 ± 3.14
Median	2.50

Table (4): Wart size reduction in patients after the treatment

Wart size reduction (%)	(N=20)
After 1/3 sessions	
Mean ± SD	11.25 ± 14.67
Median	5
After 2/3 sessions	
Mean ± SD	29.80 ± 28.72
Median	25
After all sessions	
Mean ± SD	55.55 ± 42.65
Median	63.50

Table (5): Overall response of the patients to the treatment

Response	(N=20)	
	No.	%
Overall response		
Inadequate	8	40%
Moderate	4	20%
Marked	1	5%
Complete	7	35%
Time to CR (weeks)		
Mean ± SD	1.42 ± 4.11	
Median	10	

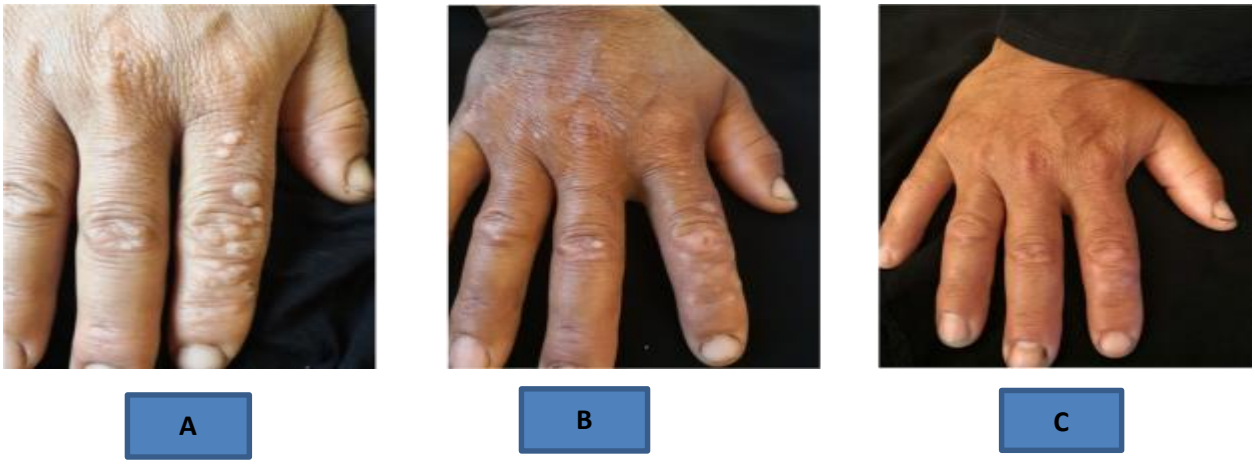

Figure (1): A 40 year's old female with multiple common warts on the dorsum of the hand showed complete response after six sessions of intralesional PPD injection. A) Before treatment with PPD. B) After the 4th session showed partial response. C) After the 6th session with complete response.

DISCUSSION

Intralesional immunotherapy with injection of various antigens including PPD is one of the modalities that have been used for treatment of multiple common warts. It has been found to be a safe, effective and tolerable treatment [(11)]. Through the induction of delayed type hypersensitivity and activation of cytotoxic and natural killer cells against the virus, intralesional immunotherapy can increase the host immunity to HPV [(12)]. Many studies have already used PPD injection for wart treatment but with different treatment protocols regarding the amount injected, session intervals, and the total number of sessions. This leads to variable results.

Regarding our study protocol, At 2-week intervals, we used an insulin syringe to inject PPD at 0.1ml per session into the largest wart, up to six sessions, without pre-sensitization as all patients are expected to be immune taking the advantage of our vaccination schedule in our country including tuberculosis, This approach showed easy eligibility, saving cost, time and showed very good satisfying results. **Nimbalkar *et al.*** [(13)] have already used it. Pain during the injection of PPD was a noticeable finding, but was tolerable and not necessitated stoppage of treatment. This comes in agreement with **Shaheen *et al.*** [(10)] and **Abo-Taleb *et al.*** [(14)]. Also, we reported erythema, edema and mild constitutional symptoms in the next day following the injection in some patients. We noticed that most of those patients had a good response to treatment. This observation is also reported by **Kaimal *et al.*** [(14)], who observed pain and edema in 7 patients and 5 of them had complete resolution for their lesion, reporting that this may be a beneficial response and an indicator for the patient good immunity.

Complete response was achieved in 35% of patients, which is higher than that was achieved by **Kus *et al.*** [(16)] (29.4%). This may be attributed to the lower number of sessions (3), longer session interval (3 weeks), and the nature of wart recalcitrance in Kus study. On the other hand, our clearance rate was lower than that was reported by **Eassa *et al.*** [(7)] (50%), **Amirnia *et al.*** [(10)] (77%), **Shaheen *et al.*** [(12)] (60%), and **Abo-Taleb *et al.*** [(14)] (72%). This may be related to the difference in the treatment approach in each study, type of warts (common warts in our study), number of the studied patients, amount of antigen injected (0.1 ml was only injected in our study), number of sessions and the interval between them.

Additionally, at the end of the follow up period, which extended for 6 months, no patients showed recurrence of lesion that is matching with **Abo-Taleb *et al.*** [(10)] **and Kaimal *et al.*** [(15)] results. Induction of long-term cell-mediated immunity, which allows the body to recognize HPV, stimulates the production of memory T-cells against the virus, and intensifies effector response mechanisms of memory T-cells against the virus [(17)]. On the other hand, **Abd-Elazim *et al.*** [(18)], reported recurrence of the lesion in two cases who explained it by the long duration of the disease and high viral load, which will need more sessions and more volume of the drug to stimulate the immune response. **Amirnia *et al.*** [(12)] also reported recurrence of the disease.

CONCLUSION

Intralesional immunotherapy with PPD is a safe, effective and tolerable therapeutic modality for the treatment of common warts. It is of low cost and produce sustained immunity against HPV.

REFERENCES

1. **Leung L (2011):** Recalcitrant nongenital warts. Aust Fam Physician, 40: 40-42.
2. **Sterling J, Gibbs S, Haque Hussain S *et al.* (2014):** British Association of Dermatologists' guidelines for the management of cutaneous warts. Br J Dermatol., 171: 696–712.
3. **Nofal A, Nofal E, Yosef A *et al.* (2015):** Treatment of recalcitrant warts with intralesional measles, mumps, and rubella vaccine: a promising approach. Int J Dermatol., 54: 667–671.
4. **Johnson S, Horn T (2004):** Intralesional immunotherapy for warts using a combination of skin test antigens: A safe and effective therapy. J Drugs Dermatol., 3: 263-5.
5. **Clifton M, Johnson S, Roberson P *et al.* (2003):** Immunotherapy for recalcitrant warts in children using intralesional mumps or Candida antigens. Pediatr Dermatol., 20: 268–271.
6. **Luo Y, Henning J, O'Donnell M (2011):** Th1 cytokine-secreting recombinant Mycobacterium bovis bacillus Calmette-Gue´rin and prospective use in immunotherapy of bladder cancer. Clin Dev Immunol., 2011: 728930.
7. **Eassa B, Abou-Bakr A, El-Khalawany M (2011):** Intradermal injection of PPD as a novel approach of immunotherapy in anogenital warts in pregnant women. Dermatol Ther., 24: 137–143.
8. **Nofal A, Salah E, Nofal E *et al.* (2013):** Intralesional antigen immunotherapy for the treatment of warts: current concepts and future prospects. Am J Clin Dermatol., 14: 253-260.
9. **Johnson S, Roberson P, Horn T (2001):** Intralesional injection of mumps or Candida skin test antigens: a novel immunotherapy for warts. Arch Dermatol., 137: 451- 455.
10. **Abou-Taleb D, Abou-Taleb H, El-Badawy O *et al.* (2019).** Intralesional vitamin D3 versus intralesional purified protein derivative in treatment of multiple warts: A comparative clinical and immunological study. Dermatol Ther., 32 (5): 13034-13038.
11. **Aldahan A, Mlacker S, Shah V *et al.* (2016):** Efficacy of intralesional immunotherapy for the treatment of warts: A review of the literature. Dermatol Ther., 29: 197–207.
12. **Amirnia M, Khodaeiani E, Fouladi D *et al.* (2016):** Intralesional immunotherapy with tuberculin purified protein derivative (PPD) in recalcitrant wart: A randomized, placebocontrolled, double-blind clinical trial including an extra group of candidates for cryotherapy. J Dermatolog Treat., 27 (2): 173-8.
13. **Nimbalkar A, Pande S, Sharma R *et al.* (2016):** Tuberculin purified protein derivative immunotherapy in the treatment of viral warts. Indian J Drugs Dermatol., 2: 19-23.
14. **Shaheen M, Salem S, Fouad D *et al.* (2015):** Intralesional tuberculin (PPD) versus measles, mumps, rubella (MMR) vaccine in treatment of multiple warts: a comparative clinical and immunological study. Dermatol Ther., 28 (4): 194-200.
15. **Kaimal S, Gopinath H, Premalatha V (2020):** Intralesional immunotherapy with purified protein derivative (PPD) for cryotherapy-resistant warts. Int J Dermatol., 59 (6): 726-729.
16. **Kus S, Ergun T, Gun D *et al.* (2005):** Intralesional tuberculin for treatment of refractory warts. J Eur Acad Dermatol Venereol., 19: 515-516.
17. **Nofal A, Marei A, Amer A *et al.* (2017):** Significance of interferon gamma in the prediction of successful therapy of common warts by intralesional injection of Candida antigen. Inter J Dermatol., 56: 1505-1506.
18. **Abd-Elazeim F, Mohammed G, Fathy A *et al.* (2014):** Evaluations of IL-12 serum level in patients with recalcitrant multiple common warts, treated by intralesional tuberculin antigen. J Dermatolog Treat., 25 (3): 264-7.