ORIGINAL ARTICLE

Intradermal *vs* intralesional purified protein derivatives in treatment of warts

Ibraheem M Abo Elela, MD, Ahmed R Elshahid, MD, Al-Sadat Mosbeh, MD

Department of Dermatology, Venereology and Andrology, Faculty of Medicine, Al-Azhar University, Cairo, Egypt

ABSTRACT

Background: The most common therapies for warts are limited by cost, poor patient compliance, pain and efficacy. Intralesional immunotherapy employs the ability of the immune system to recognize certain viral and fungal antigens. It is believed that the delayed-type hypersensitivity reaction induced by antigens increases the ability of the immune system to recognize and clear human papilloma virus (HPV).

Aim: This study was designed to evaluate the effect of intradermal and intralesional Purified Protein Derivatives (PPD) in treatment of warts.

Patients and Methods: One hundred and ten patients with warts were included and classified into 3 groups: first group included 40 patients treated with intralesional PPD, second group included 50 patients treated with intradermal PPD & the third group included 20 patients as a control group treated with intralesional saline with a dose of 0.1 ml.

Result: The response to PPD in the first group was complete cure in 32 cases 94.1% .In the second group, the response to intradermal PPD was complete cure 48 cases 96%. There was no significant difference between intradermal and intralesional PPD in treatment of warts .The response to PPD in the control group was complete cure in 3(15%) cases and failure of response in 17(85%) cases. Statistical analysis of the response to PPD injections showed that, there were highly significant differences between control group, first and second group ($P < 0.001$).

Conclusion: Purified protein derivative seemed to be safe and effective in treatment of warts. Intradermal injection of PPD was effective as well as intralesional PPD in warts treatment.

KEYWORDS: warts, purified protein derivatives, intralesional, intradermal

INTRODUCTION

Although the prevalence of common warts in general population is unknown, warts occur in approximately 5% to 20% of children and young adults.[1] Viral warts occur equally in both sexes. In children aged between 2 to12 years warts are among the three most common dermatoses treated.[2] Approximately 23% of warts regress spontaneously within 2 months, 30% within 3 months and 65% to 78% within 2 years.[3]

Previously infected patients have a higher risk for development of new warts than those never infected.[4] The rate of clearance is influenced by many factors such as viral type, host immune status, extent and duration of warts.[5]

The role of immunity is documented by the appearance and persistence of warts in immunosuppressed, spontaneous regression of the majority of warts is related to cellular immunity.[6] A fully functional immune system is necessary to clear HPV from the epidermis. This is evident in immunosuppressed transplant patients, 77% of whom develop warts at some time.[7] The body's immune response to HPV infection is a multifactorial. It includes a reduction in epidermal Langerhans cells,[8,9] expression of human leukocyte antigen HLA-DR+ by keratinocytes, and intraepithelial up-regulation of intracellular adhesion molecule-1 (ICAM-1)

Correspondence: *Dr. Ahmad R. Elshahid, Lecturer of Dermatology, Venereology and Andrology, Al-Azhar University, Cairo, Egypt*
Email: ahmedandro@yahoo.com

and lymphocyte function–associated antigen-1.[10]
A decrease in epidermal Langerhan's cells, an increase in dermal Langerhan's cells, CD4+ and CD8+ cellular infiltrates, and HLA-DR+ cells in the dermis are all seen with flat warts. Similarly, a reduction in Langerhan's cells and HLA-DR+ cells in the epidermis is seen in lesions with HPV antigen. Expression of HLA-DR+ likely represents the presence of keratinocytes as opposed to Langerhans cells because, in HPV infection, keratinocytes express HLA-DR and not HLA-DQ.[9]
The most common therapies for warts include destruction (Cryotherapy, salicylic acid, laser, electrodessication and curettage), topical immunotherapy, and chemotherapy. These treatments are limited by cost, poor patient compliance, pain and efficacy.[11,12]
Intralesional (IL) immunotherapy employs the ability of the immune system to recognize certain viral and fungal antigens. It is believed that the delayed-type hypersensitivity reaction induced by these antigens increases the ability of the immune system to recognize and clear HPV. The regression of warts at distant sites has not been established with other therapies.[5] Intralesional Purified protein derivative tuberculin injection is an acceptable and safe modality in the treatment of warts. It is especially promising in countries where vaccination against tuberculosis is performed routinely.[13] The aim of this study was to evaluate the effect of intradermal (ID) and intralesional(IL) PPD in treatment of warts.

MATERIALS AND METHODS

Our study included 110 patients having different types of wart. They were 58 females and 52 males aged between 5 to 38 years. All patients were collected from Al-Azhar university hospitals. Informed consent was obtained and the diagnosis of warts was made by clinical examination. Exclusion criteria consisted of patient with immunosuppression, pregnant or lactating women, and patients with past history of tuberculosis or negative tuberculin test. Inclusion criteria consisted of Patients with past history of B.C.G vaccination or with positive tuberculin test.
Patients were classified into 3 groups: First group included 40 patients treated with IL (in the wart) PPD with a dose of 0.1 ml by insulin syringe. Second group included 50 patients treated with ID PPD into the right forearm with a dose of 0.1 ml away from verrucae by insulin syringe. Third group included 20 patients as a control group treated with IL saline with a dose of 0.1 ml by insulin syringe. Injections were repeated for all patients every 2 weeks for a total of 10 injections or less in cases of resolution of warts. At the first visit; the duration, location, number, diameter of all warts were reported. As long as there was some clinical response, a subject was permitted to receive a maximum of 10 injections. After the tenth injection, if the wart was not completely healed, the patient was excluded from the study. Response of distant, anatomically-distinct, untreated warts was also noted.

STATISTICAL METHODS

SPSS (version 12.0) was used in data management. Chi-square/Fisher exact were tests of proportion independence. Non parametric (Mann Whitney) t test compared means of independent groups. P value< 0.001 is significant.

RESULTS

In the first group out of 40 patients, six patients did not complete the study. The average age was

20.35 years (range 5-36 years) for the first group, 17.04 years (range 6-32 years) for the second group, and 18.02 years (range 5-38 years) for controls group. In the first group, there were 10(25%) women and 24(54.5%) men while in the second group there were 30(60%) women and 20(40%) men. While, in control group there were 8(40%) male and 12(60%) female.

In first group 6(17.6%) cases with plantar warts achieved complete cure at the end of the study. Also, 24 cases out of 28(82.4%) cases from group 1 with common wart achieved complete cure, and 2 cases failed to respond. Whereas, In the second group 8 cases (16%) with plane warts, 18 cases (36%) with plantar warts achieved complete cure at the end of the study. while the common wart cases 24 (48%) the response was complete cure in 22 cases and failure of response in 2 cases. In the control group all cases were with common warts.

As regard the number of the warts 4 cases (11.8%) had one wart in the first group while 2 cases (4%) in the second group had one wart. In first group 2 cases (5.9%) had 2 warts while 4 cases (8%) in the second group had 2 warts. In first group 28 cases (82.4%) had 3 or more warts while 44 cases (44%) in the second group had 3 or more warts.

The response to PPD injection showed complete cure in 32 cases (94.1%) for the first group and 48 cases (96%) for the second group. Failure of response was in 2 cases (5.9%) for first group. Also, failure of response was in 2 cases (4%) for the second group. There was no significant difference between intradermal and Intralesional PPD in treatment of warts (Table 1), (Fig. 1,2).

The response to PPD in the control group was complete cure in 3 cases (15%) and failure of response in 17 cases (75%). Statistical analysis of response to PPD injections between control group and intradermal group showed that there were highly significant differences. Also Statistical analysis of response to PPD injections between control group and Intralesional group showed that there were highly significant differences ($P < 0.001$) (Table 1).

Table 1 Response to treatment in ID, Intalesional and control groups

Group	Count	Response		Total
		Complete	Failed	
Group 1 (ID)	Count	48	2	50
	% within the Group	96.0%	4.0%	100.0%
Group 2 (IL)	Count	32	2	34
	% within the Group	94.1%	5.9%	100.0%
Controls	Count	3	17	20
	% within the Group	15.0%	85.0%	100.0%
Total(a)	Count	83	21	104
	% within the Group	69.4%	30.6%	100.0%

P value < 0.001 highly significant difference in response of ID & IL injection compared to controls

DISCUSSION

The immune system plays a central role in the regression of warts. Cellular immunity appears to be the prime means of repelling HPV infection. Spontaneously regressing warts show significant epidermal and dermal influx of CD4+-activated memory lymphocytes compared to non-regressing lesions. Antibodies to HPV proteins have been well documented in the serum of patients with HPV infection, but their role is uncertain as they do not correlate with the wart clearance.[6]

The exact mechanism of the clearance of warts with PPD is not known. Its injection into the HPV infected tissue probably generates strong pro-inflammatory signals and attracts antigen presenting cells, which also recognize and process low-profile HPV particles in the infected tissue. This

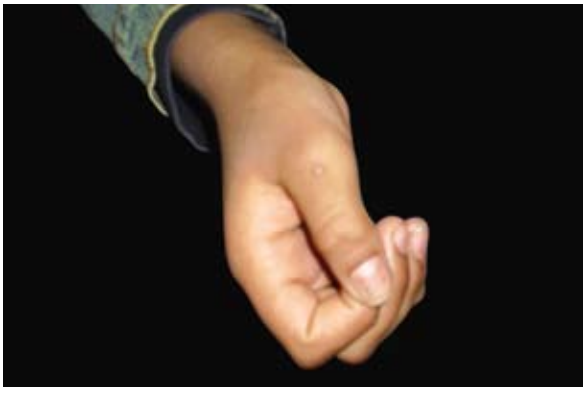

Fig. 1 A. female patient before treatment with ID injection of PPD.

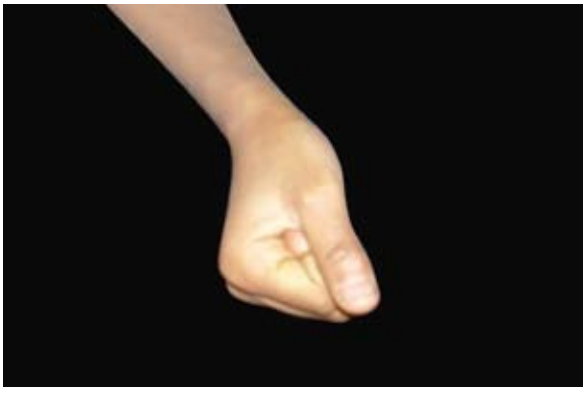

Fig. 1 B. female after treatment with ID injection of PPD (2 sessions).

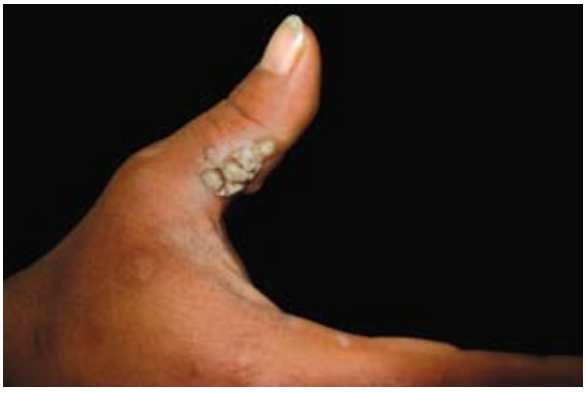

Fig. 2 A. male patient (35 years) before treatment with IL of PPD.

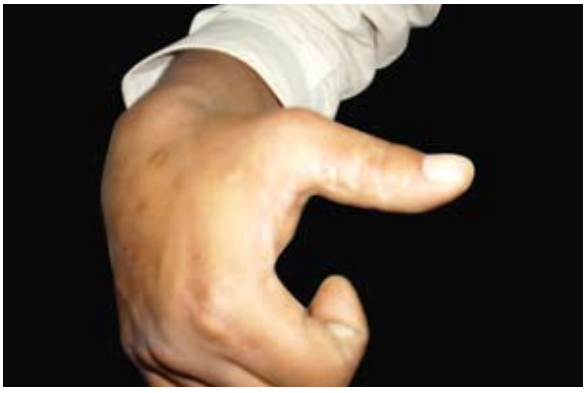

Fig. 2 B. Male patient (35 years) after treatment with IL of PPD (3 sessions).

leads to a strong adaptive immune response not only against mycobacterium tuberculosis but also against HPV, which otherwise successfully evades the host immune response. A similar mechanism has been proposed for the resolution of warts with skin test antigens such as mumps, Candida and Trichophyton antigens both at the injected as well as distant sites.[13]

In this study, the response obtained with using PPD was via ID injection was 96%. Kus et al[14] found that the result of treatment of common wart especially periungual wart was around 29.4%. It seems that the cure rate is different from that obtained by Kus et al due to small number of the patients or short duration of treatment in Kus et al study.

Lahti and Hannuksela[15] used tuberculin (PPD) as topical jelly in treatment of common warts, 8 out of 14 patients (57%) showed complete disappearance of their warts. The mean duration of the warts was 2.9 years. The mean age of the patients was 24.1 years. The disappearance of warts usually occurred in the 3rd or 4th month. The strength of the tuberculin reactivity was not correlated with the disappearance of the warts. There were no side effects as pain and edema as seen with ID injection of PPD. The major disadvantage of topical tuberculin jelly is the long duration of treatment as the disappearance of warts occurred after 3-4 months of treatment. Intradermal tuberculin (PPD) injection is better than topical tuberculin (PPD) in spite of its tolerable pain due to its short duration of therapy and the strength of the tuberculin reactivity was correlated with the disappearance of the warts.

In a study done by Gupta et al[16] for treatment of

warts especially anogenital warts, killed Mycobacterium vaccine was initially injected (0.1 mL) intradermally in the deltoid region on both sides, followed two weeks later by IL injection into the warts. Intralesional injections were repeated weekly until either complete clearance or a maximum of 10 injections was achieved. Eight out of 9 patients (88.9%) showed complete clearance. The treatment was well tolerated by the majority of the patients. The adverse reactions were noted in four patients, which were reversible. No recurrence was seen after a mean follow-up of 5.1 months. They concluded that IL immunotherapy of warts with this vaccine seems to be a promising new approach in comparison with intradermal PPD injection.

In current study, statistical analysis of response to PPD showed that there was an insignificant statistical difference between males and females as regard to response to treatment. The mean age of the responders was 24.3 years while the mean age of non responders was 19.8 years, so it seems that the response is better with older age group. This may be explained by well established immune system in the responders group.

The mean duration of the resolved lesions in the patients was 1.4 years in ID group and 2.2 years in IL group while the mean duration of non resolved lesions was 3 years in both groups. So it seems that the response to PPD injection is affected by the duration of the lesions, the longer the duration the less the response to PPD. The results of the present study are not matched to that obtained by Kus et al[14] who reported that the response to PPD injection is not affected by the duration of the lesions.

This study showed that, the response was better in the patients with plain and plantar warts than these with common warts as the non responders were having common warts. The results of the present study are matched to that obtained by Kus et al[14] who reported good response in the lesions of the feet. He also reported good response in the distant plane warts that were far from the site of PPD injection. As, the immune response is not restricted to the site of the injection.

The current study found that, the response was 96% in ID group and 94.1% in IL group there was no significant deference between both groups. These findings indicate that PPD can give a good clinical cure rate in the treatment of warts through any approach.

CONCLUSION

Purified protein derivative seemed to be a safe and an effective in treatment of warts. Intradermal PPD was effective as well as Intralesional PPD in wart treatment. We recommend that the use of PPD injection in treatment of warts especially plantar and plane warts.

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