

Intralesional injection of purified protein derivatives versus zinc sulfate 2% in recalcitrant palmar and/or plantar warts

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Received 6 February 2016

Accepted 7 May 2016

Journal of the Egyptian Women's Dermatologic Society 2016, 13:151–158

Background

The immune system plays an essential role in the clearance of warts, and thus recently there is a trend to use immunotherapy in wart treatment. Tuberculin-purified protein derivatives (PPDs) and zinc sulfate 2% were not previously compared regarding their efficacy in the treatment of warts.

Objective

The aim of this study was to determine the efficacy and safety of intralesional (IL) immunotherapy with tuberculin PPD versus zinc sulfate 2% in multiple recalcitrant palmar and/or plantar warts.

Patients and methods

Forty-five patients who presented with resistant palmar and/or plantar warts were divided randomly into two groups: the first group included 23 patients treated with IL tuberculin PPD, and the second group included 22 patients treated with IL zinc sulfate 2%.

Results

The target wart in the tuberculin-PPD-treated group showed a statistically nonsignificant higher rate of complete clearance compared with the zinc sulfate 2%-treated group (87 vs. 72.7%, respectively). Partial response was seen in 13 versus 13.6% and no response was seen in 0 versus 13.6%. In untreated distant warts, the tuberculin-PPD-treated group showed statistically significant higher rates of complete response compared with the zinc sulfate 2%-treated group (73.9 vs. 40.9%, respectively); the partial response was 13 versus 36.4% and no response was 13 versus 22.7%, respectively.

Conclusion

IL immunotherapy with tuberculin PPD was more effective than zinc sulfate 2% in the treatment of cutaneous warts. It is a simple, effective, safe procedure, with tolerable pain, and it may represent an alternative treatment for multiple resistant palmar and/or plantar warts.

Keywords:

immunotherapy, intralesional, tuberculin-purified protein derivative, warts, zinc sulfate

J Egypt Women Dermatol Soc 13:151–158
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1687-1537

Introduction

Viral wart is a common, benign, and usually self-limited skin disease, which infects the stratified squamous epithelium. Basal keratinocytes of the epidermis, which serve as primary targets for human papillomaviruses (HPV) infections, are exposed to the virus through minor abrasions, and infection is promoted by maceration of the epithelia [1,2]. Viral wart affects all ages, but it is more common among children. Spontaneous clearance is observed in 40% of children within 2 years without treatment because of their native immunity [1,2].

No single treatment can completely cure warts. Recurrence is common after treatment. The cellular immunity plays a pivotal role in the clearance of warts [1–3].

The treatment of warts includes variable methods, such as topical agents, cryosurgery, electrocautery, laser ablation,

surgical excision, and immunotherapy. The initial line treatment is topical salicylic acid, with a 75% cure rate [1–4].

Intralesional (IL) immunotherapy with certain fungal and viral antigens induces a delayed-type hypersensitivity reaction that increases the ability of the immune system to recognize and clear HPV. The regression of warts at distant sites had not been established with other therapies [5].

IL purified protein derivative (PPD) injection is an acceptable and safe modality in the treatment of warts [6]. Zinc sulfate has been used successfully in the treatment of common warts and genital warts orally [7], as well as IL, in a single study in recalcitrant common warts [8]. Tuberculin PPD and zinc sulfate 2% were not previously compared regarding their efficacy in

the treatment of warts. This study compared the safety and efficacy of IL injection of tuberculin PPD and zinc sulfate 2% in the treatment of patients with multiple recalcitrant palmar and/or plantar warts.

Study design

This randomized controlled clinical trial (the untreated distant warts of the same patients were used as control) was approved by the Institutional Ethics and Research Committee of Faculty of Medicine, Assiut University, Assiut, Egypt. All patients were informed of the study procedure, benefits, and potential complications, and they were included in the study after obtaining their written informed consent.

Patients

Forty-five patients who presented with multiple palmar and/or plantar warts were enrolled in the study. They were recruited from the Outpatient Dermatology Clinic of the Department of Dermatology and Venereology, Assiut University Hospital and Assiut Dermatology Hospital.

Patients were randomly divided into two groups.

Group 1: this group included 23 patients who were treated with IL injection of tuberculin-PPD.

Group 2: this group included 22 patients who were treated with IL injection of zinc sulfate 2%.

Inclusion criteria

Patients with ages ranging from 3 to 40 years with a positive tuberculin test or with a past history of BCG vaccination were included.

Exclusion criteria

Patients with immunosuppression, pregnancy, or lactation, with negative tuberculin test or with past history of tuberculosis, and those who received any wart treatment 1 month before the start of the study were excluded.

Methods

Complete history taking included name, age, sex, occupation, and residence, and general and local examinations (site and number of warts and size of the largest one) were carried out in all patients included in the study. The target wart is injected using a built-in insulin syringe in both groups.

Evaluation

Evaluation was performed by photographing the patients using a 16.2-megapixel Sony DSC-WX50 digital camera (Sony, Tokyo, Japan) before treatment and 2 weeks after each session and monthly up to 6 months. Clinical response evaluation was performed by at least two expert dermatologists in addition to the main study researchers. The clinical response was graded into complete (complete cure), partial (if there was a decrease in the size of

the injected wart or a decrease in the total number of distant warts), and no response (no change of the target and distant warts).

Treatment protocols

First group

The first group received an IL injection of tuberculin PPD at a dose of 10 IU (0.1 ml) with an insulin syringe in the largest wart. Injections were repeated for all patients into the same lesion (largest wart) every 2 weeks for three treatment sessions.

Storage

A 2 ml vial of tuberculin PPD (Mantoux test), which is an intradermal test manufactured by Vacsera Company, Cairo, Egypt, was used. The product was stored in the dark, except when doses are actually being withdrawn from the vial [9] between 2 and 8°C [10]. The expiry date of a vial of tuberculin PPD is 1 month from the date of opening it [11].

Second group

The second group received an IL injection of zinc sulfate 2% with an insulin syringe, in the largest wart. This wart was injected with the solution until blanching or bleb formation. Subcutaneous injection and acral parts such as fingers and toes were avoided, as it may cause vascular necrosis. Injections were repeated for all patients into the same lesion (largest wart) every 2 weeks for three treatment sessions.

Preparation of zinc sulfate 2%

A measure of 2 g of zinc sulfate powder was dissolved in 100 ml of sterile distilled water and autoclaved at 95°C for 20 min [8].

Postprocedure care for all patients in both groups

- (1) Topical, systemic antibiotics, and analgesic anti-inflammatory drugs were prescribed to the patient to guard against infection and to relieve pain.
- (2) The patients were asked to return after 2 weeks for the assessment of healing, to check for the need for another session, and to check for complications.
- (3) Photographs were taken before and after response.

Follow-up of all patients was carried out during treatment every 2 weeks for three treatment sessions. After the end of treatment, follow-up was done monthly for at least 6 months to detect recurrence or appearance of new lesions.

Statistical analysis

Data were analyzed using SPSS, version 19.0 (SPSS Inc., Chicago, Illinois, USA). The frequencies, percentages, and the mean \pm SD were computed. χ^2 -test was used to compare qualitative variables. Mann-Whitney test was used as a test of significance to compare quantitative data between groups. The 5% level was chosen as the level of significance and 95% confidence interval.

Results

Forty-five patients who presented with multiple palmar and/or plantar warts were included in the study (their ages ranged from 3 to 39 years, with a mean of 21.54 ± 9.39 years in the first group, and 5 to 40 years, with a mean of 22.36 ± 11.33 years in the second group); 52.2% of patients of the first group were male and 47.8% were female, compared with 50% male and 50% female patients in the second group. All patients had multiple warts with the number of warts in the first group ranged from 2 to 25, with a mean number 6.70 ± 5.84 warts, and the number of warts in the second group ranged from 2 to 15, with a mean of 5.00 ± 4.06 warts. The percentage of palmar warts was 43.5% and the percentage of plantar warts was 56.5% in the first group, compared with 50 and 50% in the second group, respectively.

Complete clearance (complete response) occurred in the first group (tuberculin-PPD-treated group) in 5.88% of patients after one session, in 5.88% of patients after two sessions, and in 82% of patients after three sessions, compared with 22.2, 44.4, and 33.3% in the second group (zinc sulfate 2%-treated group), respectively.

In the target wart, higher rates of treatment responses, although statistically nonsignificant, were observed in the first group compared with the second group. The response rates in the first group versus the second group

were as follows: complete response was observed in 87 versus 72%, partial response in 13 versus 13.6%, and no response in 0 versus 13.6% (Table 1 and Figs 1–4).

Untreated distant warts in the first group showed statistically significant higher rates of complete response ($P < 0.025$) compared with the second group. The response rates in the first group versus the second group were as follows: complete response was observed in 73.9 versus 40.9%, partial response was observed in 13 versus 36.4%, and no response was observed in 13 versus 22.7% of patients (Table 2 and Figs 1–4).

The response in the first group according to age, sex, and site showed a statistically nonsignificant higher rate of complete clearance in the age group of less than 20 years (52.9%); the response rate was nonsignificantly higher in female patients (52.9%) and in patients with plantar warts (52.9%) (Table 3). In the second group, there was a statistically significant higher rate of complete response in those in the age group less than 20 years (66.7%), which was nonsignificantly higher in female patients (66.7%) and in patients with palmar warts (66.7%) (Table 4).

The main complaint was tolerable pain during IL injection. Other side effects reported after treatment were pain, swelling, painful purpura, and flu-like symptoms, which

Table 1. Comparison between group 1 (IL injection of tuberculin PPD) and group 2 (IL injection of zinc sulfate 2%) as regards the response of target warts

| Response | Group 1 (n=23) [n (%)] | Group 2 (n=22) [n (%)] | P value |
|-------------------|------------------------|------------------------|---------|
| Complete response | 20 (87.0) | 16 (72.7) | 0.412 |
| Partial response | 3 (13.0) | 3 (13.6) | 0.635 |
| No response | 0 (0.0) | 3 (13.6) | 0.067 |

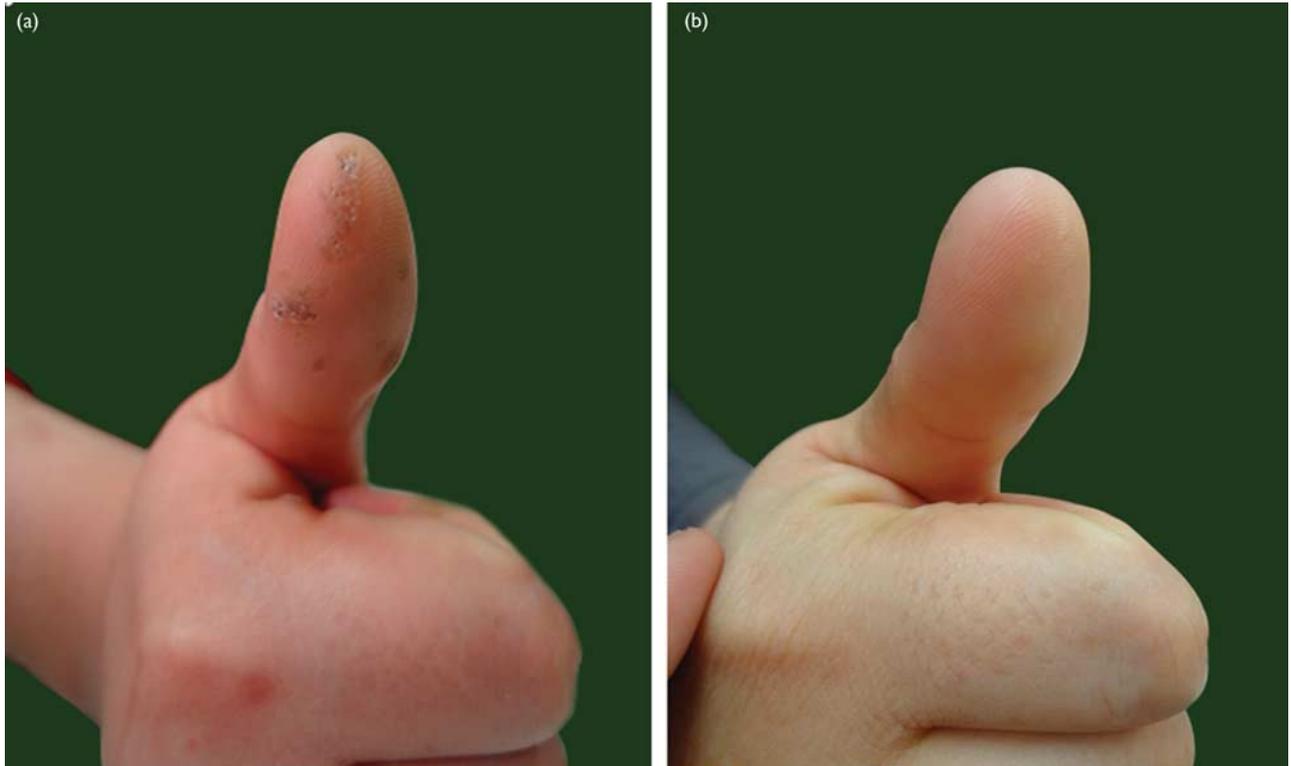
IL, intralesional.

Figure 1.



(a) Female patient with multiple plantar warts (mosaic pattern) before treatment with intralesional PPD injection. (b) Complete response after three sessions of intralesional PPD injection. PPD, purified protein derivative.

Figure 2.



(a) Female patient with multiple palmar warts before treatment with intralesional PPD injection. (b) Complete response after three sessions of intralesional tuberculin PPD injection. PPD, purified protein derivative.

Figure 3.



(a) Male patient with multiple plantar warts before treatment with intralesional zinc sulfate 2% injection. (b) Complete response after three sessions of intralesional zinc sulfate 2% injection.

Figure 4.



(a) Female patient with multiple palmar warts before treatment with intralesional zinc sulfate 2% injection. (b) Partial response after three sessions of intralesional zinc sulfate 2% injection.

Table 2. Comparison between group 1 (IL injection of tuberculin PPD) and group 2 (IL injection of zinc sulfate 2%) as regards the response of distant warts

| Response | Group 1 (n=23) [n (%)] | Group 2 (n=22) [n (%)] | P value |
|-------------------|------------------------|------------------------|---------|
| Complete response | 17 (73.9) | 9 (40.9) | 0.025* |
| Partial response | 3 (13.0) | 8 (36.4) | 0.069 |
| No response | 3 (13.0) | 5 (22.7) | 0.646 |

IL, intralesional; PPD, purified protein derivatives.

*P value <0.05 is considered statistically significant.

Table 3. Clearance in the first group according to age, sex, and site

| | Complete clearance (n=17) [n (%)] | Incomplete clearance (n=6) [n (%)] | P value |
|---------------|-----------------------------------|------------------------------------|---------|
| Age (years) | | | |
| <20 | 9 (52.9) | 2 (33.3) | 0.408 |
| ≥20 | 8 (47.1) | 4 (66.7) | |
| Sex | | | |
| Male | 8 (47.1) | 4 (66.7) | 0.408 |
| Female | 9 (52.9) | 2 (33.3) | |
| Site of warts | | | |
| Palmar | 8 (47.1) | 2 (33.3) | 0.560 |
| Plantar | 9 (52.9) | 4 (66.7) | |

occurred in a few patients in group 1 and disappeared in a few days. Side effects in group 2 were only observed in one patient (4.5%) after the first session only, in the form of pain, swelling, and hematoma (Table 5).

No recurrence or appearance of new lesions was observed during last 6 months of the follow-up period after the last treatment session in both groups.

Table 4. Clearance in the second group according to age, sex, and site

| | Complete clearance (n=9) [n (%)] | Incomplete clearance (n=13) [n (%)] | P value |
|---------------|----------------------------------|-------------------------------------|---------|
| Age (years) | | | |
| <20 | 6 (66.7) | 3 (23.1) | 0.041* |
| ≥20 | 3 (33.3) | 10 (76.9) | |
| Sex | | | |
| Male | 3 (33.3) | 8 (61.5) | 0.193 |
| Female | 6 (66.7) | 5 (38.5) | |
| Site of warts | | | |
| Palmar | 6 (66.7) | 5 (38.5) | 0.193 |
| Plantar | 3 (33.3) | 8 (61.5) | |

*P value <0.05 is considered statistically significant.

Table 5. Complications in the studied population

| | Group 1 (n=23) [n (%)] | Group 2 (n=22) [n (%)] | P value |
|--|------------------------|------------------------|---------|
| First session complications | | | |
| Pain | 4 (17.4) | 0 (0.0) | 0.127 |
| Pain and swelling | 1 (4.3) | 0 (0.0) | 0.323 |
| Pain, swelling, hematoma | 0 (0.0) | 1 (4.5) | 0.982 |
| No side effects | 18 (78.3) | 21 (95.5) | 0.209 |
| Second session complications | | | |
| Pain | 1 (4.3) | 0 (0.0) | 0.323 |
| Pain, swelling, redness | 1 (4.3) | 0 (0.0) | 0.323 |
| Painful erythema, swelling, flu-like manifestation | 1 (4.3) | 0 (0.0) | 0.323 |
| No side effects | 20 (87.0) | 22 (100.0) | 0.248 |
| Third session complications | | | |
| Pain, swelling | 2 (8.7) | 0 (0.0) | 0.489 |
| No side effects | 21 (91.3) | 22 (100.0) | |

We noticed that some patients (who reported to have partial clearance at the end of treatment period in the tuberculin PPD group) showed complete cure after 1 year from the last session.

Discussion

The immune system plays an essential role in the spontaneous resolution of warts. The stimulated immune response would subsequently destroy all warts on the body, rather than the locally treated lesion [12].

The present study showed complete clearance of 87% of target warts and 73.9% of distant warts in the tuberculin-PPD-treated group, with no recurrence for 6 months after the last treatment session. Our study showed a higher response rate compared with other IL PPD studies, such as the study by Amirnia *et al.* [13] in which a 77.1% clearance in recalcitrant warts was reported, as well as the studies by Saoji *et al.* [14] (with 76% clearance of plane, common, and plantar warts), Abd-Elazeim *et al.* [15] (with 75% clearance in recalcitrant common warts), Eassa *et al.* [16] (47.5% clearance in distant genital warts after weekly intradermal PPD injection in the forearms), and Lahti and Hannuksela [17] (57% complete clearance of common warts after tuberculin PPD topical jelly use). However, the response rate of the present study was lower than that reported by Wananukul *et al.* [18] (with complete clearance in 93% of the target warts and 87% of distant warts) and Abo Elela *et al.* [19] (with 94.1% clearance of target plantar warts, after IL PPD injection). This may be explained by the fact that those studies were based on six and 10 sessions, whereas our study had three sessions only.

Our results showed findings similar to the studies by Gupta *et al.* [20] and Garg and Baveja [21] who used IL *Mycobacterium w* vaccine for the treatment of anogenital warts, with 88.9% clearance in target warts and no recurrence for 5.1 months. Similar results were obtained in other studies that used IL measles, mumps, and rubella vaccine, such as the studies by Gamil *et al.* [22], with 87% clearance in target plantar warts, Mohamad *et al.* [23], with 82% clearance of target and 87% of distant plantar warts, and Nofal and Nofal [24], with 81.4% clearance in target common warts.

Our results were higher than those of other studies that used different skin test antigens, such as in the studies by Johnson and Horn [25], with 74% clearance of target warts and 78% of distant warts, and Clifton *et al.* [5], with clearance of 47% of target warts and 34% of distant warts, using mumps or *Candida* spp. antigens, and Brunk [26], with (85%) clearance, Phillips *et al.* [12], with (72%) clearance, and Signore [27], with 51% clearance using *Candida* spp. antigen.

The different response in the present study compared with the other studies that used either a single antigen or a combination of antigens may be explained by the differences in the number of patients, the duration, and the resistance of warts. The difference might be attributed also to the number of sessions (three sessions were performed in our study, and other studies reached up to six or 10 sessions maximally according to patient response to treatment to reach higher stimulation of the immune system).

The clearance of untreated distant warts strongly indicated the development of a widespread cell-mediated

immunity against HPV as a response to IL antigen injection, and it represents the main advantage of the IL immunotherapy [23].

The exact mechanism of the clearance of warts with tuberculin PPD is not known. Its injection into the HPV-infected tissue probably generates strong proinflammatory signals and attracts antigen-presenting cells, which also recognize and process low-profile HPV particles in the infected tissue. This leads to a strong adaptive immune response not only against mycobacterium tuberculosis but also against HPV [19]. A similar mechanism had been proposed for the resolution of warts with skin test antigens such as mumps, *Candida* spp., and *Trichophyton* spp. antigens both at the injected and distant sites [6]. It has been proposed that injectable antigens elicit a cell-mediated hypersensitivity reaction leading to T-helper 1 activation with cytokine release. However, El-Samahy *et al.* [28] found that serum interleukin-12 and interferon- γ levels were higher in patients with multiple warts than in controls, but were not increased after PPD tuberculin injection.

The use of zinc in the treatment of warts was proven in many studies either in the topical form or systemic oral therapy [29]. However, only a single study showed its IL efficacy [8].

Our study reported 72.7% complete clearance in target warts and 40.9% in distant warts with IL zinc sulfate 2% injection. Sharquie and Al-Nuaimy [8] showed different response rates, as they reported total cure rate in 98.2% of target common warts, and most of them (80.92%) needed just a single injection. This difference might be because of the use of different techniques of injection, as in their study each patient had multiple warts, and some of the warts were injected while others were left as controls, whereas in our study the largest wart only was injected in every session.

Cusini *et al.* [30] reported a complete cure rate in 90% of external genital warts after one and up to four applications of nitric-zinc solution. Sharquie *et al.* [31] studied the efficacy of 10 and 5% topical zinc sulfate solution applied three times daily for 4 weeks; they reported complete clearance in plane warts in 85.7 and 42.8% of cases, respectively, whereas it was 11 and 5% of common warts, respectively. However, Khattar *et al.* [32] showed complete cure in 50% of common warts after 3 months of topical 20% zinc oxide use.

Al-Gurairi *et al.* [7] observed complete clearance of 86.9% of resistant warts (plane, common, and plantar) after 2 months of daily oral zinc sulfate (10 mg/kg up to 600 mg/day). However, Mun *et al.* [33] reported only 50% clearance rate with the same dose and also after 2 months.

The mechanism of action of zinc sulfate cannot be speculated, but it is probably similar to the action of zinc sulfate in cutaneous leishmaniasis [34,35] and bleomycin on viral warts, as both induce necrosis and inflammation [36–39]. Its mechanism of action as a treatment of recalcitrant warts is not clear. It may enhance the patient's immunity via its immunomodulatory action [7].

Immunotherapy with tuberculin PPD is well tolerated in patients included in the present study. Tolerable pain during injection was the main complaint. Some complications occurred after treatment, in the form of pain, swelling, painful purpura, and flu-like manifestations, which were observed in other studies [18,23]. Side effects in group treated with zinc sulfate 2% were less compared with the tuberculin-PPD-treated group, in the form of pain, swelling, and hematoma in one patient (4.5%) after the first session only, which was different from the study by Sharquie and Al-Nuaimy [8], where they reported these side effects in all their studied patients. This difference might be because of the fact that in their study each patient had multiple warts and some of them were injected, whereas in our study the largest wart only was injected every session.

In our study, no recurrence or appearance of new lesions was observed for 6 months of follow-up after the last treatment session, in both groups, which was consistent with other studies [8,18].

Conclusion

IL tuberculin PPD was more effective than IL zinc sulfate 2% in the treatment of cutaneous warts. In IL immunotherapy, treatments with two or more injections are needed, after which clearance of untreated distant warts occurred. It is a simple, inexpensive, effective, and safe procedure with no residual scars. It may represent an alternative treatment for multiple resistant palmar and plantar warts.

Recommendation

Further studies on IL tuberculin PPD and zinc sulfate are needed to show whether results would be improved by larger population studies, increasing the volume of injected tuberculin PPD and using zinc sulfate in different concentrations, treatment of more than one wart at a time (not only the target wart), and more than three treatment sessions.

Acknowledgements

Conflicts of interest

There are no conflicts of interest.

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