

Intralesional Quadrivalent Human Papilloma Virus Vaccine Versus Candida Antigen in the Treatment of Multiple Recalcitrant Non-Genital Warts

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ABSTRACT **Introduction:** Warts are the most prevalent clinical manifestation of Human Papilloma Virus (HPV) infections, which vary in morphological pattern depending on the site of the body affected.

Objectives: To evaluate the safety and efficacy of intralesional quadrivalent HPV vaccine versus candida antigen in treatment of multiple recalcitrant non-genital warts.

Methods: A randomized- control clinical trial included 60 cases with multiple recalcitrant warts who were randomly distributed into three groups; Group I included 20 patients who received intralesional candida antigen at a dose of 0.3 mL of 1/1000 solution, Group II included 20 patients who received intralesional quadrivalent HPV vaccine at a dose of 0.3ml and Group III included 20 patients who received intralesional injection 0.3 ml of normal saline 0.9% as a control group). Each agent was injected at the base of the largest wart every three weeks until it was completely cleared, or for a total of four sessions.

Results: the highest response rate was detected in the quadrivalent HPV vaccine group (75% complete response) followed by the candida vaccine group (40% complete response and 15% partial response). Also, regarding the distant response rate, the highest response rate was detected in the quadrivalent HPV vaccine group (72.7% complete response and 27.3% partial response) followed by the candida vaccine group (33.3% complete response and 50% partial response).

Conclusions: Intralesional immunotherapy appears to be effective and safe in treating multiple recalcitrant non-genital warts, with intralesional quadrivalent HPV vaccine outperforming intralesional candida antigen.

Introduction

Warts are benign epithelial proliferations resulting from more than 200 serotypes of Human Papilloma Virus (HPV) infection occurring on the skin and mucosa [1]. Warts are not life-threatening or harmful, but they can be embarrassing to the patient when present in the exposed areas of the body. Warts are infectious and can spread by skin-to-skin contact. However, the strains vary in their intensity of contagiousness [2].

Warts are categorized into two types: cutaneous and extracutaneous. Common warts, filiform warts, planter warts, plane warts, anogenital warts are among the cutaneous lesions. Oral common warts, oral condylomata acuminata, focal epithelial hyperplasia, oral florid papillomatosis, nasal papillomas, conjunctival papillomas, laryngeal papillomatosis, and cervical warts are extracutaneous lesions that affect the mucous membranes [3].

Unfortunately, a specific antiviral agent against HPV is lacking and while most warts spontaneously disappear, some persist and are resistant to treatment. All available treatment modalities intend to destroy lesions by chemical agents such as salicylic acid, 5- fluorouracil, and/or by physical destructive methods; eg (electrocautery, cryotherapy, photodynamic therapy and surgical excision). These methods, however might be associated with scarring, pain and high rates recurrence [4-6].

Intralesional antigen immunotherapy represents a promising therapeutic approach for the treatment of different types of warts, particularly if multiple and/or recalcitrant. Immunotherapeutic approaches act by enhancing the host cell-mediated immunity to eliminate the virus rather than just clearing the skin lesions [7].

The efficacy of immunotherapy using a single test antigen and multiple test antigens in the treatment of warts has been investigated with various degrees of success. Tuberculin purified protein derivative (PPD), measles, mumps, and rubella (MMR) vaccine, mycobacterium w vaccine, interferon- α or β , Candida antigen, and Bacillus Calmette-Guerin (BCG) vaccine are a few examples of immunotherapeutic drugs that have been researched [8-10]. The efficacy of Candida skin-test antigen in wart resolution was demonstrated in the first such trial [11].

Several studies have confirmed the role of a prophylactic quadrivalent HPV vaccine (HPV types 6, 11, 16, and 18) in the prevention of HPV-associated precancerous and cancerous lesions. There might be some cross-reactivity of antigenic epitopes in the HPV types covered by the vaccine and other HPV types responsible for common warts [12-14].

Objectives

In this study we aimed to evaluate and compare the safety and efficacy of intralesional Candida antigen versus

quadrivalent HPV vaccine in treatment of multiple recalcitrant non-genital warts.

Methods

Patients

This is a three arm, single blinded, randomized controlled clinical trial included 60 cases.

Inclusion Criteria

patients who have multiple recalcitrant non-genital warts.

Recalcitrant warts were defined as warts that persisted for more than one year and were resistant to at least two therapeutic modalities.

Exclusion Criteria

patients on any treatment modality for warts during the last month prior to enrollment, pregnant and lactating females; patients with known hypersensitivity to Candida albicans antigen, with acute febrile illness, autoimmune disease or immunodeficiency were excluded from the study.

Assessments

All patients enrolled in the study were subjected to full history taking, general and dermatological examination to determine number, site, and size of warts and to detect presence or absence of distant warts or other skin diseases. Digital photography was done for all patients at baseline, follow up visits and after completion of treatment sessions.

Patients were randomly distributed into three equal groups:

Group I included 20 patients who received intralesional candida antigen at a dose of 0.3 mL of 1/1000 solution.

Group II included 20 patients who received intralesional quadrivalent HPV vaccine at a dose of 0.3ml.

Group III included 20 patients who received intralesional injection 0.3 ml of normal saline 0.9% as a control group). Following the study completion, these patients were treated.

Each agent was injected every three weeks at the base of the largest wart until it was entirely removed or for a maximum of four sessions. The study was approved by an Ethics Committee of Damietta Faculty of Medicine IRB (00012367-20-12-004), Al-Azhar University, Egypt. Written informed consent was obtained from adult patients and parents of children included into the study.

Evaluation of the Clinical Response

The evaluation of therapeutic response was carried out by evaluating the size and counting the number of injected and distant warts by digital photographic comparison at baseline and at each visit. Complete response (disappearance of the warts and appearance of normal skin), partial response

(50%-99% reduction in size) and no response (0%-49% reduction in size). Patients were examined and asked to report any local adverse effects such as erythema, pain, edema, hypopigmentation and hyperpigmentation, as well as systemic side effects like fever, myalgia, headache, and vomiting.

Follow-up

A 6-month follow-up assessment was performed every month after the therapy was completed to detect any recurrence of warts.

Statistical Analysis

The data collected were coded, processed and analyzed with SPSS version 27 for Windows® (Statistical Package for Social Sciences) (IBM, SPSS Inc). Qualitative data as number (frequency) and percent was presented. The Chi-Square test (or Monte-Carlo test) made the comparison between groups.

The Kolmogorov-Smirnov test tested quantitative data for normality. Parametric data were expressed as median \pm SD while the non-parametric data were expressed as median (Range). To compare three groups with normally distributed quantitative variables, one-way analysis of the variance (one-way ANOVA) test was used and Kruskal-Wallis test was used if the data were abnormally distributed. For all tests, P values <0.05 are considered significant.

Results

The study included 60 patients with multiple non-genital warts. The median age in group I was 16 years with range between 10 and 39 years, the median age in group II was 14 years with range between 9 and 34 years and the median age in group III was 20 years with range between 10 and 38 years. There was no statistically significant difference between the cases in the different studied groups regarding the age ($P = 0.114$).

As regards to the sex, there were 40% males and 60% females in group I, there were 35% males and 65% females in group II and there were 25% males and 75% females in group III with no statistically significant difference between the studied groups regarding the sex distribution ($P = 0.293$).

In regard to type of warts, in group I, the most common type of wart was common warts in 80% of the cases followed by plantar wart in 20% with no cases with plane warts in this group. In group II, the most common type of wart was common warts in 60% of the cases followed by plantar wart in 30% and plane warts in 10% of the cases. In group III, the most common type of wart was plantar warts in 85% of the cases followed by common wart in 15% with no cases with plane warts in this group.

As regards to number of warts, the median number of warts in group I was 3 with range between 3 and 13, the

median number of warts in group II was 4 with range between 3 and 12 and the median number of warts in group III was 3 with range between 3 and 7. There was no statistically significant difference between the cases in the different studied groups regarding the number of warts ($P = 0.282$).

The median disease duration in group I was 20 months with range between 18 and 24 months, the median disease duration in group II was 24 months with range between 18 and 28 months and the median disease duration in group III was 20 months with range between 12 and 24 months. There was no statistically significant difference between the cases in the different studied groups regarding the disease duration ($P = 0.059$).

Presence of distant warts was reported in 30%, 55% and 15% in group I, II and III respectively with statistically significant difference between the studied groups ($P = 0.025$, Table 1).

Regarding the therapeutic response within the three studied groups, in group I, complete response was reported in (40%) of the cases, partial response in (15%) and no response in (45%). In group II, complete response was detected (75%) of the cases and no response in (25%). In group III, partial response in (10%) of the cases and no response in (90%) there was a statistically significant difference as regarding the local response between the three studied groups with the highest response in group II (quadrivalent HPV vaccine) followed by group I (Candida antigen).

Regarding the response in the distant warts within the three studied groups, in group I, complete response was detected in 2 out of 6 patients (33.3%), partial response in 3 out of 6 patients (50%) and no response in 1 out of 6 patients (16.7%). In group II, complete response was detected in 8 out of 11 patients (72.7%) and partial response in 3 out of 11 patients (27.3%). In group III, no distant partial or complete local response was detected. There was a statistically significant difference as regarding the response between the three studied groups with the highest response in group II (quadrivalent HPV vaccine) followed by group I (Candida antigen, Table 2).

Regarding the local side effects, tolerable pain during injection was reported in all the included cases. In group I, other local side effects included erythema in 30%, swelling in 30% and tenderness in 15% of the cases while in group II, erythema was detected in 25% of the cases.

Regarding the distant side effects, fever was detected in 55% and 10% in group I and group II respectively while bone ache was reported in 15% of the cases in group I only (Table 3).

No statistically significant difference in the adverse effects was observed between all studied groups.

No recurrence of warts was reported during the 6-month follow-up period in both groups.

Table 1. Baseline characteristics of the studied patients

Variable	Group I Candida antigen (N = 20)	Group II Quadrivalent HPV vaccine (N = 20)	Group III Normal saline (N = 20)	P value
Sex				
Males	8 (40%)	7 (35%)	5 (25%)	0.293
Females	12 (60%)	13 (65%)	15 (75%)	
Age (years)	16 (10-39)	14 (9-34)	20 (10-38)	0.114
Number of warts				
Median (Range)	3 (3-13)	4 (3-12)	3 (3-7)	0.282
Duration of warts (Months)				
Median (Range)	20 (18-24)	24 (18-28)	20 (12-24)	0.059
Distant warts	6 (30%)	11 (55%)	3 (15%)	0.025
Type of warts				
Common warts	16 (80%)	12 (60%)	3 (15%)	< 0.001
Plantar warts	4 (20%)	6 (30 %)	17 (85%)	
plane wart	0 (0%)	2 (10%)	0 (0%)	0.468
Distant warts				
	6(30%)	11 (55%)	3 (15%)	0.025
Previous treatment				
Cryotherapy	17 (85%)	18 (90%)	20 (100%)	0.236
Salicylic acid	19 (95%)	16 (80%)	18 (90%)	
Laser	1 (5%)	0 (0%)	0 (0%)	
Topical retinoid	0 (0%)	1 (5%)	0 (0%)	
Electrotherapy	1 (5%)	2 (10%)	2 (10%)	
MMR intralesional injection	0 (0%)	1 (5%)	0 (0%)	

HPV = Human Papilloma Virus.

Table 2. Therapeutic response among the studied patients

Variable	Group I Candida antigen (N = 20)	Group II Quadrivalent HPV vaccine (N = 20)	Group III Normal saline (N = 20)	P value
Complete response	8 (40%)	15 (75%)	0 (0%)	< 0.001
Partial response	3 (15%)	0 (0%)	2 (10%)	
No response	9 (45%)	5 (25%)	18 (90%)	
Distant response				
	Group I Candida antigen (N = 6)	Group II Quadrivalent HPV vaccine (N = 11)	Group III Normal saline (N = 3)	
Complete response	2 (33 %)	8 (72.7 %)	0 (0%)	0.002
Partial response	3 (50 %)	3 (27.3 %)	0 (0%)	
No response	1 (16%)	0 (0%)	3 (100 %)	

HPV = Human Papilloma Virus.

Table 3. Local and distant side effects among the studied patients

Variable	Group I Candida antigen (N = 20)	Group II Quadrivalent HPV vaccine (N = 20)	Group III Normal saline (N = 20)	P value
Local side effects				
Tolerable pain during injection	20 (100%)	20 (100%)	20 (100%)	0.011*
Erythema	6 (30%)	5 (25%)	0 (0%)	
Swelling	6 (30%)	0 (0%)	0 (0%)	
Tenderness	3 (15%)	0 (0%)	0 (0%)	
Distant side effects				
No distant lesions	9 (45%)	18 (90%)	20 (100%)	< 0.001*
Fever	11 (55%)	2 (10%)	0 (0%)	
Bone ache	3 (15%)	0 (0%)	0 (0%)	

HPV = Human Papilloma Virus.

Conclusions

In general, practice, non-genital warts are a common. Despite following evidence-based treatment guidelines, a significant percentage of warts do not cure and become recalcitrant.

This current study was conducted to evaluate the efficacy of intralesional quadrivalent human papillomavirus (HPV) vaccine versus Candida antigen in treatment of multiple recalcitrant non-genital Warts.

The current study included 60 cases with multiple recalcitrant non-genital warts who were randomly distributed according to the treatment regimen into three groups; group I that included cases who received intralesional treatment with candida antigen, group II that included cases received intralesional treatment with quadrivalent HPV vaccine and group III that included cases received normal saline as a control group.

In the current study, the incidence of complete response after intralesional candida antigen was 40% and after intralesional injection of quadrivalent HPV vaccine was 75% with no cases with complete response in the control group. Also, partial response was noticed in 15% and 20% in the candida antigen group and control group respectively.

The rate of response to candida antigen was similar to an Egyptian study conducted by Marei et al who showed that 58.3% of studied patients showed complete response [15].

However, although Nassar and her colleagues showed superiority of both candida antigen and HPV vaccine over control, the rate of response was different from our study. In their study, complete clearance of warts was reported in 63.3% of the Candida antigen group, 50% of the bivalent HPV vaccine group and 0% of the control group. A statistically significant difference in the therapeutic responses was found between the treatment and control groups and between both the Candida anti- gen and bivalent HPV vaccine.

The difference between the Candida antigen and bivalent HPV vaccine groups was statistically insignificant [16].

The difference between our study and this study may be explained by the differences in the nature of the treated warts (recalcitrant in our study). Also, the previous study used bivalent vaccine and our study used quadrivalent vaccine that provide greater cross-protection against HPV strains than provided by bivalent vaccine.

The rate of response in the candida antigen group was similar to many other studies including Signore (51%), Clifton et al (47%), Horn et al (54%), King et al (50%), Majid and Imran (56%), Alikhan et al (39%), and Nofal et al. (33.3%) [17-23].

An earlier study has shown higher response rate. Johnson et al showed 74% complete clearance of wart among studied group [24].

The disparities in the success rates between our study and the other related studies might be attributed to factors related to differences in the nature of the treated warts (multiple recalcitrant in our study), degree of HPV resistance and different HPV serotypes, and the number of the studied patients. Also, different injection regimens regarding the manufacturer of the antigen, the amount and concentration of the injected antigen per session, the number of the treatment sessions and the interval between the sessions

Candida antigen works primarily by inducing Th1 cytokines including IFN- and IL-2, which stimulate cytotoxic and natural killer cells to eliminate HPV infection not only at the injection site but also at nearby and distant non-injected sites Nofal et al [25].

In the current study, regarding the distant response rate, the highest response rate was detected in the HPV vaccine group followed by the candida antigen group. In the candida antigen group, complete response was detected in 33.3%

and partial response in 50% while in the quadrivalent HPV vaccine group, complete response was detected in 72.7% and partial response in 27.3%.

This disagreed with Nassar et al who showed that the rate of resolution of distant, non-injected warts was 71.4% in the Candida group versus 41.2% in the HPV vaccine group [16].

The difference could be explained due to that the previous study used bivalent vaccine and our study used quadrivalent vaccine that provide greater cross-protection against HPV strains than provided by bivalent vaccine.

The mechanism of action of HPV vaccines in the treatment of warts is not yet established. This might be mediated by the development of IgG neutralizing antibodies directed against HPV-L1 capsid proteins generated as a result of vaccination. Although the HPV strains that cause common warts may be less genetically related to those implicated in cervical, vulvar, and anal cancer, it has been previously postulated that HPV vaccines can provide cross-protection against HPV strains other than those targeted by the individual vaccine administered [26,27].

The combination of drugs, with different mechanisms of action, has been postulated to improve treatment response, decrease adverse effects, and minimize recurrence rate. Many authors have reported better control of HPV infections using combined therapeutic modalities compared with monotherapy in the treatment of warts, particularly the recalcitrant ones [25,28].

One of the advantages of HPV vaccines is that the VLPs are not infectious, since they lack the virus DNA. Therefore, they can be used safely in case of immunosuppression, a major obstacle for other types of immunotherapies. Furthermore, the development of HPV-directed immunity after receiving the vaccine has a double benefit in the treatment of current infection and the prevention of future one [29].

In the current study, in the control group who received intralesional saline, local partial response was achieved in 10% of the cases with no distant response.

Fathy and his colleagues reported that intralesional injection of saline was associated with 20.7% good response and 79.3% poor response after the 5th session in cases with planter warts with no complete clearance of any wart [30].

Also, Mohamed and his colleagues reported a statistically significant decrease in the number of warts after 5 sessions of injection of intralesional saline of warts. The mechanism of action of intralesional saline is unknown; it may be due to exposure of the viral particles to the immune system that later attacks them through the trauma produced during the injection [31].

The difference between our study and these studies may be explained by the differences in the nature of the treated warts (recalcitrant in our study) as the duration of the warts show a significant inverse correlation with the treatment response (the longer the duration, the lower the response). Also the number of the treatment sessions (5 sessions versus 3 sessions in our study).

The main strength point of the current study, the first to evaluate the effectiveness of the quadrivalent HPV vaccine in comparison to the candida antigen and the placebo.

However, the current study had some limitations as it is a single center study and recruited a relatively small sample size that could decrease the power of the obtained results, and there was no efficacy analysis taking into account the size and duration of the lesions. Also, the short duration of follow up did not enable to comment on the long-term outcomes especially the rate of recurrence.

Based on our findings, intralesional antigen immunotherapy seems to be an effective therapeutic option for the treatment of non-genital warts. Additionally, we came to the conclusion that the efficacy of intralesional quadrivalent HPV vaccine was superior to intralesional candida antigen.

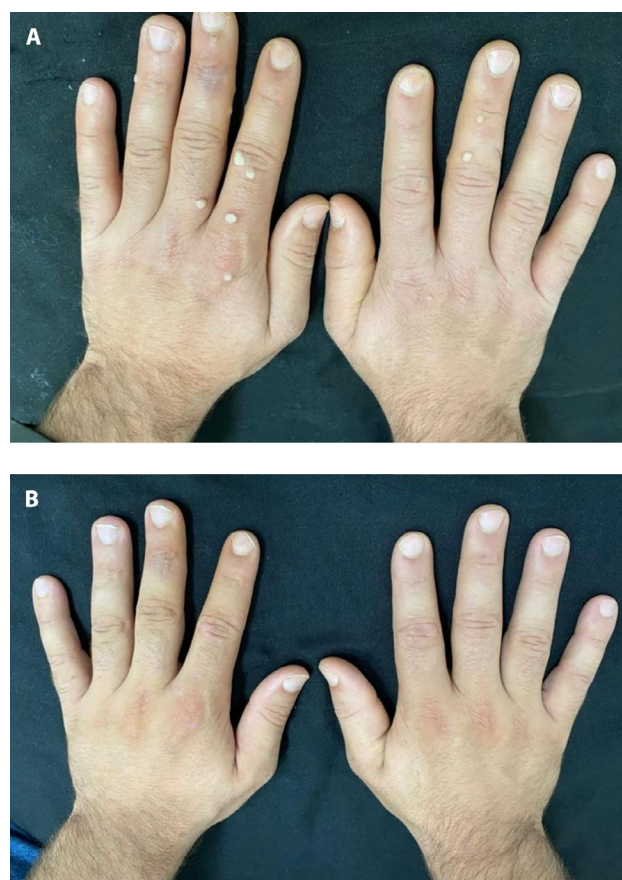


Figure 1. Male patient 21-year-old with multiple common warts on both hands (A) before, (B) after treatment with intralesional candida antigen.

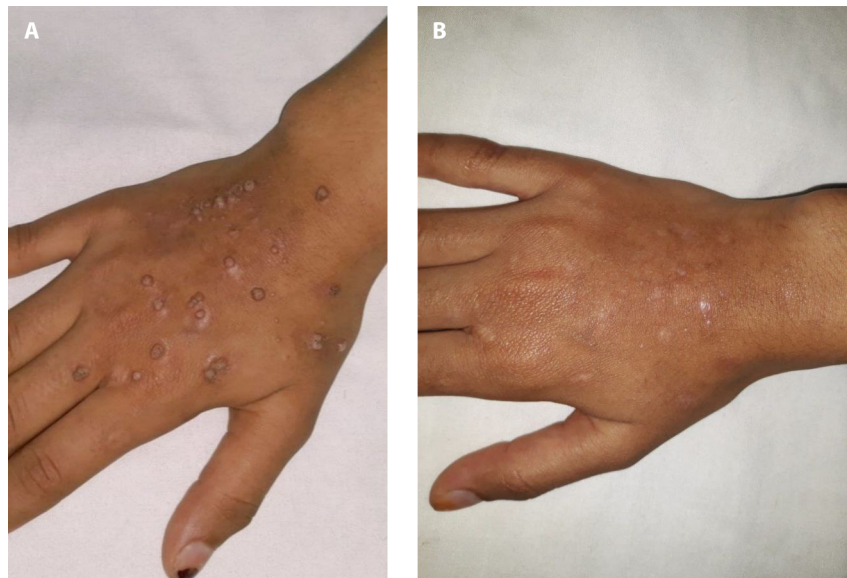


Figure 2. Female patient 15-year-old with multiple common warts on the right hand (A) before, (B) after treatment with intravesicular quadrivalent HPV vaccine.

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