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ORIGINAL RESEARCH

Triple Intralesional Antigen Immunotherapy versus Monoantigen in the Treatment of Multiple Recalcitrant Warts

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ABSTRACT

Introduction: Warts can be resistant to treatment or recur despite the use of various destructive and immunotherapeutic modalities. Combination immunotherapy might contribute to better response rates. The aim of this study was to assess the effectiveness and safety of a triple intralesional immunotherapy combination composed of purified protein derivative (PPD), *Candida* antigen, and measles–mumps–rubella vaccine (MMR), versus each agent alone, in the management of multiple recalcitrant warts.

Methods: In total, 160 patients with numerous resistant extragenital warts were included in the research. They were randomly assigned to one of four groups (each with 40 patients): PPD, *Candida* antigen, and MMR, or combination of the three antigens. Injections into the biggest wart were repeated every 2 weeks until clearance or for a total of five sessions.

Results: Complete wart clearance was reported in 31 patients (77.5%) who received triple-antigen immunotherapy, 23 patients (57.5%) who received intralesional PPD, 29 patients (72.5%) injected with *Candida* antigen, and 25 patients (62.5%) who received MMR. The combined therapy was found to be superior to the other therapies and had the lowest recurrence rate, but the difference was not statistically significant.

Conclusions: Triple intralesional antigen immunotherapy is as safe as, and more effective than, monoantigen immunotherapy, and can be added to the armamentarium against recalcitrant human papilloma virus (HPV) infections.

Keywords: Warts; Triple intralesional immunotherapy; Combined immunotherapy; Tuberculin purified protein derivative; *Candida* antigen; Measles–mumps–rubella vaccine

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Key Summary Points

Why carry out this study?

Despite the existence of numerous immunotherapeutic modalities, treatment of warts remains challenging and an optimal treatment is yet to be developed. In fact, no treatment is 100% effective for multiple warts.

No studies to date have objectively compared the safety and efficacy of a triple combination immunotherapy composed of purified protein derivative (PPD), *Candida* antigen, and measles–mumps–rubella (MMR) vaccine, versus each monoantigen alone, in the treatment of multiple recalcitrant warts.

What was learned from the study?

Triple immunotherapy is a safe and effective therapeutic option for multiple recalcitrant warts, and can be added to the armamentarium against recalcitrant human papilloma virus (HPV) infections.

Intralesional *Candida* antigen seems to be more favorable in patients with plantar warts, whereas the triple immunotherapy was superior in common warts.

INTRODUCTION

Warts are very common benign tumors caused by human papilloma virus (HPV) infection. They are classified according to their appearance or site into different types, including common warts, plane warts, plantar warts, and genital warts [1].

Many destructive and immunotherapeutic modalities have been used in the treatment of warts. Destructive therapies are commonly associated with significant pain, tissue destruction with subsequent scarring, and high recurrence rate. Additionally, these modalities are not practical for patients presenting with numerous warts [2].

On the other hand, several immunotherapeutic agents have been introduced for the treatment of warts to overcome the challenges associated with destructive therapies. Among these immunotherapeutic agents is intralesional antigen immunotherapy, which stimulates cell-mediated immunity (CMI) against HPV to clear not only the injected warts but also distant lesions and has shown promising efficacy and safety in the treatment of different wart types [3].

Despite the existence of numerous immunotherapeutic modalities, treatment of warts remains challenging and an optimal treatment is yet to be developed. In fact, no treatment is 100% effective for multiple warts [4].

The idea of combining different antigens was first tested in 2004 by Johnson and Horn [5], who assessed the efficacy of intralesional injection of a combination of *Trichophyton*, mumps, and *Candida* antigen in the treatment of warts in an open-label single-arm study and paved the way for further studies on combining different antigens, in an alternating or in a concomitant manner. This concept was also suggested and proposed by other authors in the following years [6, 7].

In this study, we compared the efficacy and safety of intralesional triple-antigen immunotherapy composed of purified protein derivative (PPD), *Candida* antigen, and measles–mumps–rubella vaccine (MMR) with that of each monoantigen alone in the management of multiple resistant extragenital warts.

METHODS

Patients

This study included 160 patients with multiple (three or more warts) recalcitrant (warts of at least 6 months duration that did not respond to at least two treatment modalities) extragenital warts of different types, sites, sizes, and durations with or without distant warts, after approval by the institutional review board (IRB)

of Medical School at Zagazig University, Egypt. Prior to enrollment, each patient provided informed consent. This study was performed in accordance with the Helsinki Declaration of 1964 and its later amendments. Patients were excluded from the study if they had acute febrile illness, past history of asthma, severe allergic skin disorders, immunodeficiency, autoimmune disease, meningitis, or convulsions. Pregnant or lactating women and those who had any other form of wart management in the month preceding enrollment were also excluded.

Methods

In total, 160 patients were allocated in a random fashion to one of four groups (40 patients each).

Group A: intralesional injection of 0.3 ml of PPD.

Group B: intralesional injection of 0.3 ml of 1/100 solution of *Candida* antigen.

Group C: intralesional injection of 0.3 ml of MMR.

Group D: intralesional injection of 0.3 ml of PPD, *Candida* antigen, and MMR, 0.1 ml each, combined in the same syringe.

In each of the four study groups, injections into the largest wart were made, without presensitization testing, using an insulin syringe at 2-week intervals until full clearance, or for a maximum of five sessions.

Evaluation of the clinical response

The size and number of warts were assessed at baseline and at each visit to determine response to therapy. Complete response of warts was recorded if there was complete disappearance of the warts and return of normal skin markings; partial response if the warts regressed in size by 50–99%; and no response if there was less than 50% decrease in wart size. Following each treatment session, adverse effects were examined both immediately and later.

Follow-up

Every month for 6 months, a follow-up was performed to identify possible recurrence of warts.

Statistical analysis

SPSS version 24 was used to enter, check, and analyze data. For quantitative data, mean and standard deviation (SD) were used; for qualitative variables, number and percentage were used. As appropriate, ANOVA (F test), χ^2 test, and Kruskal–Wallis test were employed. P values less than 0.05 were considered significant.

RESULTS

The study and the follow-up period were completed by all patients. The patients were 71 males and 89 females who varied in age from 12 to 67 years (average 27.15 years), with warts lasting between 6 and 72 months. The number of lesions varied between 3 and 40, and the majority of patients had warts greater than 1 cm in diameter ($n = 102$ patients). Among the studied groups, distant wart prevalence showed no statistically significant difference. Cryotherapy was the most often utilized therapeutic method prior to the study. A total of 72 palmoplantar warts, 68 common warts, 17 subungual/periungual warts, 2 filiform warts, and 1 plane wart underwent injection treatment. The studied groups did not show any significant differences in baseline characteristics (Table 1).

Therapeutic response

1. Treated warts

In triple immunotherapy group, complete response rate was observed in 77.5%, partial response in 7.5%, and no response in 15%.

In the PPD group, 57.5% of patients had complete response, while partial response was noted in 15%, and no response in 27.5%.

In the *Candida* antigen group, complete clearance was achieved in 72.5%, partial response in 10%, and no response in 17.5%.

Table 1 Baseline characteristics of the studied patients

Variables	Group A (PPD) $N = 40$		Group B (*Candida* Ag) $N = 40$		Group C (MMR) $N = 40$		Group D (combined) $N = 40$		χ^2 KW#	*P*
	N	%	*N*	%	*N*	%	*N*	%		
Age (years)	25.1 ± 11.96		26.4 ± 12.3		28.5 ± 13.3		28.6 ± 15.2		0.967#	0.82
Median	22		23		29		28			NS
Range	12–67		12–59		12–62		14–60			
Sex										
Male	20	50.0	21	52.5	15	37.5	15	37.5	3.11	0.36
Female	20	50.0	19	47.5	25	62.5	25	62.5		NS
Duration (months)	24.7 ± 15.8		29.6 ± 20.3		16.2 ± 9.8		18.2 ± 7.3		12.5#	0.106
Median	24		24		22		20			NS
Range	6–72		7–60		6–60		8–63			
Size										
< 1 cm	18	45	13	32.5	19	47.5	8	20	2.25	0.52
1–5 cm	22	55	27	67.5	21	52.5	32	80		NS
Site										
Head/face	6	15.0	4	10.0	4	10.0	2	5.0	Fisher	0.53 NS
Leg/foot	15	37.5	20	50.0	16	40.0	23	57.5	5.93	0.12 NS
Arm/hand	27	67.5	25	62.5	25	62.5	26	65.0	0.88	0.83 NS
Number of lesions										
Median	5.5		8.5		7.5		9.5		1.82	0.61
Range	3–40		3–36		3–25		3–30			NS
Previous therapy										
Cryocautery	10	25%	13	32.5%	14	35%	19	47.5%	4.62	0.21
Electrocautery	15	37.5%	9	22.5%	7	17.5%	11	27.5%	4.52	0.22
Immunotherapy	11	27.5%	7	17.5%	5	12.5%	3	7.5%	3.45	0.19
Other medications (retinoids, zinc, etc.)	17	42.5%	13	32.5%	9	22.5%	5	12.5%	2.98	0.33
Trichloroacetic acid or salicylic acid	5	12.5%	6	15%	9	22.5%	3	7.5%	4.11	0.15
Laser	3	7.5%	5	12.5%	1	2.5%	2	5%	2.88	0.43
Surgical excision	5	12.5%	3	7.5%	1	2.5%	5	12.5%	3.44	0.33
Types										
Palmar	10	25%	3	7.5%	12	30%	6	15%	7.81	0.05
Plantar	12	30%	19	47.5%	3	7.5%	7	17.5%	18.7	< 0.001

Table 1 continued

Variables	Group A (PPD) $N = 40$		Group B (*Candida* Ag) $N = 40$		Group C (MMR) $N = 40$		Group D (combined) $N = 40$		χ^2 KW#	*P*
	N	%	*N*	%	*N*	%	*N*	%		
Common	11	27.5%	13	32.5%	20	50%	24	60%	11.3	0.01
Subungual	5	12.5%	4	10%	5	12.5%	3	7.5%	0.72	0.87
Filiform	1	2.5%	1	2.5%	0	0.0	0	0.0	0.77	0.91
Plane	1	2.5%	0	0.0	0	0.0	0	0.0	0.82	0.98
Distant warts	25	60%	26	65%	27	67.5%	25	60%	0.3	0.96 NS

NS, not significant, i.e., *P* value > 0.05

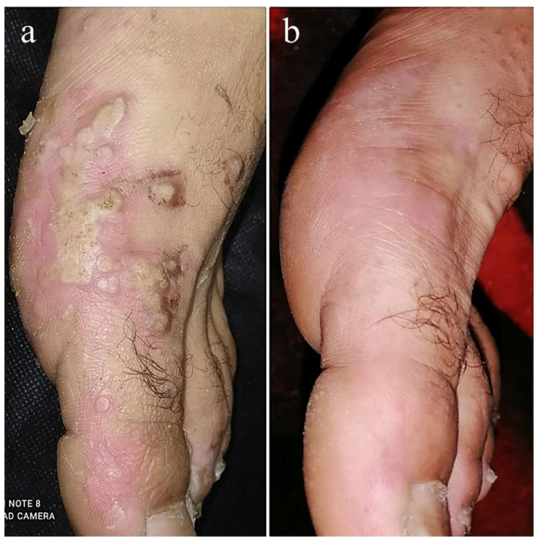

Fig. 1 **a** Multiple plantar and common warts on the left foot, **b** Complete clearance after only one session of triple immunotherapy

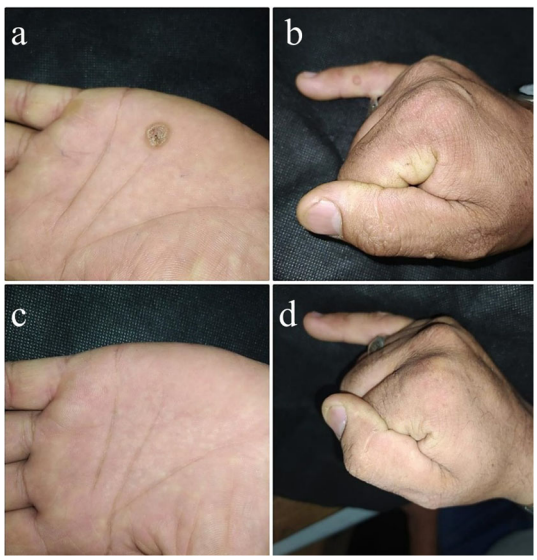

Fig. 2 **a** A single palmar wart injected on the left hand. **b** Multiple distant common warts on the dorsum of the right hand, **c** and **d** Complete response of all the warts after five sessions of intralesional PPD injection

In the MMR group, 62.5% experienced complete clearance, 17.5% showed partial response, and 20% had no response.

The complete response rate was higher in the triple intralesional immunotherapy group than in the other three groups; however, the difference was not statistically significant. Similarly, there was no statistically significant difference in the rate of wart clearance (time to complete response) (Figures 1, 2, 3, 4; Table 2).

2. Distant warts

Complete response of the distant warts was noted in 48%, 61.5%, 55.5%, and 65% of the PPD, *Candida* antigen, MMR, and triple immunotherapy groups respectively, with no statistically significant difference among the studied groups.

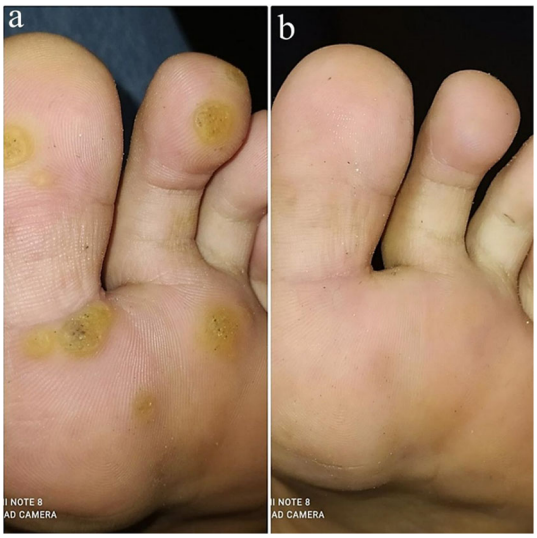

Fig. 3 **a** Multiple plantar warts on the sole of the left foot. **b** Complete clearance of all warts after five sessions of intralesional *Candida* antigen injection

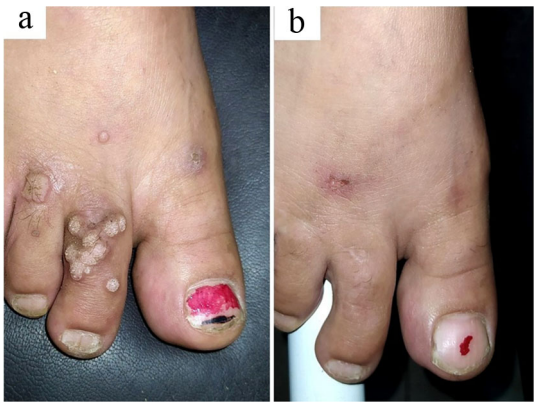

Fig. 4 **a** Multiple common warts on the dorsum of the right foot. **b** Complete clearance of all warts after five sessions of intralesional MMR

Relationship between therapeutic response and different clinical variables

No significant relationship was found between the therapeutic response and the different clinical variables, including type, size, number, and duration of warts, in any of the four groups.

Complete cure of common warts was noted in 6/11 (54.5%), 7/13 (53.8%), 10/20 (50%), and 20/24 (83.3%) in the PPD, *Candida* antigen, MMR, and triple immunotherapy groups, respectively. Palmoplantar warts were cleared in 15/22 (68.2%), 20/22 (90.9%), 11/15 (73.3%), and 10/13 (76.9%) in the PPD, *Candida* antigen, MMR, and triple immunotherapy groups, respectively. For subungual/periungual warts, complete response was achieved in 2/5 (40%), 2/4 (50%), 4/5 (80%), and 1/3 (33.3%) in the PPD, *Candida* antigen, MMR, and triple immunotherapy groups, respectively.

Adverse effects

There was no statistically significant difference in adverse effects among groups. The most common side effect was pain during injection, which was present in all cases, followed by edema and erythema (Table 3).

Recurrence

No statistically significant difference in the recurrence rate after the 6-month follow-up period was observed between the studied groups, where recurrence was reported in 8.7%, 13.8%, 12%, and 6.45% of the PPD, *Candida*, MMR, and triple immunotherapy groups, respectively.

DISCUSSION

The idea of combining different antigens was conceptualized in 2004 by Johnson and Horn [5], who assessed the efficacy of intralesional injection of a combination of *Trichophyton*, mumps, and *Candida* antigen in the treatment of warts and paved the way for further studies on combining different antigens, in an alternating or concomitant manner.

Moreover, Aldahan et al. [6] and Marei et al. [7] have proposed that the combination of antigens with different modes of action might improve the efficacy, and decrease the adverse effects and recurrence potential, by targeting multiple immune pathways simultaneously.

Table 2 Therapeutic response among the studied patients

Therapeutic response	Group A (PPD) $N = 40$		Group B (*Candida* Ag) $N = 40$		Group C (MMR) $N = 40$		Group D (combined) $N = 40$		χ^2 KW	*P* value
	N	%	*N*	%	*N*	%	*N*	%		
No	11	27.5%	7	17.5%	8	20.0%	6	15.0%	5.27#	0.41
Partial	6	15.0%	4	10.0%	7	17.5%	3	7.5%		NS
Complete	23	57.5%	29	72.5%	25	62.5%	31	77.5%		
Time to complete response (months)										
Median	3.25		3		2.5		3		1.14#	< 0.001
Range	3–4.5		2–3.5		2–3.5		2–4			NS

Table 3 Adverse effects among the studied groups

Adverse effect	Group A (PPD) $N = 40$		Group B (*Candida* Ag) $N = 40$		Group C (MMR) $N = 40$		Group D (combined) $N = 40$		χ^2	*P* value
	N	%	*N*	%	*N*	%	*N*	%		
Pain during injection	40	100%	40	100%	40	100%	40	100%	–	–
Erythema and desquamation	8	20	8	20	6	15	7	17.5	0.46	0.93
Blisters at injection site	2	5	3	7.5	1	2.5	2	5	1.05	0.79
Edema/induration	11	27.5	13	32.5	10	25	9	22.5	1.13	0.96 NS
Flu-like symptoms	5	12.5	7	17.5	0	0.0	4	10.0	4.94	0.18 NS
Hypopigmentation	0	0.0	0	0.0	1	2.5	0	0.0	0.98	0.33 NS

S, significant, i.e., *P* value < 0.05; *NS*, not significant, i.e., *P* value > 0.05

On the basis of these observations, we decided to evaluate the efficacy and safety of a triple intralesional immunotherapy combination composed of PPD, *Candida* antigen, and MMR, versus each agent alone, in the treatment of multiple recalcitrant warts.

In the triple intralesional immunotherapy group, complete clearance of warts was observed in 31 patients (77.5%) (5 palmar warts, 5 plantar warts, 20 common warts, and 1 subungual wart). To the best of our knowledge, this triple combination was not previously studied. However, Johnson and Horn [5] used another combination of *Trichophyton*, mumps, and *Candida* antigen (0.1 ml each; combined in one syringe) and observed a very similar response rate (70.9% complete clearance). .

Furthermore, Horn et al. [8] compared a combination of single-agent antigen (mumps, *Candida*, or *Trichophyton*) plus interferon alpha-2b (IFNα-2b) versus single-agent intralesional antigen and intralesional IFNα-2b. The superiority was in favor of the combined therapy (68%) followed by the individual antigen (54%) and intralesional IFNα-2b (26%); however, the differences were not statistically significant.

Adding IFNα-2b did not improve response compared with injection of antigen alone. Notably, the combined group reported more side effects (73%), compared with only 13% in the antigen alone group. These results suggest a slightly increased immunogenic effect of combination therapy at the expense of greatly increased adverse effects.

King et al. [9] further tested the idea of antigen combination immunotherapy for the treatment of genital warts. Patients received either single-agent treatment (mumps, *Candida*, or *Trichophyton*) or combination treatment with mumps, *Candida*, and *Trichophyton* skin test antigens (combination 1), or with *Candida*, and *Trichophyton* skin test antigens (combination 2). Complete clearance of genital warts (50%) was observed only in those receiving the combination therapies.

Combined immunotherapy, in an alternating manner, was also tried by Nofal et al. [10], who compared an alternating therapy of PPD and *Candida* antigen versus therapy of each individual antigen. A statistically significant difference in the therapeutic response was found between the alternating therapy group (complete clearance in 70.6%) and the individual antigen groups (61.1% of the PPD group and 36.8% of the *Candida* antigen group). Adverse effects were insignificant in the studied groups.

Moreover, a statistically significant difference in favor of a combination immunotherapy (70% cure rate) composed of bivalent HPV vaccine (injected intramuscularly) and *Candida* antigen (injected intralesionally) versus *Candida* antigen monotherapy was noted in a study conducted by Marei et al. [7]. A summary of the studies concerned with combination intralesional antigen immunotherapy is presented in Table 4.

In the PPD group of the current study, 57.5% of the 40 studied patients showed complete response (23 patients; nine palmar warts, six plantar warts, six common warts, and two subungual warts). Our results for PPD were very similar to those reported by Kaimal et al. [11] (55%), Shaheen et al. [12] (60%), Nofal et al. [10] (61.1%), and Mohammed et al. [13] (60%).

On the other hand, the clearance rate with intralesional PPD in the present study was much lower than that reported by Wananukul et al. [14] (93%), Elela et al. [15] (94.1%), Abd-Elazeim et al. [16] (75%), Amirnia et al. [17] (77.1%), and Saoji et al. [18] (76%). This difference may be explained by the lower number of treatment sessions and injection of PPD in the largest wart only in our study compared with a higher number of treatment sessions and injection of multiple warts in other related studies.

In the *Candida* antigen group, complete clearance was achieved in 72.5% of the studied patients (29 patients; 1 palmar wart, 19 plantar warts, 7 common warts, and 2 subungual warts). This clearance rate was much lower than that reported by Perman et al. [19] (100%), Maronn et al. [20] (87%), and Kim et al. [21] (82%), but similar to those reported by Phillips et al. [22] (72%), Johnson et al. [23] (74%), and Johnson and Horn [5] (71%).

Our clearance rate (72.5%) was much higher than that reported by King et al. [9] (50%), Horn et al. [8] (54%), Majid and Imran [3] (56%), Alikhan et al. [24] (39%), Nofal et al. [25] (33.3%), Marei et al. [7] (40%), and Eldahshan et al. [26] (43.33%). Our higher response rate may be attributed to the injection of a higher dose of *Candida* antigen (0.3 ml) compared with doses (0.1 ml) injected in many of the previously mentioned studies.

In the MMR group, 62.5% of the treated 40 patients showed complete clearance (25 patients; eight palmar warts, three plantar warts, ten common warts, and four subungual warts). This response rate was very similar to that reported by Nofal et al. [27] (63%) and Fawzy et al. [28] (62.5%), higher than that reported by Shaker et al. [29] (30% cure rate), and lower than that reported by Eldahshan et al. [26] (73.33%) and Mohammed et al. [13] and Shaheen et al. [12] (80%). The higher clearance rate in these studies might be attributed to the higher reactivity to MMR and the higher number of the treatment sessions.

In the present study, no statistically significant relationship was found between the therapeutic response to intralesional PPD, *Candida* antigen, MMR, and combined therapy, and the different clinical variables. This was in agreement with many of the related studies that also

Table 4 Summary of studies on combination intralesional antigen immunotherapy for the treatment of warts

References	Combination immunotherapy	Age (years), sex of patients	Dose, number of sessions	Therapeutic response (%)	Response of distant warts	Adverse effects	Recurrence
Johnson and Horn [5]	*Trichophyton*, *Candida* antigen, and mumps	Mean of 21.4 years 98 males and 108 females	0.3 ml Up to ten sessions	70.9	67.9%	Erythema and edema in 25.7% Flu-like symptoms in 13.6%	No recurrence
Horn et al. [8]	Interferon α-2b plus mumps, *Candida*, or *Trichophyton* antigens	Mean of 38 years 12 males and 29 females	0.3 ml of antigen and 0.08 ml of IFN α-2b Up to five sessions	68	57%	Fever and myalgia in 73%	Not mentioned
King et al. [9]	Mumps, *Candida*, and *Trichophyton* *Candida* and *Trichophyton*	Mean of 39.8 years Five males and five females	0.1 ml of each antigen Up to ten sessions	50	50%	Local erythema and edema in 30%	Not mentioned
Marei et al. [7]	Combined bivalent HPV vaccine and *Candida* antigen	Mean of 29 years 13 males and 7 females	0.2 ml of *Candida* antigen; up to five sessions 0.5 ml of IM HPV vaccine at 0, 1, 6 months	70	Not mentioned	Edema, erythema, and flu-like in few patients	No recurrence
Nofal et al. [10]	Alternating therapy of PPD and *Candida* antigen	Mean of 22.4 years 14 males and 20 females	0.1 ml of each antigen in an alternating manner Up to six sessions	70.%	Not mentioned	Insignificant	No recurrence

Table 4 continued

References	Combination immunotherapy	Age (years), sex of patients	Dose, number of sessions	Therapeutic response (%)	Response of distant warts	Adverse effects	Recurrence
Current study	Triple immunotherapy of PPD, *Candida* antigen, and MMR versus monoantigen	Mean of 28.6 years 15 males and 25 females	0.3 ml Up to 5 sessions	77.5	65%	Erythema in 17.5%, edema in 22.5%, and flu-like symptoms in 10%	6.45%

reported absence of significant associations between the therapeutic response to the injected antigen and most of the clinical variables [12, 23, 28].

Adverse effects were mild and insignificant in all the groups, as was the case in many of the previous trials of intralesional antigen immunotherapy [5, 23, 30]. It is worth noting that the adverse effects were not statistically higher in the combination therapy group than in the other monotherapy groups, indicating that combining more than one antigen is still associated with high safety profile.

In the current study, no statistically significant difference in the recurrence rate was reported between the studied groups. Recurrence was noted in 2/23 patients treated with PPD (8.7%), 4/29 patients treated with *Candida* Ag (13.8%), 3/25 cases treated with MMR (12%), and 2/31 patients injected with triple immunotherapy (6.45%). This recurrence rate is relatively higher than that observed in most of the related studies. [12, 23, 28]. This may be attributed to the different baseline characteristics and the recalcitrant nature of warts in this study.

It worth noting the heterogeneity of results of intralesional antigen immunotherapy, which is mostly attributed to the variable baseline characteristics of patients, and the different features and nature of warts. Studies of *Candida* antigen, MMR, and PPD provided comparable complete response rates of injected warts, ranging from 39% to 88% for *Candida*, 26.5% to 92% for MMR, and 23.3% to 94.4% for PPD [12, 31].

One of the important observations in the current work is that intralesional *Candida* antigen seems to be more favorable in patients with plantar warts, whereas the triple immunotherapy was superior in common warts. Thus, *Candida* antigen may be recommended as immunotherapy for plantar warts and the triple immunotherapy, when available, for common warts.

Ultimately, it seems that triple intralesional immunotherapy has its pros and cons. The advantages are that triple immunotherapy was superior to, and as safe as, monoantigen immunotherapy in recalcitrant warts, which

may be attributed to more robust stimulation of CMI by induction of diverse immune pathways by various microbial antigens and differential nature of vaccines, each acting on a specific arm of the immune response, resulting in optimization of results.

Moreover, since most people are reactive to at least one skin test antigen, there is no need to conduct a skin test when administering three skin test antigens for warts. For physicians who prefer to routinely adopt presensitization tests, eliminating skin tests enhances the cost-effectiveness of triple therapy and saves time as well as an extra-office visit for the intradermal test.

The main disadvantage is that it is difficult to have all three antigens available at the same time. Nevertheless, when available simultaneously, the combination therapy could be tried in warts recalcitrant to monoantigen injection. Moreover, the difference between triple immunotherapy and monoantigen immunotherapy was not statistically significant; however, this needs to be confirmed by further studies on larger populations. Therefore, we do not recommend triple immunotherapy as a routine therapeutic modality.

Spontaneous regression of warts is a well-recognized phenomenon; however, in the present study, the long duration of warts (lowest median was 20 months) that failed to respond to at least two treatment modalities makes it unlikely that the complete resolution reported in our patients was spontaneous. The clearance of the distant, non-injected warts, a well-established effect of the intralesional antigen immunotherapy, in a significant proportion of patients in the four studied groups further confirms that the wart regression was not spontaneous.

Limitations of the present study include the relatively small sample size and the short follow-up duration. Therefore, further studies on larger populations with long term follow-up of the patients are highly warranted to assess the long-term efficacy of each therapeutic modality in prevention of recurrence.

CONCLUSION

In conclusion, triple immunotherapy is a safe and effective therapeutic option for multiple recalcitrant warts, and can be added to the armamentarium against recalcitrant HPV infections.

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Compliance with Ethics Guidelines. The protocol of the study was approved by IRB at Zagazig University, Egypt. IRB# 6526/-15–11-2020. Prior to enrollment, each patient provided an informed consent. This study was performed in accordance with the Helsinki Declaration of 1964 and its later amendments.

Disclosures. Ahmad A. Nofal, Basma M. Elkholy, Esraa R Abd-Elmonsef and Hagar O. Nofal have nothing to disclose.

Data Availability. The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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