ORIGINAL ARTICLE

Clinical and Dermoscopic Study of Intra-lesional Injection of Acyclovir Versus Candida Antigen in Treatment of Plantar Warts

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Abstract

Background: Plantar wart is a common viral infection occurring in the plantar aspect of the foot, caused by human papillomavirus (HPV). Intra-lesional immunotherapy has emerged as a front-runner treatment option for plantar warts. **Objectives:** This study aimed to compare the efficacy and tolerability of intra-lesional injections of acyclovir versus candida antigen in patients with plantar warts. **Methods:** This randomised-controlled clinical trial was conducted on 40 patients with plantar warts. The included patients were randomly assigned into two groups: Group 1 (n = 20) was treated with intra-lesional injections of acyclovir. Group 2 (n = 20) was treated by intra-lesional injections of candida antigen. Injections were every 2 weeks for 5 sessions. All the patients were evaluated before and after treatment through clinical, photographic, and dermoscopic assessments. All side effects (local and systemic), during or after injections were recorded. **Results:** In acyclovir intra-lesional injected warts, a score of 3 (complete clearance clinically, and dermoscopically) was achieved in 65% of target warts, 15% had a score of 2 (patients' dermoscopy confirmed the persistence of warts despite the fact that the warts had disappeared clinically), 20% had a score of 1 (warts were smaller and thinner but not completely gone upon clinical or dermoscopic examination). In candida intra-lesional injected warts, a score of 3 was achieved in 70% of target warts and 25% had a score of 1. **Conclusion:** Both intra-lesional acyclovir and candida antigen appear to be effective and tolerated treatment modalities for plantar warts. Although there were similar reports of side effects for both treatments, the success rate of curing warts using intra-lesional candida antigen was slightly greater.

Key Words: *Acyclovir, candida, intra-lesional, plantar warts*

Introduction

Cutaneous warts are a type of skin growth that is completely benign and are produced by the human papillomavirus (HPV), the plantar wart is the type of wart that occurs in the plantar aspect of the foot, currently more than 150 types of HPV were identified.[1] The incidence of viral warts on the skin in the general population is about 7-12% of which common wart (42%), palmo plantar wart (20%), and plane wart (18%).[2]

Available lines of treatment of warts by destruction of the visible wart or its eradication, as well as induction of cytotoxicity against the infected cells.[2] The ablative modalities are associated with pain and return of warts even after proper removal.[3] Warts treated with ablative methods have a recurrence risk of up to 30%, primarily because the latent virus persists in the area around the original wart and antimitotic modalities are usually associated with severe pain ulceration and recurrence also.[4]

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There are a number of injectable medicines that have been studied for their potential to eradicate warts; they include the measles, mumps, and rubella vaccination (MMR), the Bacillus Calmette-Guerin vaccine (BCG), and the Candida antigen pure protein derivatives (PPD).[5]

There is no longer any need to treat each wart individually thanks to a delayed form of hypersensitive reaction created toward the injected antigen. This can boost the immune system's ability to recognize and eradicate the human papillomavirus (HPV) in different sections of the body. Intra-lesional immunotherapy, as opposed to physically ablative treatments, is suggested as a first-line therapy for many stubborn, and big warts due to its low relapse rate and low risk of adverse effects.[6]

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Since HPV is a DNA virus like herpes viruses, it may be sensitive to acyclovir, which is why it is used to treat warts.[7] This study aimed to compare the efficacy and tolerability of intra-lesional injections of acyclovir versus candida antigen in patients with plantar warts.

Patients and Methods

Design and setting

This study was a randomised-controlled clinical trial, which included 40 patients with plantar warts, who attended the Dermatology Outpatient Clinics, Faculty of Medicine, Sohag University, during the period from July 2022 to July 2023.

Exclusion criteria

Patients were excluded if they had a history of meningitis, convulsions, allergy to acyclovir or candida antigen, or fever within the 1 month prior to the trial.

Treatment protocol

After fulfillment of inclusion and exclusion criteria, patients were randomly assigned to one of two groups: Group 1 (n = 20) was treated with intra-lesional injections of acyclovir (Acyclovir 250 mg powder, each vial contains 250 mg of acyclovir as the sodium salt, Chandra Bhagat Pharma Pvt. Ltd). 250 mg acyclovir vial diluted with 3.5 ml saline to get approximately 70 mg/ml solution. During the study, the dosage of the drug and frequency of treatment were uniform in all patients. The base of each wart was injected with 0.1 ml of intra-lesional acyclovir (70 mg/ml) with maximum 1 ml at each session (10 warts), using an insulin syringe 1 ml (29 Gage × 0.5 inch) every 2 weeks until the resolution of warts or for a maximum of five sessions the solution kept in refrigerator for only 24 h. Group 2 (n = 20) was treated by intra-lesional injections of candida antigen; at a dose of 0.2 mL, injected into the largest wart using an insulin syringe 1 ml (29 Gage × 0.5 inch), every 2 weeks until complete clearance of the warts or for maximum five treatment sessions.

Patient's evaluations

The included patients were subjected to full medical history with systemic and cutaneous evaluations. Initially, the site, size, and number of warts in every patient were recorded then clinical changes and treatment-related complications were registered every 2 weeks during the period of treatment (2.5 months), and every month during the follow-up period (3 months). Clinical photographs were taken at baseline, before every session (2 weeks), and after the end of treatment sessions using a digital camera (honor 9x pro triple camera).

The studied warts were examined by a hand-held dermoscope, with a measuring scale (mm), original magnification ×10, and LED illumination, (Dermlight 1 polarised and non-polarised mode) (DL1-1401 Rev C, 3 Gen are registered trademark of 3 Gen. Inc 31521 Rancho Viejo Rd. Suite 104 san jaun Capistrano CA 92675, USA). Image capturing was performed using a digital camera attached by an adaptor to the dermoscope, and 70% ethyl alcohol was used to disinfect the dermoscope before examination. Dermoscopic examination and photographs were performed at baseline, before regularly scheduled sessions, 1 month, and 3 months after the end of treatment sessions. Dermoscopic diagnosis and evaluation were based on the Criteria reported by *Bae et al.*[8] where dermoscopic characteristics of viral warts include the presence of uniform black to red spots and globules, papilliform surfaces, or interrupted conspicuous skin lines.

Treatment response evaluation

The clinical and dermoscopy score evaluations were performed by two dermatologists, to determine how well the patient responded to treatment, according to the following score[9,10]: Score 3 (complete response): there is a total disappearance of all treated warts both by the naked eye and by dermoscopic examination. Score 2 (clinical clearance and dermoscopic remnant): there is an apparent clinical cure with incomplete dermoscopic cure. Score 1 (clinical and dermoscopic decrease): dermoscopic evidence of residual warts is present despite a clinically significant decrease in the number and/or size of warts (>50%). Score 0 (no response): neither a dermoscopic improvement nor a clinical resolution of warts has been observed.

Side effects

All side effects (local and systemic), during or after injections, were recorded.

Ethical consideration

The study was submitted to the Research and Ethical Committee of the Medical School at Sohag University, and it was approved with a protocol number (Soh-Med-22-06-06). An informed written was signed by all the patients.

Statistical analysis

Using IBM-SPSS 24.0 (IBM-SPSS Inc., Chicago, IL, USA), the researcher validated, coded, and analysed the data. Means, standard deviations, medians, ranges, frequencies, and percentages were determined for descriptive statistics. As appropriate, we compared the variance in frequency distributions between groups using the Chi-square test or Fisher's exact test. The Shapiro-Wilk test was utilised to examine the distribution of the continuous variables. Parametric and non-parametric mean and median differences across groups were tested using the independent sample *t*-test and Mann-Whitney U test, respectively, for continuous variables. For significance, a *P* value less than 0.05 was used.

Results

Forty patients between the ages of 16 and 50 who suffered from plantar warts participated in this study with a mean of 30.40 ± 4.6 years in the Acyclovir group and 32.20 ± 6.3 years in the candida group. The clinical – demographic characteristics of the studied groups are presented in Table 1. Clinical and dermoscopic responses of the studied groups are shown in Table 2 and Figures 1-4. The complications of treatment of both studied groups were elicited in Table 3. The univariate correlations between the response of treatments of both studied groups and disease determinants are depicted in Table 4.

Discussion

Plantar warts pose significant challenges for both patients and doctors because there is now no universally effective treatment,[11] also HPV antiviral medication development is challenging. To begin, it cannot be used in antiviral studies since it does not multiply in tissue cultures.

This study aimed to assess the efficacy and adverse effects of intra-lesional injections of acyclovir and candida antigen in treating plantar warts.

Of acyclovir-treated patients, a score of 3 was achieved in 65% of patients, 15% of patients had a score of 2, 20% of patients were given a score of 1, and no cases had a score of 0.

Reviewing the recent literature, the use of intra-lesional acyclovir in treating warts had been investigated in Zagzig University.[12] They had the same concentration and method of injection as our study, but they did the study on all cutaneous warts and with smaller sample size (only 31 cases) and in comparison, to saline as a control group and follow-up clinically only. Complete clearance reported in 52.6% of the patients. Patients reported a partial response rate of 36.8%, with 10.5% reporting no reaction. The difference in the results may be related to the variations among the sampled population account for their results, the sample size as we used larger sample size, response to injected material, and the number, type as they inject all types of warts not only plantar, and duration of warts.

Our results are consistent with those of a previous study that compared the efficacy of intra-lesional acyclovir to that of PPD and found that 60.0% of patients who were treated with acyclovir had a full recovery, 25.0% made a partial recovery, and 15% made no recovery. Results from the same study showed no statistically significant differences between the groups. In the PPD-treated group, 30.0% reported complete recovery, 35.0% partial recovery, and 35% no recovery.[13]

On the other hand, our study demonstrated also the efficacy of intra-lesional candida antigen, as regards

Table 1: Baseline socio-demographic characteristics and clinical characteristics of the studied groups

Parameter	Acyclovir Group (*n*=20)	Candida Group (*n*=20)	*P**
Age/years			
• Mean±SD	30.40±4.6	32.20±6.3	0.410*
• Median (range)	30 (19–50)	32 (16–50)	
Sex			
• Female	5 (25%)	4 (20%)	0.705**
• Male	15 (75%)	16 (80%)	
Duration of wart/months			0.114*
• Mean±SD	9.80±7.1	15.40±14.3	
• Median (range)	5.5 (1–60)	10.5 (1–60)	
No. of warts before treatment			0.490**
• Single	7 (35%)	5 (25%)	
• Multiple	13 (65%)	15 (75%)	
No. of injected warts			<0.001
• Mean±SD	4.55±3.8	1	
• Median (range)	3 (1–10)	1	
Size of warts			0.75183**
• Less than 1 cm	11 (55%)	9 (45%)	
• More than 1 cm	9 (45%)	11 (55%)	

*An independent *t*-test was used to compare the difference in mean between groups. **Chi-square test was used to compare the difference in frequencies among groups $Non-working (student/housewife)

Table 2: Comparison between the two groups regarding clinical and dermoscopic responses

Parameter	Acyclovir Group (*n*=20)	Candida Group (*n*=20)	*P**
Response of injected wart			
• Mean±SD	2.45±0.8	2.35±0.9	0.989*
• Median (Range)	3 (1–3)	3 (0–3)	
• Score 0	0 (0%)	1 (5%)	0.733**
• Score 1	4 (20%)	5 (25%)	
• Score 2	3 (15%)	0 (0%)	
• Score 3	13 (65%)	14 (70%)	
Response of nearby wart (score)	*n*=7	*n*14	
• Score 0	0 (0%)	3 (21.4%)	0.077**
• Score 1	0 (0%	0 (0%)	
• Score 2	1 (14.3%)	0 (0%)	
• Score 3	6 (85.7%)	11 (78.6%)	
Response of distant wart (score)	*n*=3	*n*=5	
• Score 0	0 (0%)	1 (20%)	0.625**
• Score 1	0 (0%)	0 (0%)	
• Score 2	0 (0%)	0 (0%)	
• Score 3	3 (100%)	4 (80%)	

*Mann-Whitney *U* test was used to compare the difference in medians among groups. **Fisher's exact test was used to compare the difference in frequencies among groups

response in injected warts, with a score of 3 achieved in 14 (70%) patients with target warts, and there were no cases with a score of 2, and 5 (25%) had score 1, and one patient (5%) had score 0.

Table 3: Complications and comparison of follow-up data among groups

Parameter	Acyclovir Group (*n*=20)	Candida Group (*n*=20)	*P**
Complications			
Pain during injection	20 (100%)	20 (100%)	-----
Hemorrhagic eschar	20 (100%)	9 (45%)	<.001**
Localised oedema/erythema	17 (85%)	9 (45%)	0.008**
Flu-like symptoms	0 (0%)	9 (45%)	0.001**
Abscess formation	0 (0%)	1 (5%)	0.500**
Recurrence within 3 months of follow-up			
No	19 (95%)	20 (100%)	0.311
Yes	1 (5%)	0 (0%)	
Appearance of the new lesion after the session			
No	18 (90%)	19 (95%)	0.548
Yes	2 (10%)	1 (5%)	

Table 4: Correlation between the response of injected wart (score) and other determinants

	Response of Injected Wart (Score)	
	rho*	*P*
Age	–0.186	0.125
Sex	0.060	0.357
Disease duration/months	–0.121	0.229
No. of warts	0.120	0.230
No. of sessions	0.098	0.324

*Spearman's Rank correlation. Minimal or mild when rho >0-<0.2

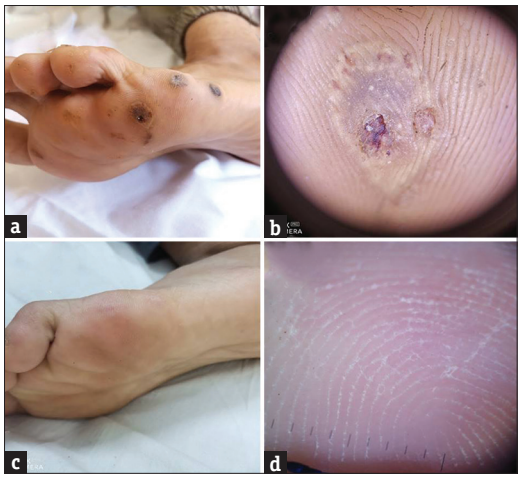

Figure 1: (a): Male patient aged 28 years with multiple plantar warts before treatment. (b): The same patient after 5 sessions of intra-lesional acyclovir with excellent response. (c): Dermoscopic picture of the same patient before treatment showing interrupted skin lines, and red and black dots. (d): Dermoscopic picture of the same patient showing disappearance of previous findings and return of normal skin lines after treatment

Marei *et al.*[14] found that intra-lesional candida antigen resulted in full eradication in seven of eight diabetic individuals with plantar warts (87.5%) and these can be explained as we did follow up of the cases clinically and dermoscopically and this gives a chance for more accurate detection of cure rate.

Our study's response rate was considerably greater than the rates reported by Fathy *et al.*,[5] Abdelaal *et al.*,[15] and Marei *et al.*,[16] all of whom reported response rates of 25%, 45%, and 50%, respectively. A greater candida antigen dose (0.2 ml) was injected in our trial than in previous studies (0.1 ml), and our study also included more sessions (5) than previous studies (3), both of which may explain our better response rate.

It is worth noting that our success rate with candida antigen for treating plantar warts was comparable to, if not slightly greater than, that reported by Nofal *et al.*,[17] Vlahovic,[18] and Nofal *et al.*,[19] but these differences were not statistically significant.

As regards side effects in the acyclovir group, we reported a few side effects as pain during injection then hemorrhagic eschar in all the patients, localised oedema, and erythema in 85% of the patients, and these were near to the adverse effects reported in previous study as pain at the injection site was reported by 93.8% of patients, followed by blistering by 50%. However, just one patient showed signs of localised erythema at the injection site. They didn't find any evidence of pigmentary alterations.[12]

As regards side effects in the candida group, we reported mild self-limited side effects that did not necessitate the stop of treatment as pain during injection was reported

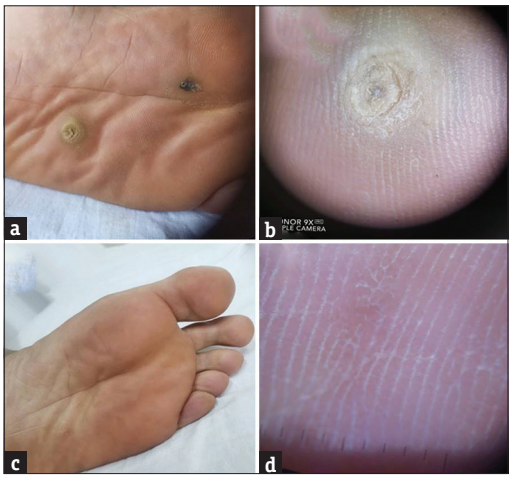

Figure 2: (a): Male patient aged 23 years with multiple plantar warts before treatment. (b): The same patient after 5 sessions of intra-lesional acyclovir with excellent response. (c): Dermoscopic picture of the same patient before treatment showing interrupted skin lines. (d): Dermoscopic picture of the same patient showing disappearance of previous findings and return of normal skin lines after treatment

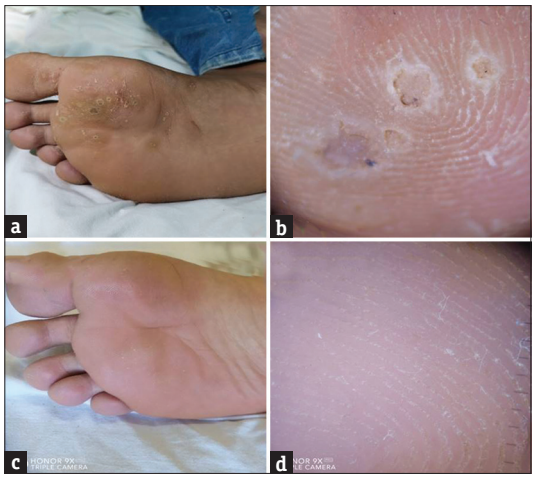

Figure 3: (a): Male patient aged 20 years with multiple plantar warts before treatment. (b): The same patient after 5 sessions of intra-lesional candida antigen with excellent response. (c): Dermoscopic picture of the same patient before treatment showing interrupted skin lines. (d): Dermoscopic picture of the same patient showing disappearance of previous findings and return of normal skin lines after treatment

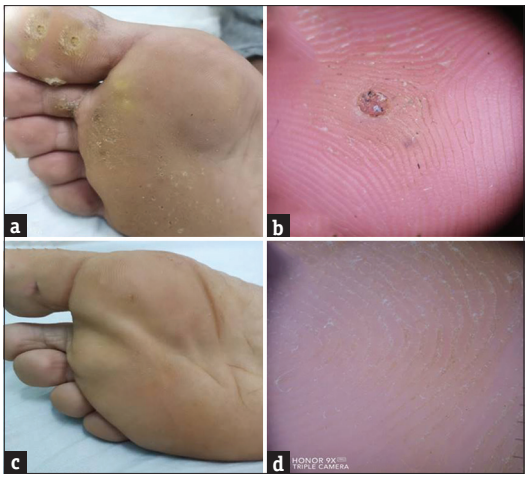

Figure 4: (a): Male patient aged 25 years with multiple plantar warts before treatment. (b): The same patient after 5 sessions of intra-lesional candida antigen with excellent response. (c): Dermoscopic picture of the same patient before treatment showing interrupted skin lines and thrombosed vessels. (d): Dermoscopic picture of the same patient showing disappearance of previous findings and return of normal skin lines after treatment

in all cases, hemorrhagic eshcar in 9 cases (45%), localised oedema and erythema in 9 cases (45%), flu-like symptoms in 9 cases (45%), abscess formation only in one case (5%). These data corroborate the superior safety profile of intra-lesional immunotherapy, which has been shown in multiple prior studies.[20-22]

As regards recurrence rate in the acyclovir group through 3 months of follow-up clinically and by dermoscopy, we had only one case (5%) that recurred again after 1 month of partial improvement and 2 cases (10%) had a new lesion within one month after 5 sessions.

On the contrary, a previous study reported that there was no recurrence over the 3-month observation period.[12] These differences could be explained as we did follow-up of the cases clinically and dermoscopically and this gives a chance for more accurate and early detection of recurrence. But still recurrence rate is less than conventional ablative treatment, in contrast to the high recurrence rates of traditional ablative treatment, antiviral therapy has a lower risk of infection spreading (average 30%).

As regards the recurrence rate in the candida group, our study showed no recurrence of improved cases and only one case had a new lesion within one month after the completion of 5 sessions which had only partial response after the end of sessions. Similar results of low recurrence rates were found in other investigations in this sector as well. The enhancement of the effector mechanism in response to HPV may account for the low recurrence rate.[23]

Neither the efficacy nor the safety of intra-lesional candida antigen against intra-lesional acyclovir for the treatment of plantar warts has been compared in any previous trials to the best of our knowledge.

Conclusion

Both intra-lesional acyclovir and candida antigen appear to be effective and tolerated treatment modalities for plantar warts. Although there were similar reports of side effects for both treatments, the success rate of curing warts using intra-lesional candida antigen was slightly greater.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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