Evaluation of topical imiquimod 5% cream alone versus combined topical imiquimod 5% cream plus cryotherapy in the treatment of plantar warts

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Abstract

Background: plantar warts are cutaneous lesions on the plantar aspect of the foot that are caused by human papillomavirus which is a pervasive virus. HPV needs an epidermal abrasion to inoculate a keratinocyte and a transiently impaired immune system. Cryotherapy is a commonly used procedure for the treatment of warts. It damages the cell membrane by freezing and thawing the tissue irreversibly. Imiquimod 5% is considered the first member of a new class of drugs that stimulates cell-mediated and innate immunity that results in potent antiviral, antitumor, and immunoregulatory effects. **Objectives:** the aim of this study is to determine the efficacy of the treatment of verruca plantaris with topical imiquimod 5% cream alone in comparison to combined cryotherapy plus topical imiquimod 5% cream. **Methods:** This study included 40 plantar wart patients, categorized into 2 groups: group I (Aldara) and group II (Aldara & cryotherapy). They were selected from the dermatology department of Fayoum University Hospital (Fayoum, Egypt) during the period from August 2019 to January 2020. **Results:** The cure rate of plantar warts treated with imiquimod 5% cream (Aldara) reported in our study to be 65% of the patients in group I & 45% of the patient in group II. This cure rate is more accurate, as the evaluation of the treatment depends on both the dermoscopic findings and clinical observations. **Conclusion:** Imiquimod 5% cream (Aldara) is considered effective in treating plantar warts, whatever the protocol of treatment and it is an economically affordable cream that needs no prior preparation or equipment.

Keywords: Plantar warts, Cryotherapy, Imiquimod 5%.

INTRODUCTION

Plantar warts are cutaneous lesions on the plantar aspect of the foot that are caused by human papillomavirus which is a pervasive virus. HPV needs an epidermal abrasion to inoculate a keratinocyte and a transiently impaired immune system **(1).**

Infection with HPV may be asymptomatic which occurs frequently, with most infections controlled by cell-mediated immunity. However, certain populations have been observed to manifest plantar warts at higher rates compared with the general population, placing them at increased risk for complications and wart-induced pain **(2).**

Although most people are asymptomatic carriers of HPV, 2% of the general population seeks medical care for warts annually. Plantar warts exhibit an annual incidence of 14%. The majority of cases occur in adolescents and children **(3).**

When a plantar wart is established, it sheds HPV via desquamated cells of the epithelium, which can spread to other people or infect other sites in the plantar aspect. HPV has a pervasive nature which makes preventive measures frequently required. Prophylaxis against HPV for populations that demonstrate high rates of plantar warts may be of benefit in controlling the spread of infection **(4).**

Aim of the work: To determine the efficacy of treatment of planter warts with topical imiquimod 5% cream alone in comparison to combined cryotherapy plus topical imiquimod 5% cream.

Subjects and Methods:

Study design:

The study was a randomized, prospective and comparative study conducted on forty patients with plantar warts recruited from the outpatient clinic of Dermatology, STDs and Andrology department, Fayoum University Hospital. This study lasted for 6 months from August 2019 to January 2020.

Sample size and type:

The random number allocation method was used to divide the patients into 2 groups, 20 patients each. Group I was treated for 6 sessions with a 1-week interval between sessions by imiquimod 5% cream (Aldara) only and group II was treated for 6 sessions with a 1-week interval between sessions by imiquimod 5% cream plus cryotherapy. They were selected from the dermatology department of Fayoum University Hospital (Fayoum, Egypt) during the period from August 2019 to January 2020.

Ethical consideration:

This study was approved by the local ethics committee of Fayoum University. Informed written consent was signed by the

patient /parent included in the study and confidentiality was assured

Inclusion criteria: All cases of verruca plantaris (plantar warts) aged more than 5 years old.

Exclusion criteria:

1- Patients below 5 years old.

2- Pregnant and lactating females.

3- Patients with chronic systemic diseases (diabetes mellitus, anemia, chronic infection, immunocompromised patients and patients with autoimmune disease).

4- All cases of thrombocytopenia (platelet count less than 50000/ ml) or thrombocytosis.

5- All cases of bleeding tendency and liver disease.

Study tools:

Each patient was subjected to the following:

1-History taking:

. Personal history: Name, Age, Sex.

. Present history: Onset, course, duration of the disease.

. Past history: Previous or current treatment and recurrence.

2- Dermatological examination:

. Number and distribution of plantar warts lesions.

. Other skin diseases.

Statistical Analysis:

The collection of data was done and coded to facilitate data manipulation and data analysis was performed using Statistical Package of Social Science **(SPSS)** software version 18 in windows 7 and double entered into Microsoft Access. Descriptive analysis in the form of numbers and percentages for qualitative data, and arithmetic means as central tendency measurement, standard deviations as a measure of dispersion for quantitative parametric data. Quantitative data included in the study was first tested for normality by the One-Sample Kolmogorov-Smirnov test in each study group then inferential statistic tests were selected. In-depended student t-Test was used for quantitative parametric data, to compare measures of two independent groups of quantitative data. The Chi-square test was used for qualitative data to compare two of more than two qualitative.

RESULTS:

This study included 40 patients, 23 males and 17 females, with clinically and dermoscopically diagnosed warts in the planter aspect, randomly categorized into 2 groups. In both study groups all patients received 6 sessions of treatment with an interval of 1 week between sessions. In group I (Aldara), imiquimod 5% cream

(Aldara) was applied in every session on the plantar wart after paring the wart to remove the associated callus with a scalpel and then applying the cream under occlusion 3 times per week for 6 weeks. In group II (Aldara & cryotherapy), the first session was preceded by cryotherapy and then imiquimod 5% cream (Aldara) was applied under occlusion 3 times per week for 6 weeks in the same session of cryotherapy.

Variables	**Aldara** (n=20)		**Aldara & cryotherapy** (n=20)		**p-value**	**Sig.**
Age (years)						
Range Mean /SD	12 32.9	60 15.1	10 28.1	52 10.6	0.2	NS
Sex						
Male	11	55%	12	60%	0.9	NS
Female	9	45%	8	40%		
Residence						
Urban	9	45%	10	50%	0.6	NS
Rural	11	55%	10	50%		
Occupation						
Not working	13	65%	8	40%	0.4	NS
Manual worker	5	25%	8	40%		
Employee	1	5%	3	15%		
Professional	1	5%	1	5%		

Group I (Aldara) included 20 patients. Their age ranged between 12 and 60 years with mean ± SD of 32.9±15.1. Males comprised more than half (55.5%) of cases (11 out of 20). Likewise, 55.5% of cases (11 out of 20) were from rural areas. As regards patient occupation; unemployment was repeated in the vast majority of the cases 65% (13/20), followed by manual workers (5/20), and only one case for employee and professional occupation. Group II (Aldara & cryotherapy) included 20 patients. Their age ranged between 10 and 52 years with mean ± SD of 28.1±10.6. Males comprised most of the cases (60.0%). Half of the cases (10 out of 20) were from rural areas. Each category of non-working and manual workers was found in 40% (8/20) of cases, followed by the employee (3/20), and only one case for professional occupation. No statistically significant difference was reported between the two groups as regards age (P=0.2), sex (P=0.9), residence (P=0.6), and occupation (P=0.4), table (1) figure (1).

Table (1): Comparisons between study groups regarding demographic characters

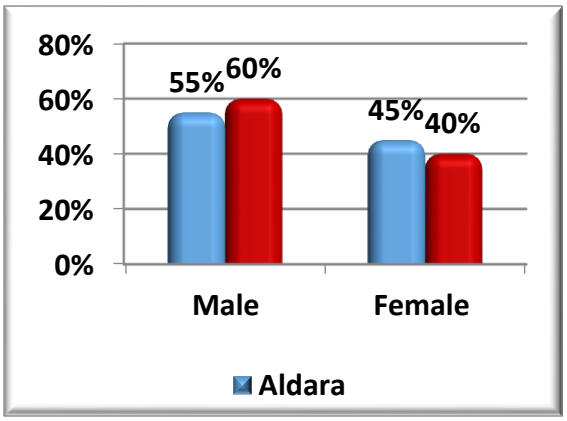

Figure (1): Sex in study groups

Regarding dermoscopic findings before treatment in all patient of both study groups, it reveals multiple prominent hemorrhages (black dots) within a well-defined, yellowish papilliform surface, in which skin lines are interrupted, but after treatment sessions the dermoscopic finding reveals complete disappearance of the hemorrhages points (black dots) in most patients 13/20 (65.0%) in group I who were dermoscopically cured after treatment. In group II, less than half 9/20 (45.0%) of patients were dermoscopically cured after treatment.

Regarding clinical improvement after treatment. In group I, complete and marked clinical improvement after treatment was identified in 11/20 (55.0%) and in 2/20 (10%) of patients, respectively while 5/20 (25%) and 1/20 (5%) of patients showed moderate and mild clinical improvement, respectively. In this group, most patients 13/20 (65.0%) reported a high level of satisfaction, and 6/20 (30%) of patients reported a moderate level of satisfaction while one case was not satisfied. In group II, complete and marked clinical improvement after treatment was identified in 6/20 (30.0%) and 3/20 (15%) of patients, respectively while 8/20 (40%) and 3/20 (15%) of patients showed moderate and mild clinical improvement, respectively. In this group, nearly half of patients 9/20 (45.0%) reported a high level of satisfaction, 10/20 (50%) reported a moderate level of satisfaction while one case was found to be not satisfied. No statistically significant difference was reported between the two groups as regards dermoscopic findings (P=0.3), improvement degree (P=0.4), and level of satisfaction (P=0.4), table (2) and figures (2-4)

Table (2): Comparisons between study groups regarding different outcomes after treatment

Variables	Aldara (n=20)		Aldara & cryotherapy (n=20)			p-value	Sig.
	No.	%	No.	%			
Dermoscopic findings after treatment							
Not cured	7	35 %	11	55 %		0.3	NS
Cured	13	65 %	9	45 %			
degree of clinical improvement after treatment							
No	1	5 %	0	0 %		0.4	NS
Mild	1	5 %	3	15 %			
Moderate	5	25 %	8	40 %			
Marked	2	10 %	3	15 %			
Complete	11	55 %	6	30 %			
Satisfaction level							
Not satisfied	1	5 %	1	5 %		0.4	NS
Moderate	6	30 %	10	50 %			
High	13	65 %	9	45 %			

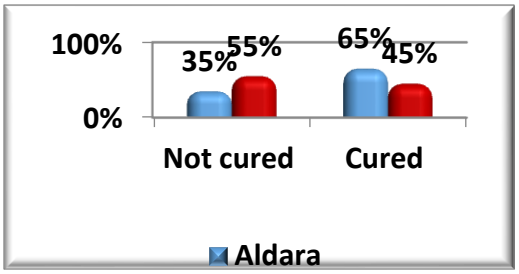

Figure (2): Dermoscopic findings after treatment in study groups.

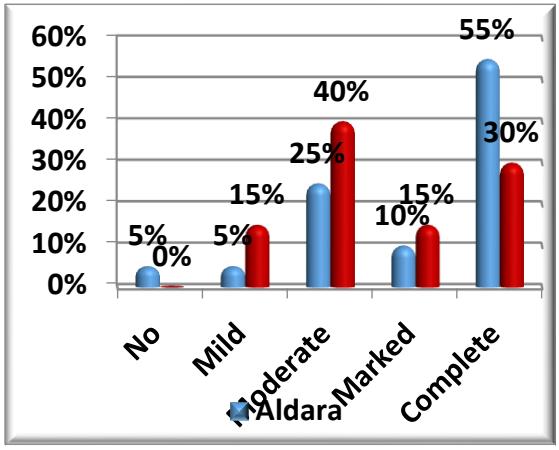

Figure (3): Degree of clinical improvement after treatment in study groups.

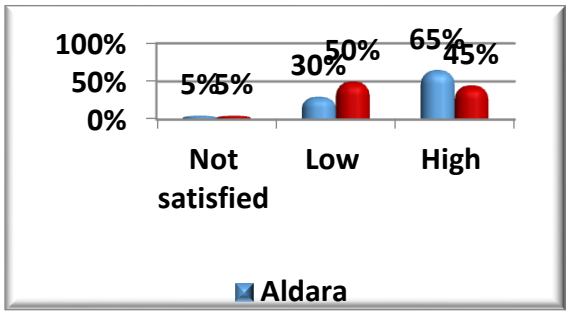

Figure (4): Satisfaction level in study groups.

Follow up was done for 1 month every 2 weeks. Among patients in group I, one case was lost to follow-up for one month after treatment. Out of the remaining patients, most cases 13/19 (68.4%) showed a complete cure of the lesion. Within group II, two cases were lost to follow-up for one month after treatment. Less than half of the examined patients 8/18 (44.4%) showed complete cure (p=0.1). Also, No cases in both group experienced recurrence after one month of follow-up, table (3)

Table (3): Comparisons between study groups regarding cure after one month of follow-up after treatment

Variables	Aldara (n=19)		Aldara & cryotherapy (n=18)		p-value	Sig.
	No.	%	No.	%		
Follow up for one month (every 2 weeks)						
Not cured	6	31.6%	10	55.6%	0.1	NS
Cured	13	68.4%	8	44.4%		
Recurrence						
No	19	100%	18	100%	1	NS
Yes	0	0%	0	0%		

The patients were asked about any side effects. Some patients reported pain that started at the first or second session after applying imiquimod 5% cream (Aldara) under occlusion and was relieved without any analgesics at the end of treatment sessions.

DISCUSSION

In our study, the rate of cure of plantar warts treated with imiquimod 5% cream (Aldara) is to be 65% of the patients in group I & 45% of the patient in group II. This was in agreement with the results of ***Sparling et al., 2001*****(5)** who reported a case of a 17-year-old young healthy female who had two large plantar warts, 1 on each plantar aspect. Appling Imiquimod 5% cream to warts nightly for 6 weeks (with duct-tape occlusion). Follow-up examination showed complete resolution of both warts in the planter aspect. ***Yesudian & Parslew, 2002*****(6)** have reported a case of a 35-year-old man with a history of verrucae on both hands and feet. Imiquimod was applied to warts daily for about 8 hours with no occlusion and the patient continues to be free of warts 1 year after treatment with imiquimod 5% cream. ***Zamiri & Gupta, 2003*****(7)** reported two cases of plantar warts. Complete clearance of the warts was observed in both cases over a period of 12 weeks after treatment with imiquimod 5% cream. ***Leong et al., 2007*****(8)** have reported a case of a 26-year-old male presented with a history of a plantar wart on the left foot. Appling of imiquimod 5% was done daily at a dose of 12.5 mg/week for 6 weeks, with duct tape occlusion. There was near complete resolution of the wart After 8 weeks of treatment. Three weeks after, the treated wart had completely healed. ***López-Giménez, 2013*****(9)** reported five plantar warts cases in which applying imiquimod

5% cream was done at night, without occlusion, 3 times a week, until the lesions disappeared. 17% SA with Petrolatum was applied On days when imiquimod was not applied. All cases responded to imiquimod 5% cream positively and showed complete resolution of the wart after 8 –10 weeks of treatment. ***Stefanski et al., 2016*****(10)** reported a comparative study in which imiquimod 5% cream combined with SA versus cryotherapy was used in the treatment of cutaneous warts in children. Group I was subjected to cryotherapy every two weeks for 3 months. Group II was subjected to imiquimod 5% cream plus SA daily for 6–10 hours for five days per week for 3 months. The cure rate is 81.1% of children in group II & 67.3% of children in group II.

The previous old studies demonstrated the successful use of imiquimod 5% cream, either in combination or alone therapy in the treatment of plantar warts. Most of these studies, included a small number of patients and were non-comparative unlike our study which is comparative and includes a large number of patients (40 patients), but the last study is a comparative one in which they used SA in combination with imiquimod 5% cream in the treatment of cutaneous warts in children, but in our study we used the cream alone to treat plantar warts which makes our study more accurate in determining the efficacy of the cream alone in the treatment of plantar warts. In our study, the cure rate of plantar warts treated with imiquimod 5% cream (Aldara) reported is 65% of the patients in group I & 45% of the patient in group II. This cure rate is more accurate, as the evaluation of the treatment depends on both the dermoscopic findings and clinical observations.

This is the first study, to the best of our knowledge, to evaluate the efficacy of the application of topical imiquimod 5% cream (Aldara) alone or in combination with other therapeutic measures such as cryotherapy in the treatment of plantar warts.

From our point of view, the routine use of dermoscopy strongly recommends in the evaluation of treatment success, as it can accurately tell if the wart needs further treatment, thus decreasing the possibility of recurrence and preventing premature stoppage of the treatment. **Conclusion:** Imiquimod 5% cream (Aldara) is considered effective in treating plantar warts, whatever the protocol of treatment and it is an economically affordable cream that needs no prior preparation or equipment.

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Conflict of interest: None declared

Ethical approval: The study was approved by the institutional Ethics Committee

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