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## 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

**Introduction:** Plantar warts are cutaneous lesions on the plantar aspect of the foot that is 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.

**Aim of the study:** The study aimed 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.

**Subjects and methods:** This study included 40 plantar wart patients, categorized into two groups, the 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 depended 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.

## 1. Introduction

Plantar warts are cutaneous lesions on the plantar aspect of the foot that is 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].

## **2. Subjects and methods**

### **2.1. Study design**

The study was a randomized, prospective and comparative study conducted on 40 patients with plantar warts recruited from the outpatient clinic of the Dermatology, STDs, and Andrology department, at Fayoum University Hospital. This study lasted for 6 months from August 2019 to January 2020.

### **2.2. Sample size and type**

The random number allocation method was used to divide the patients into two 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

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].

The current study aimed 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.

the period from August 2019 to January 2020.

### **2.3. 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

### **2.4. Inclusion criteria**

All cases of Verruca plantaris (plantar warts) aged more than 5 years old.

### **2.5. Exclusion criteria**

Young patients (<5 years old), pregnant, lactating females, patients with chronic systemic diseases (Diabetes mellitus, anemia, chronic infection, immunocompromised patients, and patients with autoimmune disease), all cases of

thrombocytopenia (platelet count less than 50000/ ml) or thrombocytosis, and all cases of bleeding tendency and liver disease were excluded.

## **2.6. Experimental design**

### **Medical history reporting**

That included Age and Sex information, besides, all clinical characteristics of the present history (Onset, course, duration of the disease) and past history (previous or current treatment and recurrence).

### **Dermatological examination**

That included the number and distribution of plantar warts lesions and other skin diseases.

## **3. Results**

This study included 40 patients, 23 males, and 17 females. They were clinically and dermoscopically diagnosed with warts in the planter aspect. Patients were randomly categorized into two 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

## **2.7. 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. Independent 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.

3 times per week for 6 weeks in the same session of cryotherapy.

Group I (Aldara) included 20 patients. Their age ranged between 12 and 60 years with mean  $\pm$  SD of  $32.9 \pm 15.1$ . Males comprised more than half (55.5%) of cases (11 out of 20). Likewise, 55.5% of cases (11 out of 20) were from the rural area. As regards patient occupations; 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 occupations.

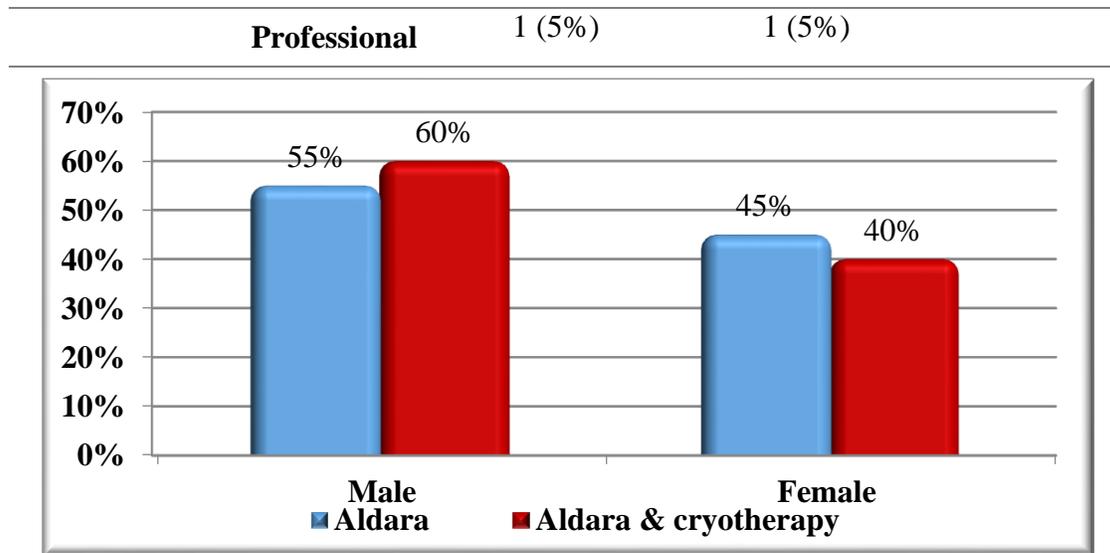
Group II (Aldara & cryotherapy) included 20 patients. Their age ranged between 10 and 52 years with mean  $\pm$  SD of

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 ( $P=0.4$ ), as shown in Table 1 and Figure 1.

**Table 1:** Comparisons between study groups regarding demographic characters.

Variables		Aldara (n=20)	Aldara & cryotherapy (n=20)	P-value
Age (years)		32.9±12 (12-60)	28.1±10.6 (10-52)	0.2
Sex	Male	11 (55%)	12 (60%)	0.9
	Female	9 (45%)	8 (40%)	
Residence	Urban	9 (45%)	10 (50%)	0.6
	Rural	11 (55%)	10 (50%)	
Occupation	Not working	13 (65%)	8 (40%)	0.4
	Manual worker	5 (25%)	8 (40%)	
	Employee	1 (5%)	3 (15%)	



**Figure 1: Sex distribution according to the treatments used in the study.**

Regarding dermoscopic findings before treatment in all patients 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 the complete disappearance of the

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,

Variables	Aldara (n=20)	Aldara & cryotherapy (n=20)	P-value
hemorrhage's 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 of 9/20 (45.0%) of patients were dermoscopically cured after treatment.		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 ( $P=0.4$ ), as shown in Table 2 and Figures 2-4.	

**Table 2:** Comparisons between study groups regarding different outcomes post-treatment.

<b>Dermoscopic findings</b>	<b>Not cured</b>	7 (35%)	11 (55%)	0.3
	<b>Cured</b>	13 (65%)	9 (45%)	
<b>Degree of clinical improvement</b>	<b>No</b>	1 (5%)	0 (0%)	0.4
	<b>Mild</b>	1 (5%)	3 (15%)	
	<b>Moderate</b>	5 (25%)	8 (40%)	
	<b>Marked</b>	2 (10%)	3 (15%)	
	<b>Complete</b>	11 (55%)	6 (30%)	
<b>Occupation</b>	<b>Not satisfied</b>	1 (5%)	1 (5%)	0.4
	<b>Moderate</b>	6 (30%)	10 (50%)	
	<b>High</b>	13 (65%)	9 (45%)	

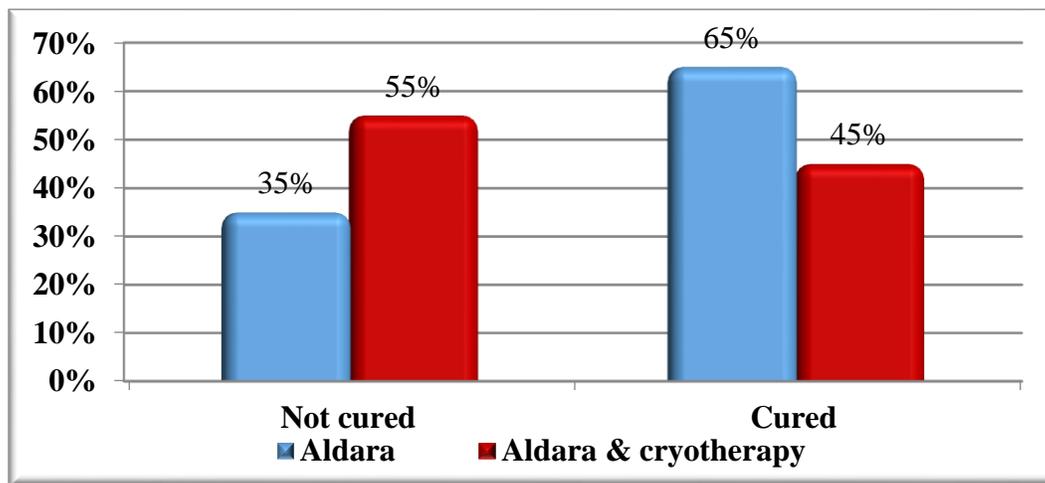
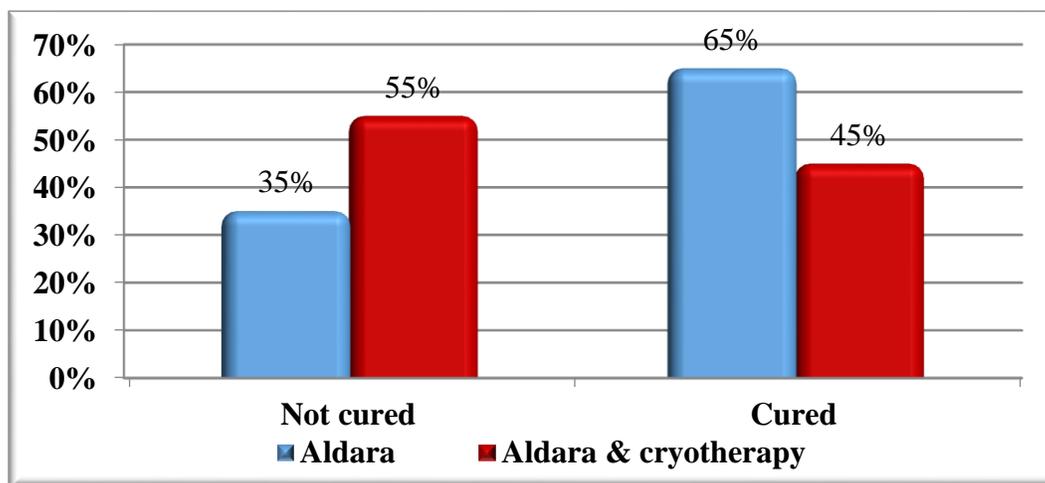
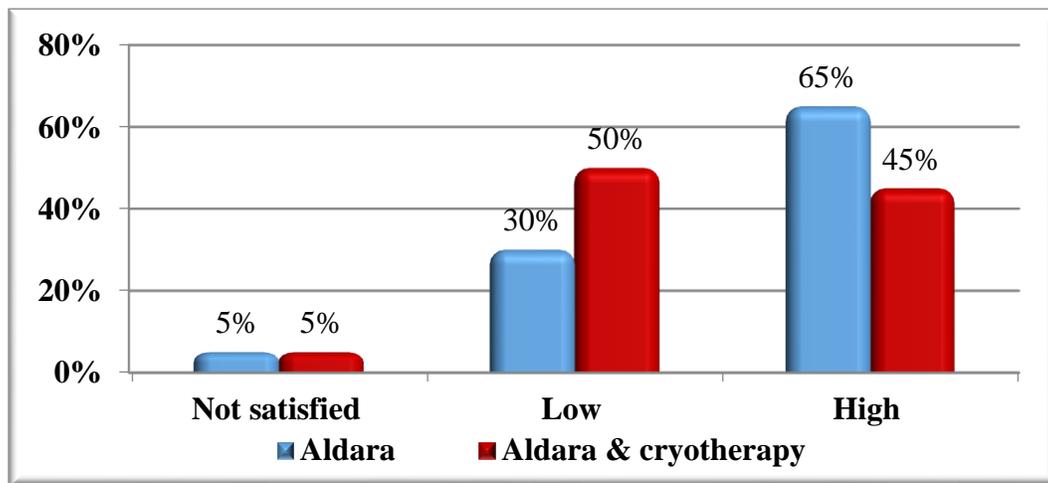


Figure 2: Dermoscopic findings post-treatment.



**Figure 3: Degree of clinical improvement post-treatment.**

Variables	Aldara (n=19)	Aldara & cryotherapy (n=18)	P-value
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**Figure 4: Satisfaction level post-treatment.**

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 a one-month follow-up (Table 3).

**Table 3:** Comparisons between study groups regarding cure after a one-month follow-up post-treatment.

<b>Follow up for one month (every 2 weeks)</b>	<b>Not cured</b>	6 (31.6%)	10 (55.6%)	0.1
	<b>Cured</b>	13 (68.4%)	8 (44.4%)	
<b>Recurrence</b>	<b>No</b>	19 (100%)	18 (100%)	1
	<b>Mild</b>	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)

#### 4. 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. That was in agreement with the results of the study conducted by Sparling *et al.*, (2001), in which a 17-year-old young healthy female had two large plantar warts, one on each plantar aspect [5]. They applied Imiquimod 5% cream to warts, nightly, for six weeks (with duct-tape occlusion), where the follow-up examination showed complete resolution of both warts in the planter aspect [5]. Yesudian & Parslew, (2002), reported a case of a 35-year-old man with a history of verrucae on both hands and feet, in which Imiquimod 5% cream was applied to warts daily for about eight hours with no occlusion and the patient continues to be free of warts for a year post-treatment [6]. The study conducted by Zamiri & Gupta, (2003), reported two cases of plantar warts, in which a complete clearance of the warts was observed in both cases over a period of 12 weeks post-treatment with imiquimod 5% cream [7]. Furthermore, Leong *et al.*, (2007) reported a case of a 26-year-old male

under occlusion and was relieved without any analgesics at the end of treatment sessions.

presented with a history of a plantar wart on the left foot, where imiquimod 5% cream was applied daily at a dose of 12.5 mg/week for six weeks, with duct tape occlusion [8]. In that study, there was near complete resolution of the wart eight weeks post-treatment and after more than three weeks, the treated wart was completely healed [8]. López-Giménez *et al.*, (2013), 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, where all cases responded to imiquimod 5% cream positively and showed complete resolution of the wart after 8 –10 weeks of treatment [9]. Stefanski *et al.*, (2016), reported a comparative study in which imiquimod 5% cream combined with SA versus cryotherapy was used in the treatment of cutaneous warts in children [10].

In the current study, a group of patients was treated with cryotherapy every two weeks for three months, while another group was subjected to imiquimod 5% cream plus SA daily for 6–10 hours/five days/week/3 months. The cure rate was

81.1% in Group I children versus 67.3% in Group II. Some previous 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 are non-comparative. The current comparative study included a large number of patients (40 patients). Furthermore, in the comparative study conducted by Stefanski *et al.*, (2016), they used SA in combination with imiquimod 5% cream in the treatment of cutaneous warts in children [10]. However, in the current study, we used the cream alone to treat plantar warts, which increases the accuracy in determining the efficacy of the cream alone.

In our study, the cure rate of plantar warts treated with imiquimod 5% cream (Aldara) was reported in 65% and 45% of the patients in groups I and II, respectively. The higher accuracy of that cure rate is due to the evaluation of the treatment depending on both the dermoscopic findings and clinical observations.

## 5. Conclusion

To the best of our knowledge, this is the first study 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. 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.

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. This decreases the possibility of recurrence and prevents premature stoppage of the treatment.

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**Conflict of interest:** All authors declare no conflict of interest.

**Ethical approval:** The study was approved by the institutional Ethics Committee of the faculty of medicine, Fayoum University, Fayoum, Egypt.

**Informed Consent Statement:** Written informed consents were obtained from all patients (parents).

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