

## **Treatment of Plane Wart with Topical Adapalene Gel 0.1%: An Open Therapeutic Trial**

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### **Abstract**

Plane wart is a common dermatological disease with a high rate of spontaneous recovery. Topical adapalene gel 0.1% is a known keratolytic agent with many dermatological uses. To evaluate the efficacy and tolerability of topical adapalene gel 0.1% in the treatment of plane warts. Fifty patients with plane warts consulting the department of Dermatology and Venereology of Al-Kindy Teaching Hospital from August 2011 to April 2012 were enrolled in this opened therapeutic trial. All patients were instructed to apply adapalene gel 0.1% twice daily for 4 weeks duration to be assessed clinically and by digital photograph. If at the end of 4<sup>th</sup> week no or partial response occurred, the patients were instructed to continue using the treatment and then they were re-evaluated clinically and photographically by the end of 8<sup>th</sup> week. The response rate was evaluated according to number of lesions. After 4 weeks of treatment, patients who achieved an excellent response were those with 1-10 lesions (8%), while no one with 11-  $\geq$ 20 achieved an excellent response. The response to treatment in the view of different grades of response and according to no. of lesions were statistically significant (P-value=0.015, p-value=0.031 respectively). After 8 weeks of treatment, the highest figure of excellent response was in those with 1-10 lesions group (30%). The overall response of different grades was statistically significant (P-value=0.014). Whereas response according to number of lesions was not significant (P-value =0.235). According to duration of lesions, after 4 weeks of treatment, patients who achieved an excellent response were mostly those with 1-4 months (8%), while no one with duration of > 4 months achieved an excellent response. After 4 weeks treatment, the response to treatment in the view of different

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grades was statistically significant (P-value=0.025). The response according to duration of lesions was also significant (P-value=0.003). After 8 weeks of treatment, the highest figure of patients that showed an excellent response was still those with duration of lesions between 1-4 months (28%). On the other hand, patients with duration of lesions more than 8-12 months show the lowest figure (6%). The overall response in different grades was not significant (P-value=0.062). The response according to duration of lesions was also not significant (P-value=0.084). Topical Adapalene gel 0.3% is an effective and safe option of treatment of plane warts.

**Keywords:** Plane wart, Topical Adapalene gel, dermatological disease

## 1 Introduction

Warts are benign proliferation of skin and mucosa that result from infection with human papilloma virus (HPVs) [1]. The actual number of types may range between 100 and 150, and HPV types are often associated with distinct regional predilection and specific histopathology [1, 2, 3].

Warts occur at any age but unusual in infancy and early childhood. The incidence increases in the school years to reach a peak between the age 12 and 16 years then declines sharply to age of 20 and more gradually thereafter [4].

Plane warts occur mostly in children and young adults [5]. The face, back of the hands and the shins are the site of predilection [4]. Lesion usually presented as 2-4 mm flat topped papules that are slightly erythematous or brown on pale skin and hypopigmented on darker skin [6]. Useful finding is the tendency of warts to koebnerize forming linear, slightly raised papular lesions [6]. Resolution is usually complete within one month (when inflamed) [4]. Of all clinical HPV infections, plane warts have the highest rate of spontaneous remission [6].

Many modalities of treatment were used to treat plane warts, but none is uniformly effective, Cryotherapy [6], salicylic acid [4], retinoids [4], 5-Fluorouracil [8], imiquimod [9], laser [10], oral cimetidine [4].

Adapalene is a stable naphthoic acid derivative with potent retinoid pharmacology, controlling cell proliferation and differentiation. In addition it has a significant anti-inflammatory action [11]. Adapalene is used in the treatment of acne vulgaris [12].

## 2 Preliminary Notes

### Definition 2.1

HPV= human papilloma virus

## 3 Patients and Methods

### 3.1 Study Design

This is an open therapeutic trial conducted at the Department of Dermatology and Venereology of Al-Kindy Teaching Hospital during the period from August 2011 to April 2012.

### **3.2 Inclusion Criteria**

All patients with plane warts attending the Outpatient Department of Dermatology & Venereology in Al-Kindy Teaching Hospital were included in this study

### **3.3 Exclusion Criteria**

Patients with one or more of the following were excluded from this study:

1. Those who are receiving steroid or other immune suppressant drugs.
2. Those with history of chronic illnesses or immune suppressed conditions.
3. Pregnant and nursing woman.
4. Those who receive any modality of treatment for their warts at least for the previous two months.
5. Patients refusing this therapeutic trial.

After full explanation to each patient about the nature of the disease, course, prognosis and full information related to the therapy including; the side effects, action and way of application, a formal consent was taken from each patient prior to their inclusion in this study. The approval of the ethical Committee of Scientific Council of Dermatology and Venereology of Al-Kindy Teaching Hospital was also obtained.

### **3.4 History and Physical Examination**

A full history was taken from each patient according to written questionnaire regarding the name, age, sex, occupation, marital status, duration of disease, family history of warts, past medical history (states of immune suppression, organ transplantation or any chronic diseases), drugs history especially for corticosteroids and other immune suppressants or any previous treatment modality received for their warts.

Physical examination was performed for each patient to assess the number, presence of other types of warts, the examination was aided by taking several photos for each patient using the same digital camera (Sony /cyber shot) from approximately the same view and distance.

### **3.5 Baseline Assessment**

The number of lesions were calculated and categorized into three groups as follows; (1-10) lesions, (11-20) lesions and (20-30) lesions.

### **3.6 Method of Application**

The patients were instructed to apply Adapalene gel 0.1% twice daily for 4 weeks duration to be assessed. If at the end of 4<sup>th</sup> week no or partial response occurred, the patients were instructed to continue using the treatment and then they were re-evaluated at the end of 8<sup>th</sup> week.

### **3.7 Evaluation of the Response to Treatment**

All patients were reexamined at the end of 4<sup>th</sup> week and 8<sup>th</sup> week to evaluate the response to treatment depending on clinical and photographic assessment and to record any

possible local & systemic side effects.

The response to treatment was graded as follows:

0= no response

1= mild response (1-25% reduction in lesion no.)

2= moderate response (26-50% reduction in lesion no.)

3= significant response (51-75% reduction in lesion no.)

4= excellent response (76-100% reduction in lesion no.)

### 3.8 Statistical Analysis

Data were analyzed by using MINITAB VIR 16. Chi square test was used to determine the differences between percentages. P-values less than 0.05 were considered significant [6, 8].

## 4 Main Results

During the period from August 2011 to April 2012, a total of 50 patients with plane warts 17 males (34%), and 33 females (66%) attended the Department of Dermatology and Venereology in Al-Kindy Teaching Hospital and included in this study.

### 4.1 Age and Gender Distribution

A total of 50 patients with plane wart were included. Their ages varied between 5 to 37 year with a mean  $\pm$  SD of  $14.34 \pm 9.06$  years.

Plane wart was seen in 17 male patients (34%). Their ages varied between 5 to 22 years with mean  $\pm$  SD of  $13.06 \pm 5.68$  years.

Female patients were 33 patients (66%). Their ages varied between 5 to 37 years with a mean  $\pm$  SD  $15 \pm 10.4$  years.

### 4.2 Number of Lesions

The number of warts in each patient ranged from 1 to 30 with a mean  $\pm$ SD of  $7.93 \pm 13.72$  lesions. Patients who had 1-10 lesions represent the major group in our study {26 patients (52%)} (Table 1).

Table 1: Distribution of patients with plane warts according to number of lesions

No. of lesions	No. of patients
1-10	26 (52%)
11-20	15 (30%)
20-30	9 (18%)

P value=0.002

### 4.3 Duration of Lesions

As shown in Table 2, the patients included in this study have variable lesion duration ranged from 1-12 months with a mean  $\pm$ SD of  $3.18 \pm 4.28$  months. Patients with the

shortest duration (1-4) months represent the major group in our study.

Table 2: Distribution of patients with plane warts according to duration of lesions

Duration of lesions	No. of patients
1-4 month	30 (60%)
>4-8 month	13 (26%)
>8-12 month	7 (14%)

P value=0.001

#### 4.4 Family History

The family history of plane warts or any other type of warts was looked for and found to be positive in 32(64%) patients. Twenty four (48%) of them had more than ten lesions.

#### 4.5 Response to Therapy According to the Number of Lesions

The response rate was evaluated according to number of lesions. After 4 weeks of treatment (Fig. 5, 7&8), patients who achieved an excellent response were mostly those with 1-10 lesions (8%), while none of the patients with number of lesions 11-20 or more than 20 achieved an excellent response. The response to treatment in the view of different grades of response was statistically significant after 4 weeks of treatment with P-value=0.015. The response according to number of lesions was also significant after 4 weeks of treatment with P =0.031 (Table 3).

Table 3: The response rate of patients with plane wart to Adapaline after 4 weeks according to number of lesions

Warts no. range	No response	Mild response	Moderate response	Significant response	Excellent response	Total
No. 1-10	3 (6%)	5 (10%)	9 (18%)	5(10%)	4 (8%)	26 (52%)
No. 11-20	1 (2%)	4 (8%)	9 (18%)	1 (2%)	0 (0%)	15(30%)
No. >20	2 (4%)	4 (8%)	3 (6%)	0 (0%)	0 (0%)	9(18%)
total	6 (12%)	13(26%)	21(42%)	6 (12%)	4 (8%)	50(100%)

P value for different grades of response = 0.015\*

P value for different grades of response according to the no. lesions = 0.031\*

After 8 weeks of treatment (Fig.6&8), the least figure of excellent response was in those with more than 20 lesions (4%), while the highest figure of excellent response was in those with 1-10 lesions group (30%). The overall response of different grades was statistically significant after 8 weeks of treatment with P-value=0.014. The response according to number of lesions was insignificant after 8 weeks of treatment with P-value =0.235 (Table 4).

Table 4: The response rate of patients with plane wart to Adapaline after 8 weeks according to number of lesions

Warts no. range	No response	Mild response	Moderate response	Significant response	Excellent response	Total
No. 1-10	0	0	0	11 (22%)	15 (30%)	26(52%)
No. 11-20	0	0	1 (2%)	6 (12%)	8 (16%)	15(30%)
No. >20	2 (4%)	0	0	3 (6%)	4 (8%)	9(18%)
Total	2 (4%)	0	1(2%)	20 (40%)	27(54%)	50(100%)

P value for different grades of response = 0.014\*

P value for different grades of response according to the no. lesions = 0.235

#### 4.6 Response to Therapy According to the Duration

The response rate was also evaluated according to duration of lesions. After 4 weeks of treatment (Fig. 5, 7&8), patients who achieved an excellent response were mostly those with 1-4 months (8%), while none of the patients with duration of lesions more than 4 months achieved an excellent response. The response to treatment in the view of different grades of response was statistically significant after 4 weeks of treatment with P-value=0.025. The response according to duration of lesions was also significant after 4 weeks of treatment with P-value = 0.003 (Table 5).

Table 5: The response rate of patients with plane wart to Adapaline after 4 weeks according to duration of lesions

Duration of lesions/ month	No response	Mild response	Moderate response	Significant response	Excellent response	Total
1-4	5 (10%)	6(12%)	9 (18%)	6 (12%)	4 (8%)	30(60%)
>4-8	1 (2%)	3 (6%)	8 (16%)	1 (2%)	0 (0%)	13(26%)
>8-12	2 (4%)	3 (6%)	2 (4%)	0 (0%)	0 (0%)	7 (14%)
total	8 (16%)	12(24%)	19(38%)	7(14%)	4(8%)	50(100%)

P value for different grades of response = 0.025\*

P value for different grades of response according to the duration of lesions = 0.003\*

After 8 weeks of treatment, the highest figure of patients that showed an excellent response was still those with duration of lesions between 1-4 months (28%). On the other hand, patients with duration of lesions more than 8-12 months show the lowest figure (6%). The overall response in different grades was statistically insignificant after 8 weeks of treatment with P-value=0.062. The response according to duration of lesions was also insignificant after 8 weeks of treatment with P-value=0.084 (Table 6).

Table 6: The response rate of patients with plane wart to Adapaline after 8 weeks according to duration of lesions

Duration of lesions/month	No response	Mild response	Moderate response	Significant response	Excellent response	Total
1-4	0 (0%)	1 (2%)	4 (8%)	11 (22%)	14 (28%)	30(60%)
>4-8	0 (0%)	0 (0%)	4 (8%)	5 (10%)	4 (8%)	13(26%)
>8-12	1 (2%)	0 (0%)	1(2%)	2(4%)	3(6%)	7 (14%)
Total	1(2%)	1(2%)	9(18%)	18(36%)	21(42%)	50(100%)

P value for different grades of response = 0.062

P value for different grades of response according to the duration of lesions = 0.084

As shown in table (8), the overall number of patients who achieved significant to excellent response 47 (94%). The response rate after 4 weeks and 8 week were compared to each other and the difference in response for different grades was statistically significant. P-value=0.001 (Table 7).

Table 7: Response rate of patients with plane wart to adapaline after 4and 8 weeks of treatment

Grade	4 weeks	8 weeks
0 (No response)	6 (12%)	2 (4%)
1 (Mild response)	13 (26%)	0 (0%)
2 (Moderate response)	21 (42%)	1 (2%)
3 (Significant response)	6 (12%)	20 (40%)
4 (Excellent response)	4 (8%)	27 (54%)
Total	50 (100%)	50 (100%)

P value=0.001\*

#### 4.7 Side Effects

The side effects of treatment were also recorded after 8 weeks. Forty two patients (82%) experienced adverse effects to treatment but these were tolerable and did not necessitate stopping the treatment in any patient (Table 8).

Table 8:Side effects related to treatment after 8 weeks

Side effects	No. of patients
Erythema	29(58%)
Scaling	27(54%)
Burning	15 (30%)
Itching	6 (12%)
Dyspigmentation	5(10%)



Figure 1: a) 12 years old female patient with plane wart before treatment, b) 12 years old female patient with plane wart after 4 weeks of treatment



Figure 2: a) 5 years old female patient with plane wart before treatment with adapalene 0.1%, b) 5 years old female patient with plane wart after 8 weeks of treatment with adapalene 0.1%





Figure 3: a) 7 years old female with plane wart before treatment with adapaline 0.1%, b) 7 years old female with plane wart after 4 weeks treatment with adapaline 0.1%



Figure 4: a) 10 years old female with plane wart before treatment, b) 10 years old female with plane wart after 4 weeks treatment with adapaline 0.1%



Figure 4: c) 10 years old female with plane wart after 8 weeks treatment with adapalene 0.1%

## 5 Discussion

Warts are benign proliferation of skin and mucosa that result from infection with human papilloma virus (HPVs). Plane warts occur mostly in children and young adults. The course of papilloma virus infection varies considerably, some lesions grow rapidly, some persist without any change, and some regress spontaneously over several weeks while others regress over long period of time. There are many modalities of therapy, reflecting that none is uniformly effective or directly antiviral. Whatever method is used in the treatment of warts, there will be failures and recurrences [1].

Adapalene is a third-generation topical retinoid primarily used in the treatment of mild-moderate acne [13].

The present study aims to determine the efficacy and tolerability of topical adapalene gel 0.1% for treatment of plane warts. To the best of our knowledge, there was no previous reported work that used Adapalene gel for the treatment of plane warts.

In present study most of our patients were children and adolescents, this age distribution is comparable to that's mentioned in the literatures. In all patients included in this study, the warts were located on the face, dorsum of hands, forearm and legs.

The mechanism by which adapalene gel is supposed to act is mostly related to its keratolytic effect that leads to destruction of virus infected cells and also probably attributed to its irritating effect that induce inflammatory response and immune reactions, so causing resolution of warts [14].

It has been shown that patients with smaller number of warts responded better to adapalene gel than patients with larger number after 4 weeks (36% showed moderate to excellent response in patients with less than 10 lesions compared to 26% for those with more than 10 lesions) which may be attributed to the relatively better immunity in this group in comparison with those with larger number of warts where the immunity is suspected to be suppressed or could be due to better use of the treating substance for the

smaller number of warts. The results were significant after 4 weeks as indicated by p value 0.015 which indicate the response in general and P-value of 0.031 which indicate response according to wart number. The results were also significant after 8 weeks as indicated by P-value 0.014 which indicate response in general, but it was not significant according to wart number as indicated by P-value of 0.235. This might be attributed to the decreasing number of wart after 4 weeks treatment.

In addition, we noticed that the response to treatment is inversely proportionate to the duration of lesions. The shorter the duration (less than 4 month) ,the better the response (38% showed moderate to excellent response compared to 22% for those more than 4 months) after 4 weeks. The same figure was noticed after 8 weeks (58% for those less than 4 months vs.38% for those more than 4 months) .this might be attributed to the fact longer the duration associated with more wart number. The results were significant after 4 weeks as indicated by p value 0.025 which indicate the response in general and P-value of 0.003 which indicate response according to duration of lesions. The response rate after 8weeks did not reach the level of significance as indicated by P-value 0.062 which indicate the response in general. Similarly, the response rate after 8 weeks according to the duration of lesion was insignificant P-value of 0.084. This might be attributed to that the duration of lesions is relatively an unchanging value unlike the wart number which is decreasing during treatment.

Various studies investigate different modalities of topical treatment in plane warts. Rodriguez found that the use of glycolic acid 15% in combination with salicylic acid 2% give 100% clearance of plane warts after 8 weeks [15]. Kubeyinje reported that 84.6% clearance was noticed after 12 weeks with tretinoin cream [16]. Salk used 5-FU cream for 12 weeks with 95% clearance [17].

This study also showed that topical adapalene gel 0.1% is an effective treatment of plane warts as it induced significant to excellent cure rate of 94% after 8 weeks treatment. The results are comparable to the above mentioned studies but taking in consideration the shorter duration of treatment and less side effects.

Regarding the side effect, previous studies showed that the patients using topical adapalene gel for the treatment of acne vulgaris developed different side effects, which included erythema, scaling, burning sensation , dyspigmentation and itching [12, 18]. These side effects also noted in our work but non of our patient found it disturbing to quit the treatment.

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