

## Evaluation of Topical Hydrogen Peroxide 30% versus Topical Zinc Sulphate 10% in Treatment of Plane Warts: Clinical and Dermoscopic Study

Eman Elsayed Abulnaser Abd Allah\*, Mohammed Fawzy EL-Kamel, Abeer Mohamed Abdelaziz Elkholy

Department of Dermatology, Andrology and STDs, Kafr Elsheikh Hospital, Egypt

\*Corresponding author: Eman Elsayed Abulnaser Abd Allah, Mobile:(+20) 0109 974 5960, Email: dremansayed9@gmail.com

### ABSTRACT

**Background:** Plane warts are caused by infection with human papilloma virus (HPV). Lesion usually presented as 2-4 mm flat topped papules, which are slightly erythematous or brown on pale skin and hypopigmented on darker skin. Many modalities of treatment were used, but none is uniformly effective.

**Objectives:** To assess the efficacy and safety of topical hydrogen peroxide (HP) 30% versus topical zinc sulphate (ZnSO<sub>4</sub>) 10% in plane warts treatment.

**Patients and Methods:** This is a parallel-group clinical study conducted on 64 patients divided into two groups; H<sub>2</sub>O<sub>2</sub> group (n=32) and ZnSO<sub>4</sub> group (n=32). Patients were evaluated clinically and by the dermoscope at the end of two, four and six weeks.

**Results:** H<sub>2</sub>O<sub>2</sub> group showed complete response (CR) in 81.3% of cases, while zinc sulphate group revealed CR in 34.4% of cases. There was a statistically significant higher proportion of “disappearance of dotted vessels and reddish gray / pale background plus appearance of normal skin markings” in H<sub>2</sub>O<sub>2</sub> group vs. zinc sulphate group. There was a statistically significantly higher ratio of CR among those with facial lesions who received treatment by hydrogen peroxide.

**Conclusion:** In the context of plane warts, hydrogen peroxide (30%) seemed to be an effective therapeutic modality with a higher satisfaction rate compared to 10% ZnSO<sub>4</sub> with minimal complications.

**Keywords:** Plane warts, Hydrogen peroxide, Zinc sulphate, Dermoscopy.

### INTRODUCTION

Warts are benign proliferation of skin, which caused by infection with human papilloma virus (HPV), which are DNA viruses that replicate inside the nucleus. The possibility increases during school years, after that drops significantly until the age of twenty, and more gradually thereafter. HPV infections are classified into clinical, subclinical, and latent <sup>(1)</sup>.

Of note, plane warts are caused by HPV type 3 and 10 and mainly affect children and teenagers as well. Plane warts could be detected as multiple small flat-topped skin-colored papules situated most frequently on the face, hands, and shins. Plane warts are self-limited and often resolved within four weeks, in particular when inflammation occurs or they may remain for a prolonged period to be resolved <sup>(2,3)</sup>. Their dermoscopic distinctive feature is multiple small red dots with regular distribution on a light brown background, which correspond to small vessels in the papillary dermis <sup>(4)</sup>.

A lot of therapeutic options were planned to manage plane wart management, however, none of them are equally effective, these involves salicylic acid, imiquimod, 5-fluorouracil, isotretinoin gel <sup>(5)</sup>, and oral zinc sulfate <sup>(6)</sup>. Topical zinc sulphate 10% was confirmed as an efficient and safe therapy in the context of plane wart management <sup>(7)</sup>. HP is formed in the body as a short-lived product in a lot of biological processes. It has been considered as one of the reactive oxygen species (ROS), and it has been demonstrated to be associated with antiviral, antifungal antibacterial activities. HP was previously tried successfully as a topical agent in the context of molluscum contagiosum (MC) <sup>(8)</sup>.

There are supportive evidences for the efficiency and safety of topical HP 45% as a promising agent in common warts. The adverse event of such uses are minor and mainly include pain on administration and irritation to regions of administration <sup>(9)</sup>.

This study aimed to evaluate efficacy of topical HP 30% twice weekly versus topical ZnSO<sub>4</sub> 10% three times per day in treatment of plane warts by clinical and dermoscopic signs.

### PATIENTS AND METHODS

This is a parallel-group clinical study conducted in outpatient clinic of dermatology, Mansoura University Hospitals, Mansoura, Egypt on 64 cases with plane warts who were haphazardly distributed, based on the therapeutic plan, into two groups; group 1 (32 cases); received treatment with topical H<sub>2</sub>O<sub>2</sub> 30% and group 2 (32 cases); received treatment with topical zinc sulphate 10%.

#### Inclusion criteria

Cooperative cases, with plane warts whose age was  $\geq 8$  years old of both genders who had never received any previous treatment for plane wart, were comprised in the current study.

#### Exclusion criteria

The current study excluded pregnant and lactating females, cases with severe systemic illness or malignancy or patients with illusive disorder or unrealistic expectations.

**METHODS**

All patients were subjected to complete history taking, which included personal history (name, age, gender, occupation, residence), history of the present illness and history of medications: nature, route, dose, compliance, duration, effect and side effects. Thorough general examination was performed to exclude any systemic diseases. Dermatological examination was also conducted to assess the number, site, size of warts (measured using ruler).

Group A (H<sub>2</sub>O<sub>2</sub> treated group) cases received topical H<sub>2</sub>O<sub>2</sub> 30% that was applied on the plane wart 2 times per week by doctor at the clinic for 6 weeks or complete clearance (which ever earlier). Wooden sticks were used to apply the solution. A layer was applied to each wart and allowed to dry for 2 minutes and the procedure was repeated 2 or 3 times till the appearance of white frost or bubbling or the patient felt a stinging sensation. No local anesthesia was used before the treatment.

Group B (ZnSO<sub>4</sub> treated group) cases received topical ZnSO<sub>4</sub> 10% that was applied 3 times per day by the patient for 6 weeks. The patients were supplied with 10% ZnSO<sub>4</sub> solution (Ten grams ZnSO<sub>4</sub> in 100 ml of distilled H<sub>2</sub>O) and informed to apply it to the warts by using a cotton swab at home three times per day.

Clinical assessment and follow up was done, which included assessment of wart size and number. Photographic pictures were taken before, during and after treatment. Digital photographs were taken by utilizing i phone 7+.

Dermoscopic examination was done using DermLite3 (3Gen, USA), which revealed multiple densely packed papillae comprising central red dots or loops and are surrounded by a whitish halo. Haemorrhages represent potential features, which appeared as irregular distribution of minor red to black tiny dots/streaks <sup>(10)</sup>. Absence of the previous features and the appearance of normal skin marks indicate cure.

At each visit, the degree of response for each lesion was noted and patients were asked about side effects. After completion of protocol, clinical cure was detected by the degree of resolution from the first visit. The response was noted in both groups at all visits and a successive clinical photographic and dermoscopic record were maintained. CR was considered when disappearance of the wart(s) and appearance of normal skin, partial response was considered when 50-99% reduction in size or number and poor response was considered when 0-49% reduction in size or numbers <sup>(11)</sup>.

Following end of the therapeutic visits, the satisfaction degree was assessed by a grading score, in which zero: not satisfied, I: partially satisfied, II: completely satisfied.

**Ethical approval:**

The study design was approved by the Ethical Committee (code number: MS.20.03.106), Mansoura Faculty of Medicine. Confidentiality and personal privacy were respected. Patients had the right to withdraw at any time. Collected data weren't used for any other purposes. A written informed consent was acquired from all adult participants and guardians of child participants prior to their participation in the study. The Helsinki Declaration was followed throughout the study's conduct.

**Statistical Methods**

The gathered data were analysed by utilizing SPSS 27.0 (IBM/SPSS Inc., Chicago, IL, USA). We used 2 kinds of statistical tests; descriptive statistics that comprised estimates for summarizing the continuous data as mean, standard deviation (SD), and range. Frequency with percentage (%) was utilized in terms of qualitative data. Analytical statistics (Chi-square ( $\chi^2$ ) test and Fisher exact test) were utilized for comparison between qualitative variable and independent t-test was used to compare quantitative variable. In all applied tests, the P-values < 0.05 were considered statistically significant.

**RESULTS**

This study involved 64 patients divided into two groups; H<sub>2</sub>O<sub>2</sub> group: 32 patients and zinc sulphate group: 32 patients.

Table (1) shows no statistically significant difference in age and sex in H<sub>2</sub>O<sub>2</sub> group vs. zinc sulphate group.

**Table (1): Sex and age distribution in the two groups:**

Characteristic	H <sub>2</sub> O <sub>2</sub> group N=32	Zinc sulphate group N=32	p-value
<b>Sex</b>			0.313
<b>Male</b>	20 (62.5%)	16 (50%)	
<b>Female</b>	12 (37.5%)	16 (50%)	
<b>Age (years)</b>	18.4 ± 6.1	16.5 ± 7.3	0.253
<b>Range</b>	9 – 30	9 – 33	

Notes: Sex data are N (%) and age data are mean ± SD.

Table (2) shows a statistically significant difference in Physician Global Assessment (PGA) at 2-, 4-, and 6-weeks between the two groups. At 2-weeks, partial response was higher in H<sub>2</sub>O<sub>2</sub> group while poor response was higher in zinc sulphate group. At 4-weeks, complete and partial responses were higher in H<sub>2</sub>O<sub>2</sub> group while poor response was higher in zinc sulphate group. At 6-weeks, complete response was higher in H<sub>2</sub>O<sub>2</sub> group while poor response was higher in zinc sulphate group and there was no difference in partial response.

**Table (2):** Physician Global Assessment (PGA) regarding response to treatment in the two groups:

Timing	PGA	H <sub>2</sub> O <sub>2</sub> group N=32	Zinc sulphate group N=32	p-value
2-weeks	Partial response	22 (68.75%)	4 (12.5%)	<0.001
	Poor response	10 (31.25%)	28 (87.5%)	
	Complete response	11 (34.4%) a	2 (6.3%) b	
4-weeks	Partial response	18 (56.3%) a	10 (31.3%) b	<0.001
	Poor response	3 (9.4%) a	20 (62.5%) b	
	Complete response	26 (81.3%) a	11 (34.4%) b	
6-weeks	Partial response	4 (12.5%) a	6 (18.8%) a	<0.001
	Poor response	2 (6.3%) a	15 (46.9%) b	
	Complete response	26 (81.3%) a	11 (34.4%) b	

Notes: Data are N (%), Different letters = significant difference, while similar letters = non-significant difference.

Table (3) shows a statistically significant difference in PaGA at 6-weeks between the two groups. At 6-weeks, complete satisfaction was higher in H<sub>2</sub>O<sub>2</sub> group while non-satisfaction was higher in zinc sulphate group.

**Table (3):** Patient Global Assessment (PaGA) at 6-weeks regarding patients' satisfaction in the two groups

Timing	PaGA	H <sub>2</sub> O <sub>2</sub> group N=32	Zinc sulphate group N=32	p-value
6-weeks	Completely satisfied	25 (78.1%) a	9 (28.1%) b	<0.001 *
	Partially satisfied	5 (15.6%) a	5 (15.6%) a	
	Not satisfied	2 (6.3%) a	18 (56.3%) b	

Notes: Data are N (%), Different letters = significant difference, while similar letters = non-significant difference.

This table (4) shows a statistically significant difference in the frequency of different dermoscopic findings in zinc sulphate and H<sub>2</sub>O<sub>2</sub> groups.

**Table (4):** The dermoscopy findings in the two groups:

Dermoscopy findings	H <sub>2</sub> O <sub>2</sub> group N=32	Zinc sulphate group N=32	p-value
Not improved	3 (9.4%)	17 (53.1%)	<0.001
Disappearance of dotted vessels	1 (3.1%)	2 (6.3%)	
Disappearance of reddish gray / pale background	2 (6.3%)	4 (12.5%)	
Disappearance of dotted vessels and reddish gray / pale background	16 (50%)	8 (25%)	
Disappearance of dotted vessels and reddish gray / pale background plus appearance of normal skin markings	10 (31.3%)	1 (3.1%)	

Notes: Data are N (%)

Table (5) shows no statistically significant difference in pain score (the visual analogue scale) at 6-weeks between the two groups. There was no statistically significant difference in hyperpigmentation at 6-weeks between the two groups, and no statistically significant difference in erythema at 6-weeks between the two groups.

**Table (5):** Complications in the two groups at 6-weeks in the two groups:

Timing	Complication	H <sub>2</sub> O <sub>2</sub> group N=32	Zinc sulphate group N=32	p-value
6-weeks	Pain (VAS)			0.183
	No pain (0)	19 (59.4%)	24 (75%)	
	Mild pain (1-3)	13 (40.6%)	8 (25%)	
	Hyper-pigmentation	13 (40.6%)	6 (18.8%)	0.055
	Erythema	8 (25%)	6 (18.8%)	0.545

Notes: Data are N (%).

Table (6) shows no statistically significant difference between the four response categories as regard sex, age, site and number of warts at 6-weeks in H<sub>2</sub>O<sub>2</sub> group.

**Table (6):** Response of topical H<sub>2</sub>O<sub>2</sub> 30% according to sex, site, and number of lesions at 6-weeks:

Factor	Response			p-value
	Complete	Partial	Poor	
<b>Sex</b>				
Male	18 (69.2%)	1 (25%)	1 (50%)	0.299
Female	8 (30.8%)	3 (75%)	1 (50%)	
<b>Age</b>				
≤17 years	11 (42.3%)	2 (50%)	0 (0%)	0.639
>17 years	15 (57.7%)	2 (50%)	2 (100%)	
<b>Site</b>				
Face	22 (84.6%)	1 (25%)	2 (100%)	0.061
Dorsum of the hand	3 (11.5%)	3 (75%)	0 (0%)	
Scalp / Nape of neck	1 (3.8%)	0 (0%)	0 (0%)	
<b>Number of warts</b>				
<5	13 (50%)	4 (100%)	1 (50%)	0.139
≥5	13 (50%)	0(0%)	1 (50%)	

Notes: Data are N (%).

Table (7) shows no statistically significant difference between the four response categories as regards sex, age, site and number of warts at 6-weeks in zinc-sulphate group.

**Table (7):** Response of topical zinc sulphate 10% according to sex, site, and number of lesions at 6-weeks:

Factor	Response			p-value
	Complete	Partial	Poor	
<b>Sex</b>				
Male	3 (27.3%)	2 (33.3%)	11 (73.3%)	0.061
Female	8 (72.7%)	4 (66.7%)	4 (26.7%)	
<b>Age</b>				
≤17 years	8 (72.7%)	4 (66.7%)	7 (76.7 %)	0.461
>17 years	3 (27.3%)	2 (33.3%)	8 (53.3%)	
<b>Site</b>				
Face	11 (100%)	4 (66.7%)	12 (80%)	0.132
Dorsum of the hand	0 (0%)	2 (33.3%)	3 (20%)	
<b>Number of warts</b>				
<5	4 (36.4%)	2 (33.3%)	8 (53.3%)	0.644
≥5	7 (63.3%)	4 (66.7%)	7 (46.7%)	

Notes: Data are N (%).

## DISCUSSION

Among the currently known therapeutic options, finding a successful and safe warts therapy without relapses and adverse effects remains difficult. HP is formed in the body and has been demonstrated to be associated with antiviral, antifungal antibacterial activities <sup>(12)</sup>.

The aim of the current study was to assess efficacy of topical HP 30% twice weekly versus topical zinc sulphate 10% 3 times per day in treatment of plane

warts by clinical and dermoscopic signs. This study was conducted on a total of 64 patients with multiple plane warts who attended to Dermatology Outpatient Clinic of Mansoura University Hospitals. The patients were divided into two groups; H<sub>2</sub>O<sub>2</sub> group and zinc sulphate group, which comprised 32 patients for each. Of note, no preceding researches compared between the effect of H<sub>2</sub>O<sub>2</sub> and zinc sulphate in the context of wart treatment.

Regarding characteristics of lesions, there were no significant differences between both groups in terms of all characteristics. Face was the most frequent site, followed by dorsum of the hand then scalp. Regarding site of the lesion, **Nouh et al.** <sup>(13)</sup> used topical hydrogen peroxide 40% for treatment of plane warts. They have found that 21 (70%) was on face, four (13.3%) on upper limbs, one (3.3%) on leg, three (10%) on neck and 1 (3.3) on nose.

Regarding physician Global Assessment and Patient Global Assessment, the current study demonstrated that H<sub>2</sub>O<sub>2</sub> was accompanied by a significant increase in satisfaction in comparison with zinc sulphate. In our study, we found in group 1, those who were treated by topical H<sub>2</sub>O<sub>2</sub> 30% twice per week, that 26 (81.3%) cases had complete resolution, 4 (12.5%) had partial response, and 2 (6.3%) had poor response and 25 (78.1%) patients were completely satisfied, 5 (15.6%) were partially satisfied, and 2 (6.3%) were not satisfied. This came in the same line with **Nouh et al.** <sup>(13)</sup> who conducted their study on a total of 30 patients with plane wart. They used topical hydrogen peroxide 40% for four sessions for each lesion with 14-days interval and a three-month follow-up period after treatment completion to determine the recurrence rate. They have demonstrated that; complete clearance of plane warts was noticed following in 27 (90%), and there was no relapse after a three-month follow-up period. Also, **Mahran et al.** <sup>(12)</sup> demonstrated that after six weeks of management of non-genital warts by topical hydrogen peroxide, 46.6% of cases in group I treated by 6% H<sub>2</sub>O<sub>2</sub> had CR and 53.4% had partial response. In group II treated by 3% H<sub>2</sub>O<sub>2</sub>, 48.3% had CR, 10.3% had partial response, and 41.4% had no response. In addition, they revealed that following-up for three months after complete cure displayed no clinical indication of recurrence.

Since HP has been considered as one of the ROS, its antiviral effects against HPV are believed to be mediated by apoptosis (programmed of single cell death) and membrane lipid peroxidation. It is recommended that the cells activate the discharge of superoxide and HP by xanthine oxidase owing to the presence of virus in the cytoplasm. Increased ROS level stimulate apoptosis of the infected cells. In addition, HP diffuses into the nearby cells and induces apoptosis. As a result, the infected cell as well as its nearby cells are eliminated, as a result preventing the viral infection spread <sup>(12)</sup>.

Regarding physician Global Assessment and Patient Global Assessment, in the current study, we

found in group 2, those who were treated by topical zinc sulphate 10% three times daily, that only 11 (34.4%) cases had complete resolution, 6 (18.8%) had partial response, and 15 (46.9%) had poor response and 9 (28.1%) patients were completely satisfied, 5 (15.6%) were partially satisfied, and 18 (56.3%) were not satisfied. Likewise, in terms of topical zinc sulfate, **Butt** <sup>(14)</sup> has demonstrated that; in the context of clearance of warts, it was demonstrated that five percent of the cases revealed complete clearance of plane warts, on the other hand 95% of the them revealed partial clearance or even no changes. As a result, they concluded that; a considerable number of cases revealed partial clearance by the usage of 10% zinc sulphate solution, while a low number of cases had complete clearance owing to the drug in the specified period of study. Topical Zn application is demonstrated to induce localized irritation, that could as a result stimulate immune responses. On the other hand, it may be owing to Zn deficiency being substituted or to the immunomodulatory actions of Zn <sup>(15)</sup>.

Common warts could be managed with Zn, which has been demonstrated to be efficient in oral and topical applications without inducing major adverse events. ZnSO<sub>4</sub> was evaluated for its efficiency in viral warts management and demonstrated to be effective. ZnSO<sub>4</sub> solution was applied 3 times per day for four weeks to ten cases with warts in a pilot study. There was complete cure for 80% of the cases <sup>(16)</sup>.

Regarding the usage of the dermoscope, we used it in our study to check for the complete clearance of the plane warts after topical treatment by H<sub>2</sub>O<sub>2</sub> and ZnSO<sub>4</sub>. The current study demonstrated a statistically significant difference in “disappearance of dotted vessels and reddish gray / pale background plus appearance of normal skin markings” in H<sub>2</sub>O<sub>2</sub> group vs. zinc sulphate group. In H<sub>2</sub>O<sub>2</sub> group: there were 10 (31.3%) of lesions showed “disappearance of dotted vessels and reddish gray / pale background plus appearance of normal skin markings” and 3 (9.4%) of lesions showed no improvement. In zinc sulphate group: there were only 1 (3.1%) of lesions showed “disappearance of dotted vessels and reddish gray / pale background plus appearance of normal skin markings” and 17 (53.1%) of lesions demonstrated no improvement. Also, **Agarwal et al.** <sup>(17)</sup> used radiofrequency ablation in warts destruction and they found that commonest dermoscopic findings noticed were existence of papillae surrounding haloes (61.67%), vascularity (58.33%), interrupted dermal lines (51.67%), and brown coloured background (48.3%). Nine cases (15%) revealed partial excision of the wart that was picked up only on dermoscopy (not seen by naked eye). On follow up, at 6 months there were four relapses (6.67%).

With regard to complications, the current study demonstrated that; pain and erythema were significantly increased in hydrogen peroxide group compared to zinc sulphate, with usage of H<sub>2</sub>O<sub>2</sub> 13 (40.6%) had mild

burning pain and 8 (25%) had erythema while there was no significant difference regarding the remaining complications. Also, **Nouh et al.** <sup>(13)</sup> have displayed that as regards follow-up of their cases who were treated by topical H<sub>2</sub>O<sub>2</sub> 40%, erythema was presented in 24 (80%), burning sensation was presented in 28 (93.3%), hypopigmentation was presented in 13 (43.3%), and there was no hyperpigmentation, and no scar. **Schianchi et al.** <sup>(8)</sup> used hydrogen peroxide 1.8% every 12 hours daily under occlusion for three weeks for treatment of molluscum contagiosum in kids. The researchers recorded only a minimal burning sensation in a single child and minimal erythema in another one at the site of application, that didn't need to stop the treatment. Such consequences, in particular among children, approve the safety of hydrogen peroxide.

**Mahran et al.** <sup>(12)</sup> used various concentrations of HP (3% and 6%) and have demonstrated that there were no reported adverse events with exception of minimal hypopigmentation that was recorded in two cases in groups I and II.

Concerning response according to sex, age, site, and number of warts, the current study demonstrated that at 6 weeks, there was no statistically significant difference between the four response categories. **Nouh et al.** <sup>(13)</sup> who used topical H<sub>2</sub>O<sub>2</sub> 40% for treatment of plane warts found the 5-year rate of cure for warts was increased for boys (95%) vs (90%) matched-age girls, with no significant difference. In addition, **Butt** <sup>(14)</sup> who used topical ZnSO<sub>4</sub> 10% for treatment of plane warts found that among fifty eight cases in the age group of 18-28 years, none of them demonstrated complete cure. The percentages of clearance in age group (29-39) and age group (40-50) were 20% and zero % respectively. This demonstrates that cases within the age from 29 to 39 were associated with a higher clearance. Among 65 female patients, five cases revealed complete clearance. While among 35 male cases none of them revealed complete cure. This displayed that the complete cure was mostly in females. The five percent of cases showing complete clearance had warts on the face. Of note, warts located outside the face revealed no response in all cases. This may be explained by that female is more anxious about her lesions especially on the face and thus may be more adherent to her treatment.

Up to based our knowledge no researches about hydrogen peroxide and zinc sulphate as a comparison are available. Patients' compliance in terms of visits in particular following complete clearance was the main problem. Further studies on plane warts have to be conducted. Further studies have to be consisted with special focus to increase the follow-up period to six months to make sure about the recurrences. Utilization of hydrogen peroxide is an effective therapeutic modality for plane warts.

## CONCLUSION

In the context of plane warts, hydrogen peroxide (30%) seemed to be an effective therapeutic

modality with a higher satisfaction rate compared to 10% zinc sulphate with minimal complications.

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