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ORIGINAL ARTICLE

A randomized controlled study on the efficacy and safety of zinc oxide 20% ointment versus salicylic acid 15% + lactic acid 15% ointment in the treatment of patients with verruca vulgaris in a tertiary hospital

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ABSTRACT

BACKGROUND Verruca vulgaris are scaly, rough papules or nodules caused by the human papilloma virus.

OBJECTIVE To determine the efficacy and safety of topical zinc oxide ointment versus topical salicylic acid + lactic acid ointment as treatment among patients with verruca vulgaris.

METHODS This randomized, double-blind, 6-week study involved 29 patients with verruca vulgaris in a tertiary center who received zinc oxide 20% ointment or salicylic acid 15% + lactic acid 15% ointment applied daily and occluded with Leukoplast™ tape. Evaluation was done every two weeks.

RESULTS There was significant decrease in number of warts in the zinc oxide group (p=0.004), while it was not significant in the salicylic acid+lactic acid group (p=0.392). Comparison between the two groups was not significant (p>0.05). Both zinc oxide (P=0.000) and salicylic acid+lactic acid groups (P=0.025) had significant decrease in size of warts from baseline to 6th week of observation. No significant differences were observed between the two groups in terms of adverse events such as erythema (P>0.05), edema (P>0.05), tenderness (P>0.05), and scaling (P>0.05); however, itching was significantly higher at 4th week in the salicylic acid+lactic acid group B (16.7%). Among the zinc oxide group, 100% would recommend the treatment, while only 71.4% would recommend salicylic acid+lactic acid. The satisfaction levels of zinc oxide group were also statistically higher than salicylic acid+lactic acid group (p=0.000).

CONCLUSION Zinc oxide 20% ointment is a safe and effective option for the treatment of verruca vulgaris especially among patients that would prefer non-traumatic measures in the removal of their warts.

KEYWORDS Verruca vulgaris, zinc oxide, salicylic acid, lactic acid

INTRODUCTION

Verruca vulgaris or common warts are scaly, rough papules or nodules caused by the human papilloma virus (HPV) that occurs through inoculation of the virus into viable epidermis through breaks in the skin barrier.[1] The rough surface of the warts together with trauma causes inoculation of the wart into adjacent sites. These may occur singly, or grouped on the hands, fingers, feet, or elsewhere. Treatment usually causes physical and emotional discomfort, and depends on the extent and duration of lesions, and the patient's immunologic status and desire for therapy.[2,3] Even though warts have a natural course and are known to spontaneously clear, recurrences are common with almost all treatment modalities.[4] The rate of resolution is highly variable and is dependent on several factors, including host immunity, age, HPV type, and site of infection. According to Lipke, spontaneous clearance rates are said to be 23% at 2 months, 30% at 3 months, and 65-78% at 2 years.[5]

Currently, there is still no gold standard of therapy for verruca vulgaris. Various treatments are available, however none has clearly been proven superior. Physical destruction of infected cells include electrocautery, cryotherapy, curette, or laser treatment. Local caustic agents such as salicylic acid, lactic acid, and trichloroacetic acid have also been used. However, treatment associated with physical destruction not limited to the epidermis is associated with irritation, pain, post-treatment hyperpigmentation, hypopigmentation, and scarring.[5] Immunotherapy has also gained

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Conflict of interest
None

Source of funding
None

ground for treatment of common warts after reports of patients receiving intralesional therapy for treatment of recalcitrant warts showed promising results. It is hypothesized to make use of the immune system's capacity to mount a type 1 helper T cell-mediated delayed hypersensitivity response to various antigens, including HPV.[6] Over the years, these various destructive procedures which carry a risk of scarring and are painful have remained the only effective remedy. For this reason, effective treatments that are less traumatic to patients are a necessity.

Zinc, a divalent cation and an essential micronutrient, is known to modulate immune response through macrophage and neutrophil functions, natural killer cell/phagocytic activity, and various inflammatory cytokines, and has been used in the treatment of many dermatological disorders due to its immunomodulatory properties. Zinc affects multiple aspects of the immune system, from the barrier of the skin to gene regulation within lymphocytes, and could counteract viral infections by having an effect on the synthesis of cytokines.[7,8] In vitro, it induces IFN-α as well as IFN-γ, and can potentiate the antiviral action of IFN-α. In addition, clearance of viral infections requires cytotoxic T lymphocytes, which are highly dependent on zinc. Both its oral and topical form has been studied in the therapy of verruca vulgaris.[9]

Oral and topical zinc sulfate, as well as topical zinc oxide have been investigated as a safe and painless treatment for warts.[10-12]

This study aimed to determine the efficacy and safety of topical zinc oxide 20% ointment versus topical salicylic acid 15% + lactic acid 15% ointment as treatment among patients with verruca vulgaris.

Specifically, it aimed to determine and compare the improvement of verruca vulgaris lesions in both treatment groups through evaluation of the following:

1. The proportion of patients with complete clearance between both treatment groups
2. The proportion of patients with decrease in number and size (measurement in cm) of warts between both treatment groups
3. The grading of cutaneous adverse events (erythema, edema, itching, tenderness, scaling, and others) reported by the patient and/or observed by the investigator
4. Patient acceptability of the treatment through a survey of visual analog scale of patient satisfaction and likelihood of recommending the same treatment for family members and friends between both treatment groups

METHODOLOGY

STUDY DESIGN

This is a randomized, double-blind, controlled study conducted from July 2018 to September 2018 at the dermatology clinic of a tertiary hospital. This study was approved by the Institutional Review Board prior to commencement.

PATIENT SELECTION AND RECRUITMENT

Patients selected for this study were males and females, aged 13 to 60 years old, diagnosed with verruca vulgaris by the primary investigator.

Patients with known hypersensitivity to zinc, immunocompromised patients, those with more than five warts, and those already on treatment for warts were excluded from the study. Once assessed as suitable to participate, the nature of the study was explained to the patients using the information sheet and they were requested to sign the informed consent. Parents of those aged 13 to 17 years old were asked to sign the consent form as well.

RANDOMIZATION AND BLINDING

For allocation of participants, we used www.randomizer.org to generate the allocation sequence.

The randomization sequence generated was the following:

- Random digits set 1 (zinc oxide group) – 1 3 6 7 9 10 12 13 17 20 21 25 31 32 33
- Random digits set 2 (salicylic+lactic acid group) – 2 4 5 8 11 16 19 22 23 24 26 27 28 29 30

The allocation followed by giving the first patient admitted in the study zinc oxide while the second patient was given lactic+salicylic acid. The process continued as the treatment reached patient 33.

The zinc oxide 20% ointment, and the salicylic acid 15% + lactic acid 15% ointment given were in identical containers labeled as A and B to blind the patients and the primary investigator from seeing the treatment.

A research assistant randomly allocated the treatment to the patients. A convenience sampling was done by giving treatment to the first 33 patients enrolled in the study. These patients satisfied the inclusion criteria before admission into the study. Following the random numbers, sequence of patients who came in from the specified time-period were given treatment assigned to them.

INTERVENTION AND DATA COLLECTION

On the first visit, demographic profiles and the following baseline data were recorded: duration of disease, number of anatomic sites, anatomic sites, number of warts, measurement of warts (cm).

Photographs limited to the site of the lesions were taken using Olympus Model No. E-MS camera (macro mode setting). The lesions were also inspected using Dermlite II Pro dermatoscope for thrombosed capillaries within the lobules and loss of normal dermatoglyphics. Dermoscopic hallmark of verruca vulgaris consists of large dotted vessels. These dermoscopic features help the diagnosis of doubtful cases, e.g. irritated warts, or difficult localizations, e.g. subungual or periungual warts.[13]

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Patients were instructed to apply either the zinc oxide (Rash free™) 20% ointment (Group A) or the compounded lactic acid 15% + salicylic acid 15% (Group B) ointment acquired from BCP Dermatological Corporation on all their warts, occluded with Leukoplast™ tape twice a day. Patients were asked to rub the affected area with 4 to 5 strokes using a pumice stone prior to the evening application.

The following data were recorded at every follow-up visit, scheduled at 2nd, 4th, and 6th week from the beginning of treatment by the primary investigator:

1. Number of warts
2. Size of warts
3. Adverse effects (erythema, edema, itching, tenderness, scaling)

Every follow-up, photographs were also taken. Cure was assessed as resolution of the wart with return to normal skin markings, assessed by dermoscopy. At the end of the treatment period (6 weeks or upon cure), survey of visual analog scale of patient satisfaction and likelihood of recommending the same treatment for family members and friends between both treatment groups were obtained. Patients were instructed to contact the primary investigator immediately if any adverse events were experienced during the course of treatment.

ASSESSMENT

Primary efficacy end points were evaluated through the decrease in number and measurement of lesions at each follow-up visit until the end of treatment. Secondary efficacy end point included the survey of visual analog scale of patient satisfaction and likelihood of recommending the same treatment for family members and friends after treatment.

Safety end points were the comparison between the two treatment groups of the following parameters: Erythema, edema, itching, tenderness, scaling, and other adverse effects noted.

STATISTICAL CONSIDERATION AND DATA ANALYSIS

For sample size computation, the research used G*Power Software. The proportions used for sample size computation was based on the results of the reference study: "Topical zinc oxide vs. salicylic acid–lactic acid combination in the treatment of warts" by Khattar et al.[12] According to this, cure rate in patients treated with zinc oxide was statistically higher than those treated with salicylic acid-lactic acid. The error used was 0.05 at 95% confidence interval. A minimum sample size of 26 corresponds or 13 respondents per group, 81.48% actual power (power of analysis).

Frequency and percentages was used to report the sex distribution of patients as well as the location of warts investigated and the duration of disease. Mean and standard deviation was used to report the mean number of anatomic sites while median and range was used to report the average age of the patients.

Independent t-test was used to compare the zinc oxide group and lactic+salicylic acid on number of anatomic sites. Mann-Whitney U test was used to compare for the age and satisfaction, and Fishers exact test was used to compare the sex distribution and location of anatomic sites.

For the comparison of baseline to 6th week observations on number of warts, chi-square test for trend proportions was used. Z-test for proportions was used for comparison between Group A and B at each treatment week. For the comparison of baseline to 6th week observations on size of warts, analysis of variance was used, and Tukey test was used for post-hoc analysis. Chi-square test was used for comparison of treatment weeks on adverse events while z-test of proportion was used to compare zinc oxide group and lactic+salicylic acid group at each treatment weeks.

Chi-square was also used to compare the two groups on recommendation, and reason for recommendation.

Line graph was used to illustrate the comparison of baseline to 6th week observations on number of warts and size of warts while column graph was used to illustrate the comparison of zinc oxide group and lactic+salicylic acid group on satisfaction, recommendation, and reason for recommendation. Microsoft Excel and SPSS version 25.0 was used for data analysis. Null hypotheses were rejected at 0.05 level of significance

RESULTS

PATIENT DISPOSITION

A total of 33 patients were assessed for eligibility. Twenty-nine out of 33 patients completed the study. Four could no longer be contacted after baseline assessment. These patients were excluded in the data analysis and were treated as per protocol leaving unequal number of samples for zinc oxide and salicylic+lactic acid groups (Figure 1).

The computed power of analysis for 29 patients and its distribution (15 patients in Group A and 14 in Group B) has 83.72% power of analysis. This means that the sample size and the omitted samples do not have any significant effect with the overall power of the study.

DEMOGRAPHIC AND BASELINE CHARACTERISTICS

The median age of the patients included in the study was 23 years old (ranging from 13 to 60 years old), 79.3% have the disease for more than 6 months while only 20.7% have the disease for less than 6 months. The average number of anatomic sites was 1.24 ± 0.51 mostly located in the arm and palmoplantar area (31%) followed by legs and dorsal areas (27.6%).

The zinc oxide group had 15 patients (7 male, 8 female) with a mean age of 15 years old. The salicylic acid + lactic acid group had 14 patients (5 male, 9 female) with a mean age of 35 years old. There was no significant difference between zinc oxide and salicylic acid + lactic acid groups in terms of age ($p=0.275$), sex ($p=0.710$), duration of disease ($p=0.651$), number of anatomic sites ($p=0.665$) and location of anatomic sites ($p>0.05$). Therefore, profile distribution of both

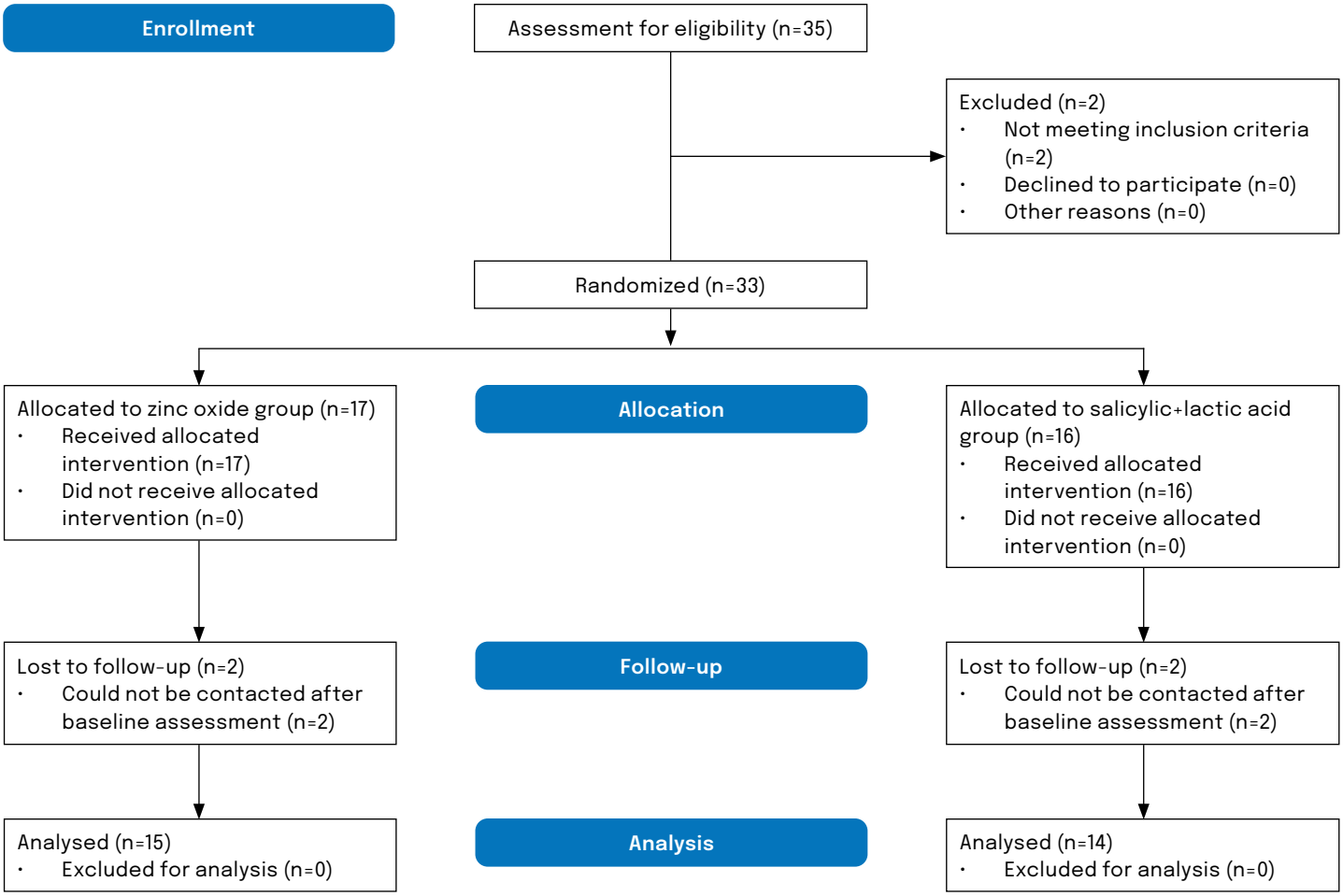

Figure 1. Participant flow

groups was statistically similar (Table 1).

EFFICACY AND SAFETY OUTCOMES

Among the 15 patients (7 males, 8 females) in the zinc oxide group, 2 patients had complete cure (100% decrease in number of warts) and 2 patients were partially cured with 50% improvement rate. In the salicylic + lactic acid group, 1 out of 14 patients (5 males, 9 females) achieved complete cure.

There was significant decrease in the number of warts of zinc oxide group with p-value of 0.049 while in the salicylic+lactic acid group, the decrease was not significant with p-value of 0.310. Comparison between the two groups, however was not significant with p-value above 0.05.

Significant results in the zinc oxide group were due to the decrease in number of warts on 4th and 6th weeks. The percentage of warts decreased to 84% at 4th week from the baseline then it went down to 80% at 6th week. On the other hand, no significant change was observed in the salicylic+lactic acid group from baseline to 6th week (Figure 2 and 3).

In terms of size, both zinc oxide (p=0.000) and salicylic+lactic acid groups (p=0.025) presented a significant improvement from baseline to 6th week of observation. The mean values showed that there was a significant decrease in the mean size of warts of the patients (Figure 4).

No significant differences were observed between both groups in adverse events such as erythema (p>0.05), edema (p>0.05), itching (p>0.05), tenderness (p>0.05), and scaling (p>0.05). Itching was significantly higher at 4th week on salicylic+lactic acid group (16.7%) but remained absent in the zinc oxide group (0%) until completion.

PATIENT ACCEPTABILITY OF TREATMENT

Among the zinc oxide group, 100% of patients would recommend the treatment, while only 71.4% will recommend salicylic+lactic acid. The model was significant in favor of zinc oxide group (p=0.042).

Among the zinc oxide group, 53.3% of patients cited that

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Table 1. Baseline characteristics of participants

	Zinc oxide group (n=15)	Salicylic+Lactic acid group (n=14)	p-value
Age (years)	15.0 (13 – 62)	32.5 (13 – 56)	0.275
Sex			
Male	7 (46.7%)	5 (35.7%)	0.710
Female	8 (53.3%)	9 (64.3%)	
Duration of disease			
<6 months	4 (26.7%)	2 (14.3%)	0.651
>6 months	11 (73.3%)	12 (85.7%)	
Number of anatomic sites	1.20 ± 0.41	1.29 ± 0.61	0.665
Location			
Neck	0 (0%)	0 (0%)	1.000
Trunk	0 (0%)	1 (7.1%)	0.483
Arms	3 (20%)	6 (42.9%)	0.245
Legs	3 (20%)	5 (35.7%)	0.427
Dorsal	5 (33.3%)	3 (21.4%)	0.682
Palmoplantar	6 (40%)	3 (21.4%)	0.427
Periungual	1 (6.7%)	0 (0%)	0.999

the reason they would recommend the treatment was because it was effective, while 28.6% of patients in the salicylic+lactic acid group said that they would not recommend it because the treatment did not give them as much effect than they expected.

The satisfaction levels of patients in the zinc oxide group were statistically higher than patients in the salicylic+lactic acid group with p-value of 0.000.

DISCUSSION

The primary treatment methods of warts are physical destruction such as electrocautery, cryotherapy, laser therapy.[14] However, these treatments are not suitable for patients with multiple lesions or those with fear of pain and scarring. Therefore, immune-modifying agents such as zinc may be a useful therapeutic alternative as they are painless and easy to apply. Zinc is said to counteract viral infections by its effect on the synthesis of cytokines such as IFN-α as well as IFN-γ. In addition, clearance of viral infections requires cytotoxic T lymphocytes, which are highly dependent on zinc. Both its oral and topical form has been studied in the therapy of verruca vulgaris.[15-17] In the study of Khattar, patients were instructed to apply the medication twice per day, wait for the medication to dry, and to rub the wart with an emery stone before the evening application. Rubbing the lesion daily with pumice stone was said to disrupt the keratinized surface, thus helping penetration of zinc oxide.[12] However, another concern would be that since the medication is topically applied to warts which are typically on exposed areas such as the

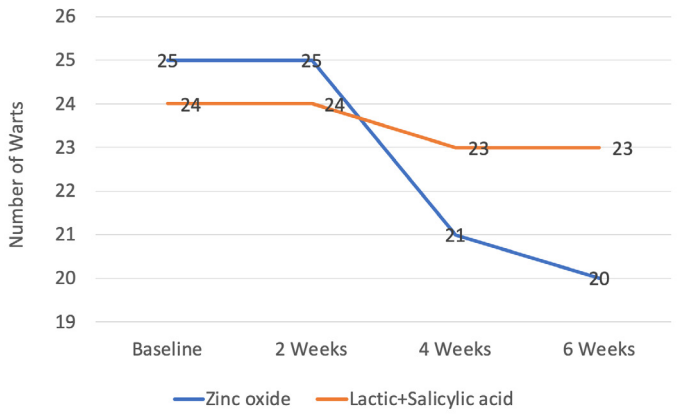

Figure 2. Number of warts between zinc oxide and salicylic acid+lactic acid at baseline and treatment weeks 2, 4, and 6.

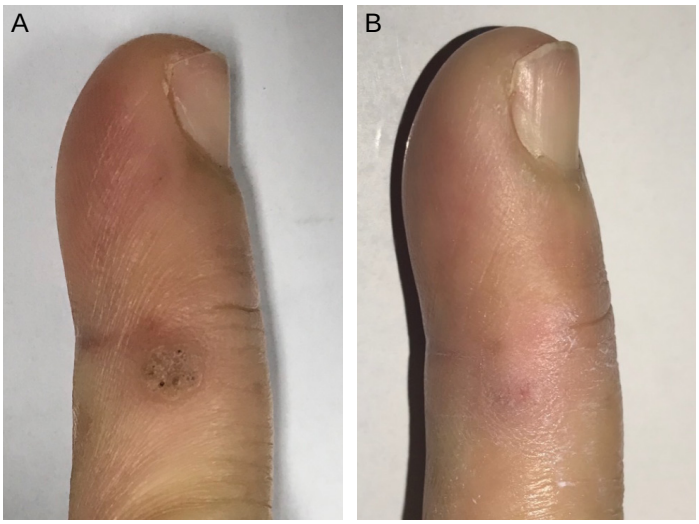

Figure 3. Wart on the finger. **A.** At baseline. **B.** Six weeks after zinc oxide application.

hands, it may be easily removed by daily activities of the patient. Occlusion by application of a durable and waterproof tape would therefore aid in penetration and keeping the topical medication in place. In the present study, topical zinc oxide was occluded by Leukoplast™ tape to aid in penetration and keeping the topical medication in place. Occlusion is covering the applied dose, either intentionally (e.g., bandaging) or unintentionally (e.g., putting on clothing) after applying a topical agent. Occlusion results in a combination of many physical factors that affect the skin and the applied compound by enhancing hydration and sometimes increasing skin temperature. It also prevents the accidental wiping or evaporation of the applied compound, ensuring a higher applied dose. This is a practical clinical method of enhancing cutaneous absorption.[18]

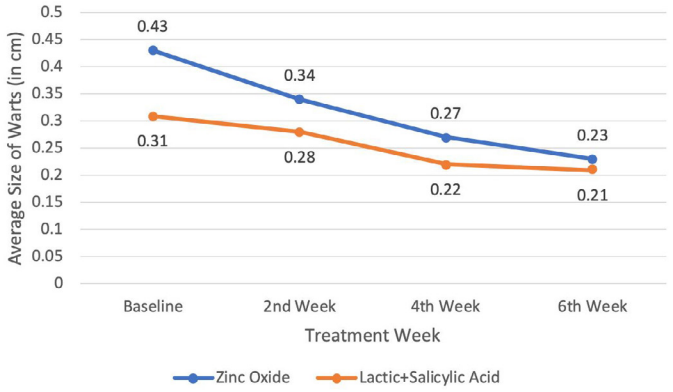

Figure 4. Average size of warts between salicylic acid+lactic acid at baseline and treatment weeks 2, 4, and 6.

This study showed a statistically significant decrease in the number of warts in the zinc oxide group compared to the salicylic+lactic acid group. The number of warts was noted to decrease at 4th and 6th week of observation. Clearance of warts was assessed clinically and using a dermatoscope, when there were no thrombosed capillaries visualized and also return of normal dermatoglyphics.

Decrease in size of warts was also higher in the zinc oxide group compared to salicylic+lactic acid group. The decrease in size of warts was noted at 2nd to 6th week of observation for respondents. The difference, however, was not statistically significant between the two groups. A longer follow-up period may be needed to show a statistically significant difference in decrease of size between the two groups.

In other studies using topical zinc oxide, there were minimal side effects noted such as erythema, swelling, scaling, and hyperpigmentation.[12] In studies using topical zinc sulphate, side effects included itching, pain, and post-inflammatory hypopigmentation.[11] In our study, no adverse effects were noted by the zinc oxide group until completion. Itching, however, was noted in some respondents in the salicylic+lactic acid group (16.7%). This was an expected finding, as salicylic acid and lactic acid are both caustic agents, which are known to cause irritation and itching.

At the end of the treatment period, 100% of patients in the zinc oxide group would recommend the treatment, while only 71.4% would recommend salicylic+lactic acid. The satisfaction levels of patients in the zinc oxide group were also statistically higher than patients in the salicylic+lactic acid group.

Among the zinc oxide group, patients cited that the reason they would recommend the treatment to family and friends was because treatment with zinc oxide ointment was effective, painless, easy to apply, and they noted decrease in size of their lesions. Most also didn't want to undergo traumatic measures to remove their warts. Among the respondents in the salicylic+lactic acid group that would recommend treatment, decrease in size of lesions and absence of pain were the main reasons. Among those in the salicylic+lactic acid group that said they would not recommend treatment, their reason was because the treatment did not give them as much effect than expected.

Our results further support that zinc oxide ointment, therefore, is a well-tolerated, painless and safe treatment option for verruca vulgaris.

Limitations of the study include the short observation period, as a longer period may document further reduction in number and measurement of warts, as well as recurrence of warts. The study also had a limited number of subjects, and the pediatric age group was not included.

CONCLUSION

Review of literature has shown that zinc can be utilized in the treatment of patients with verruca vulgaris as it targets many pathogenic factors involved in the disease. The results of this randomized controlled study show the efficacy of topical zinc oxide 20% ointment in the treatment of verruca vulgaris as well as its safety and tolerability. These data are valuable in future studies so that a safe and painless treatment option would be available for patients with verruca vulgaris. These endpoints can subsequently improve the overall quality of life of patients with verruca vulgaris.

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