

Effectiveness and safety of formalin 5% vs. combined salicylic acid 16.7% and lactic acid 16.7% in flexible collodion for common and plantar warts: a randomized clinical trial

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Background: Warts are among the most common skin diseases with various recommended treatments, including topical ablation, chemotherapy, and immunotherapy. However, given the unsatisfactory response rate, complications, and recurrence, effective treatment remains controversial. This study compared formalin against an anti-wart compound containing salicylic acid and lactic acid.

Methods: This clinical trial recruited 58 patients with wart lesions on hands and feet randomly divided into two groups of daily topical treatment: formalin 5% (n = 29) and anti-wart lotion containing salicylic acid 16.7% and lactic acid 16.7% in flexible collodion (n = 29) for eight weeks. Patient satisfaction and recovery were assessed and compared between the groups at weeks four and eight.

Results: Patient satisfaction did not change significantly in either group ($P > 0.05$), and no significant difference was observed between the groups ($P = 0.838$). The number of wart lesions fell significantly after eight weeks in both groups ($P < 0.001$), with no significant difference between them ($P = 0.225$). There was no significant difference between the two methods in terms of side effects ($P = 0.084$).

Conclusion: Both formalin and salicylic acid plus lactic acid lotion effectively treated plantar and common warts, and neither had any significant side effects. The treatment choice should be based on the patient's age, the number of lesions, and the site affected.

Keywords: warts, salicylic acid, lactic acid, formalin

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INTRODUCTION

Warts are a fairly common skin disease caused by human papillomavirus (HPV) ¹, which is a DNA virus that penetrates the top layers of the epidermis, leading to the proliferation of epithelial cells ². On average, this virus affects

7 to 10% of the population. HPV can affect any age group. However, it mostly occurs between the ages of 12-16 years, and it is most commonly found in females ^{3,4}. The ghastly appearance of the lesions can make people refrain from social activities ².

Warts are divided into genital and non-genital

groups. In terms of appearance, non-genital warts are divided into common, flat, periungual, plantar, and filiform variants⁵. Although it is generally easy and clinically possible to diagnose warts from their appearance, their treatment is unpleasant for both patients and dermatologists because they are resistant and highly recurrent⁵.

Many treatment modalities have so far been proposed for warts, including topical ablation (using acid, cryotherapy, and electric cautery), chemotherapy, and immunotherapy. Although the treatment choice depends on the age, treatment goal, treatment modality complications, and the lesion site, the search for treatments with negligible complications and desirable effectiveness has not yet concluded⁶.

One of the common treatments for warts is the application of salicylic acid at concentrations of 12%-26% in combination with lactic acid of the same concentration in flexible collodion^{3,7}. This combination is used for various common warts. The keratolytic effect of these acids helps reduce lesion thickness. Long-term treatment with this combination leads to recovery in 67% of palmar warts and 84% of plantar warts, but it is not recommended for genital and facial warts due to the scars it causes⁸. However, prolonged treatment, the risk of toxicity at high doses (especially in children), and the risk of facial and genital scarring are the disadvantages of this compound medication, leading physicians to prescribe it for only the plantar areas^{3,9}.

Formalin (formaldehyde), a disinfectant with reported effects on bacteria, fungi, and many viruses, is regarded as a virucidal treatment for warts. Formaldehyde thickens, whitens, and removes the top layer of the epidermis that contains the virus. On the other hand, the hardening of the epidermis facilitates shaving off the parts affected by lesions^{1,3}. Although this medication has long been considered for the treatment of warts, its mechanism remains unresolved¹⁰, and there is insufficient information about its effectiveness.

In light of the mentioned situation, the present study was conducted to compare formalin 5% and an anti-wart lotion containing salicylic acid and lactic acid in flexible collodion for the treatment of warts. The results can propose a new effective approach to the treatment of warts.

MATERIALS AND METHODS

Study population

The present clinical trial recruited 60 patients with wart lesions on the hands and feet referred to the Dermatology Clinic of Imam Khomeini Hospital of Ahwaz between July 2019 and March 2020. The study proposal was first approved by the Ethics Committee of Ahvaz Jundishapur University of Medical Sciences (Code: IR.AJUMS.REC.1398.287) and Iran's International Clinical Trial Registration Center (Code: IRCT 20200530047603N1). Then, the study protocol was explained to the participating patients, who were reassured of the confidentiality of data and provided written informed consent.

Patients diagnosed with palmoplantar and common warts entered the study. History of allergy to formaldehyde, immunodeficiency, severe dermatitis, diabetes, pregnancy or breastfeeding, history of respiratory diseases (e.g., asthma), receiving any treatment for warts (ablative, chemical, traditional like garlic extract, and virucidal medication methods), and use of immunosuppressive medications (e.g., systemic corticosteroids), any severe systemic diseases (chronic obstructive pulmonary disease, hepatic failure, renal failure, peripheral vascular disorder, or peripheral neuropathy), concomitant skin disease at the site of treatment (e.g., lichen planus, psoriasis, and eczema), and inability to use topical medications due to young age or mental disorders were considered as exclusion criteria. Furthermore, those who did not comply, were not present for clinical follow-ups, or needed other treatments were excluded. The patients entered the study through convenience sampling and were divided into two treatment groups (formalin vs. anti-wart lotion) through randomized four-stage blocking.

Treatment intervention

Formaldehyde solution 5%

The patients soaked the affected site in a 3-5 cm deep vessel containing formalin 5% (Barad Chemical Company-Iran) twice daily for 15-20 minutes. When the warts were not close to each other and difficult to soak, a formalin-soaked cotton ball was placed on the wart site and kept in place by a plaster band or tape. Vaseline was

used between daily treatments to moisturize the treatment site.

Anti-wart lotion containing salicylic acid 16.7% and lactic acid 16.7% in flexible collodion

This group of patients applied vaseline to the normal skin around the warts, brushed the anti-wart lotion against warts twice daily, and applied a plaster band or tape to the site for 20 minutes.

Both groups were advised to soak the site in warm water for five minutes and scrape off the dead and hyperkeratotic tissue using a pumice stone if a large amount of hyperkeratotic tissue was developed. Topical treatment continued for eight weeks twice daily in both groups. Vaseline was used to reduce skin dryness in the intervals between treatments if necessary. Photographs of the patients' lesions were taken in their first and last visits.

The dermatologist monitored patients' adherence to treatment by phone twice per week.

Assessment variables

The demographic details, including age, ethnicity, disease duration, and the number, type, and site of warts, were recorded in the study checklist.

The patients were examined at the start of the study and then every four weeks during the intervention. In addition, they were called 12 weeks after the intervention to attend for assessment of recurrence.

The patients reported their lowest and highest satisfaction in both groups by giving a score between zero and ten on a visual analog scale (VAS). A VAS score of 0 was taken as no satisfaction, 1-3 as poor satisfaction, 4-6 as moderate, 7-9 as good, and 10 as total satisfaction.

Treatment response was assessed clinically by a dermatologist in the form of the number of warts and patient satisfaction. The number of lesions was counted in each visit and recorded in the checklist. Then, changes in these numbers were assessed. Treatment response was categorized according to the reduced percentage of warts as no (0%), poor (1% to 33%), moderate (34% to 66%), good (67% to 99%), or complete response (100%).

Any treatment complications, including dryness,

cracking, burning, skin darkening, erythema, pain, and scaling, were also recorded in the checklist.

Statistical analysis

Data were analyzed in SPSS-23. Descriptive variables were reported as mean, standard deviation, absolute frequency, and frequency percentage. Univariate data were analyzed using the independent t-test (or Mann-Whitney), chi-squared (or Fisher's exact) test, and Pearson's correlation coefficient (or Spearman's), while tri-variate data were assessed using the Kruskal-Wallis test. The effect of treatment groups over time was evaluated and compared using the repeated measures test. $P < 0.05$ was taken as significant.

RESULTS

A total of 60 patients with common and palmoplantar warts were assessed, of whom one from the formalin group was excluded due to medication intolerance and coughs, and one from the salicylic acid and lactic acid lotion group was excluded because of acute renal failure (irrelevant to the use of anti-wart lotion) and use of immunosuppressive drugs (Figure 1). The remaining patients included 41 women (70.7%) and 17 men (29.3%), with a mean age of 24.1 ± 12.65 years (range: 3-54 years), of whom 29 (50%) had palmoplantar warts, and 29 had common warts. The warts were on the hands in 31 patients (53.4%) and on the feet in 27 patients (46.6%). The patients' demographic details are presented in Table 1.

The mean age was 21.48 years (range: 4-54) in the formalin 5% group and 26.72 years (range: 3-54) in the salicylic acid and lactic acid lotion group ($P = 0.116$). Table 1 shows no significant difference between the two groups in terms of gender distribution, age, number of warts, type of warts, site of warts, and disease duration ($P > 0.05$).

Although the response to treatment according to the decrease of wart numbers in both groups was not significantly related to sex, race, disease duration, or number, type, and location of warts, in the formalin group, there was a significant inverse relationship between age and response to treatment since the response to treatment decreased with age (Table 2).

Table 3 shows the satisfaction rate of the two

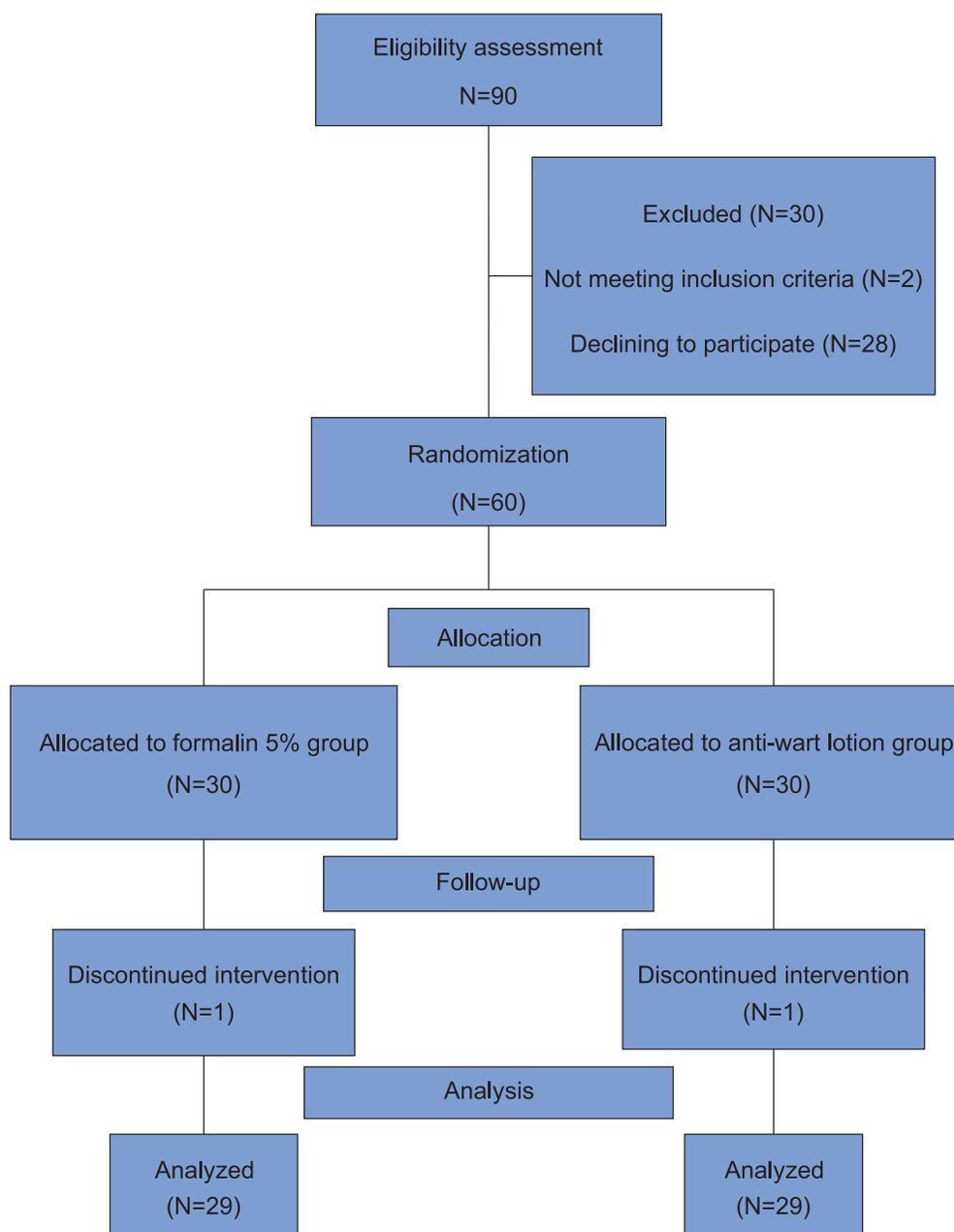


Figure 1. Consort diagram of the study population

groups of patients with treatment. No significant difference was observed in the patient's satisfaction rates between four and eight weeks after intervention in the formalin 5% group ($P = 0.079$) or the salicylic acid and lactic acid lotion group ($P = 0.056$). No significant difference was observed between the treatment methods four weeks after intervention ($P = 0.418$) or eight weeks after ($P = 0.757$). In

general, the two treatment methods showed no significant difference ($P = 0.838$).

The patients' treatment response to each medication is detailed in Table 4, indicating a significant decrease in the number of lesions over time in both groups ($P < 0.001$). Also, comparing the two groups at each interval ($P > 0.05$) and in general ($P = 0.225$) showed no significant difference

Table 1. Comparison of demographic characteristics between the study groups

Variables	Formalin 5%	Salicylic acid 16.7% and lactic acid 16.7%	P
	N (%)		
Gender, n (%)			
Male	9 (31.04)	8 (27.59)	0.773
Female	20 (68.96)	21 (72.41)	
Age, mean \pm standard deviation	21.7 \pm 12.37	26.3 \pm 12.83	0.116
Number of warts, mean \pm standard deviation	11.24 \pm 13.15	7.28 \pm 11.96	0.235
Type of warts, n (%)			
Palmoplantar	13 (44.8)	16 (55.2)	0.431
Common wart	16 (55.2)	13 (44.8)	
Wart location, n (%)			
Hand	16 (55.2%)	15 (51.7%)	0.792
Foot	13 (44.8%)	14 (48.3%)	
Race, n (%)			
Arab	12 (41.37)	12 (41.4)	0.852
Bakhtiari	7 (24.13)	8 (27.6)	
Fars	10 (34.48)	9 (31.0)	
Disease duration (days)			
Minimum	7	7	0.258
Maximum	1290	1140	

Table 2. The relationship between different variables and treatment response at the end of intervention (8th week) in each group

	Formalin 5% group (P-value)	Salicylic acid 16.7% and lactic acid 16.7% lotion group (P-value)
Wart location	0.812	0.682
Wart type	0.351	0.449
Age	0.045	0.162
Gender	0.448	0.141
Disease duration	0.752	0.262
Race	0.485	0.264
Number of warts	0.843	0.866

between them. Figure 2 shows the trend of changes in the numbers of lesions in the two groups.

Eight patients (27.58%) in the formalin 5% group

and seven (24.13%) in the other group responded to treatment in less than one month. In the formalin group, complete response to treatment (destruction of all lesions) was observed after one week in one patient (3.44%) and after two weeks in two patients (6.89%). Generally, three patients (10.34%) in the formalin group and seven patients (24.13%) in the salicylic acid and lactic acid lotion group showed no response to treatment at all. All lesions completely disappeared in 11 patients of the formalin group (37.93%) and seven patients of the salicylic acid and lactic acid lotion group (24.13%) (Figure 3).

In terms of side effects, dryness was the most common formalin-induced side effect (79.31%), while burning was the main complaint in the salicylic acid and lactic acid lotion group (48.27%).

Table 3. Comparison of two groups' satisfaction (according to VAS scores of 0 to 10)

Variable	4 weeks after	8 weeks after	P-value	P-value
Treatment with formalin 5%	6.28 \pm 2.631	7.00 \pm 2.988	0.079	0.838
Treatment with salicylic acid 16.7% and lactic acid 16.7%	6.86 \pm 2.850	7.48 \pm 2.935		
P-value	0.418	0.757		

Table 4. The two groups' response in each assessment (number of warts)

Variable	Baseline	4 weeks after	8 weeks after	P-value	P-value
Treatment with formalin 5%	13.149 \pm 11.24	9.014 \pm 7.03	7.35 \pm 3.90	<0.001	0.225
Treatment with salicylic acid 16.7% and lactic acid 16.7%	11.961 \pm 7.28	8.878 \pm 5.59	7.125 \pm 2.76		
P-value	0.077	0.376	0.178		

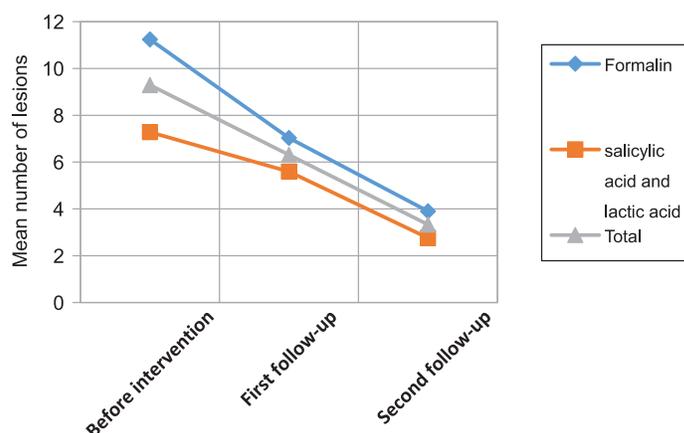


Figure 2. Mean number of wart lesions at each assessment point in the two groups

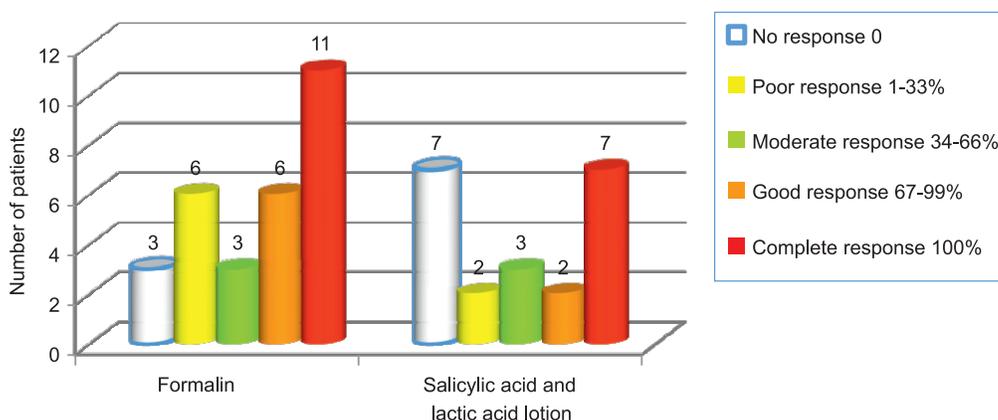


Figure 3. Patients' response to each treatment approach based on reduction in the number of lesions

Comparing the two treatment groups showed no significant difference in side effects ($P = 0.084$) (Table 5).

Recurrence occurred in two patients (6.89%) from the formalin group, while in the other group, only one patient (3.44%) experienced recurrence ($P = 0.553$). All recurrences occurred after the end of an eight-weeks course of treatment.

DISCUSSION

Various modalities are used to treat warts, but none has proven entirely successful alone. Furthermore, no treatment modality has shown complete recovery with no recurrence in any patients, which justifies the use of various methods³. Despite the spontaneous recovery of warts, one of

Table 5. Comparison of side effects in two groups

Side effect	Treatment with formalin 5%	Treatment with salicylic acid 16.7% and lactic acid 16.7%	P-value	P-value Number of side effects
	N (%)			
Dryness	23 (79.31)	0 (0)	<0.001	
Cracking	7 (24.13)	0 (0)	0.01	
Burning	3 (10.34)	14 (48.27)	0.002	
Skin darkening	10 (34.48)	3 (10.34)	0.038	0.084
Erythema	0 (0)	7 (24.13)	0.001	
Pain	3 (10.24)	0 (0)	0.633	
Scaling	1 (3.4)	0 (0)	0.548	

patients' main concerns is to prevent the spread of the virus to other parts and infect other members of the family, especially children ⁷.

The present study showed that despite favorable response to treatment with both formalin 5% versus salicylic acid 16.7% and lactic acid 16.7% lotion, no significant difference was observed in treatment response between groups according to the reduction in the number of warts. Assessment of patient satisfaction showed no significant difference between formalin 5% and the anti-wart lotion. In addition, we observed a positive trend in the reduction of the number of warts by time in both groups. Nevertheless, a remarkable finding of this study was the dramatic response of eight (27.5%) and seven (24.3%) cases in the formalin and lotion-treated patients within less than a month, respectively. Besides, all lesions improved in a formalin-treated four-year-old boy within only a week and in two other patients by the second week of treatment.

While the most common side effects were dryness (79.31%) in the formalin group and burning in the anti-wart lotion group (48.27%), side effects were generally negligible and showed no significant difference between the groups. Recurrence occurred after 12 weeks in only 3.44% of the patients treated with anti-wart lotion and 6.89% treated with formalin 5%. Although some studies have reported no recurrence, others have reported high recurrence rates with both salicylic acid and formalin ^{11,12}.

According to a review of literature, our study is the first to compare the effects of an anti-wart lotion containing salicylic acid and lactic acid against formalin 5%. Other studies have mainly assessed each of these compounds individually or in combination with other treatment methods. McKnight *et al.* reported that formalin 5% produced a 90.3% recovery from plantar warts over three months and that topical treatment can be as effective as invasive surgery under anesthesia ¹². In a study on flat warts, Mapar *et al.* compared twice-daily use of formalin 5% with a placebo over two months and stated that while 83.3% of patients responded to treatment with formalin 5%, a complete response was observed in only 11.1% of patients. Given that no serious side effects were reported, they recommended formalin 5% as a suitable medication with minor side effects

for treating flat warts. They also reported a better treatment response in women than men ¹¹, which may have occurred due to the difference in the location of warts. Such a difference was not found in the present study.

A study conducted by Ahmad in 2018 compared the effects of formalin 10% twice daily with cryotherapy every two weeks over three months. The patients were followed up three months after treatment. Both treatments produced significant clinical, histopathological, and hybridization results by the end of the study, with no significant difference between them. The researchers concluded that given its lower cost and no need for several lengthy follow-ups, formalin is preferred to cryotherapy, especially in extensive affected areas ¹³. In a study conducted in the US in 2006, Jennings *et al.* compared monochloroacetic acid plus formalin 10% with formalin 10% alone in the treatment of plantar warts over eight weeks and found no significant difference between them, thereby proposing formaldehyde as a suitable option for treatment of plantar warts ¹⁴. However, they used higher doses of formaldehyde compared to the present study, and further studies on higher doses of formaldehyde are recommended.

Salicylic acid is one of the best-known medications for treating warts, and many studies have assessed its efficiency over its long history of usage ¹⁵⁻¹⁷. Generally, because of its keratolytic property, salicylic acid destroys epidermal layers, and the pain it causes may be due to stimulation and response of the immune system, which may help remove warts ^{18,19}. While comparing salicylic acid and cryotherapy showed that both had the same effect, salicylic acid is sometimes preferred due to its fewer side effects. However, further studies are required to determine the optimum duration and dose of salicylic acid for adequate treatment response with minimum side effects ^{20,21}.

Many similar studies have recently focused on the concurrent use of salicylic acid and lactic acid because lactic acid reinforces the keratolytic properties of salicylic acid. Niazi *et al.* compared lactic acid 15% plus salicylic acid 15% against zinc oxide 20%, which were applied twice a day for three months, after which the follow-up period was three months. In agreement with the present study, their results confirmed the effectiveness of the combination of salicylic acid plus lactic acid, such

that over 60% of patients responded to treatment, and this response rate was obtained at lower doses than that of the present study. Moreover, comparing these two compounds showed the superiority of salicylic acid plus lactic acid over zinc oxide²². In another study, Handijani *et al.* compared formic acid 85% with combined salicylic acid and lactic acid at similar doses with those of the present study for one month. After two weeks of follow-up, they reported a complete response in 74.1% and relative response in 3.5% of patients treated with formic acid, which was significantly greater than the treatment response in the other group²³.

In a study by Anderson and Shirreffs in 1963 on 193 patients with plantar warts treated with formalin 3%, the treatment response rate reduced with aging¹, which agrees with the present study results showing that treatment response reduced with aging only in the formalin group. This result may be due to the effect of age and environmental factors on the skin and requires further studies on the effect of formalin in the treatment of warts in children. The limitation of the present study is its short treatment course and small sample size. Therefore, further studies with larger sample sizes and longer follow-up periods are recommended.

CONCLUSION

The results showed that topical formalin 5% could be as effective as an anti-wart lotion containing 16.7% salicylic acid and 16.7% lactic acid in treating common and palmoplantar warts. Formalin 5% can be used as a good alternative in patients unwilling to undergo cryotherapy or those who do not respond to one of the most common topical anti-wart lotions (containing salicylic acid and lactic acid). Given the higher treatment response in younger patients in the formalin group, concerns about the risk of systemic toxicity in higher concentrations of salicylic acid in children, and children's fear of ablative treatments, formalin can be a suitable option for the treatment of warts in children.

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