Comparison of the efficacy of topical 85% formic acid versus a combination of topical salicylic acid and lactic acid in the treatment of warts: A randomized, triple-blind, controlled trial

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Background: Wart is a common skin disease that can occur at any age. While they are usually benign and self-limited, they can become irritating and cosmetically disabling to patients. The objective of this study is to compare the effectiveness of a topical 85% formic acid preparation with a combination of topical salicylic acid and lactic acid.

Methods: We enrolled 66 patients, 7-60 years of age, in this triple-blind study. Patients were randomly divided into 2 groups: group 1 received a topical 85% formic acid solution and group 2 received DuoFilm (topical 16.7% salicylic acid + 16.7% lactic acid). The duration of treatment was a maximum of 4 weeks and we followed the patients every two weeks.

Results: In group 1, 74.1% of the warts completely healed and 3.5% partially healed. In group 2 complete healing occurred in 40.8% and partial healing in 26.8% of the warts ($P<0.001$). Statistical analysis showed a significant difference in the favor of formic acid on the hands ($P<0.001$) but we did not observe a better effect for the feet. The time to complete healing was less for the majority of patients in the formic acid group (1 week versus 4 weeks). There were minimal adverse effects in each group, none that necessitated cessation of treatment.

Conclusion: Topical formic acid had a higher cure rate for warts compared with a conventional preparation that consisted of both topical salicylic acid and lactic acid. This effect was particularly noted on the hands. This topical remedy could be regarded as an alternative to conventional treatments in the management of warts.

Keywords: wart, treatment, formic acid, clinical trial

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INTRODUCTION

Warts are a common skin manifestation caused by the human papilloma virus (HPV) that occur in any age group, particularly during childhood and adolescence [1,2]. Although they are benign and self-limited lesions, they can affect a patient`s quality of life and have the potential to change to malignant, resistant lesions over time, especially in immune compromised hosts [2-4]. Warts can spread widely by autoinoculation [5]. Therefore, early treatment is important and recommended in order to prevent dissemination of the lesions [6]. The most widely used treatments for warts are topical

applications of salicylic acid, 5-fluorouracil, silver nitrate solution, and dinitrochlorobenzene, as well as the use of intra-lesional bleomycin, cryotherapy, and systemic retinoids. However, none have been shown to cause complete healing and normal skin formation in all cases [7-9].

Salicylic acid is an inexpensive, highly available topical drug for wart treatment [8]. According to research, the effectiveness of topical salicylic acid is comparable with cryotherapy. However the necessity for its prolonged application, along with the associated pain and irritation are limiting factors for its use [1,10]. The use of salicylic acid is sometimes associated with scar formation as well as systemic toxicity in children [4,8,11]. The mechanism of action seems to be through immune system activation and/or mechanical destruction of the warts [12,13].

Formic acid is another topical agent that has been used to treat warts. It seems to be safe, relatively effective and not as painful, hence it can be regarded as an appropriate treatment modality for children [14,15]. It has been shown to be less effective than cryotherapy in the treatment of warts [14]. The mechanism of its action is not clear. Some researchers have suggested that its metabolite, formaldehyde, is responsible for this effect [16]. Others believe that formic acid itself stimulates the dehydration pathway that can destroy the lesion [16,17].

The available data for the level of effectiveness of formic acid in the treatment of warts is not conclusive and to our knowledge its effectiveness in comparison to common therapies such as salicylic acid has not been fully investigated. Therefore, we conducted this trial in order to assess the efficacy of topical 85% formic acid compared to a conventional topical remedy that consisted of a combination of topical 16.7% salicylic acid and 16.7% lactic acid.

PATIENTS AND METHODS

This triple-blind study enrolled 66 patients, 7-60 years of age, who referred to Shahid Faghihi Dermatology Clinic, Shiraz, Southern Iran with a diagnosis of common skin warts (with involvement of any part of the body except for the face, plantar, and genital areas). Patients received no previous treatment for their warts for at least one month prior to referral. We excluded individuals with any type of systemic disease or immune suppression as well as pregnant females. In addition, patients who had more than 10 warts or warts bigger than 0.5 cm^2 were also excluded. The Ethics Committee of Shiraz University of Medical Sciences approved this study and the patients signed an informed consent form prior to initiation of the trial. The informed consents of patients younger than legal age (18 years) were obtained from their legal executors.

We randomly divided the patients into 2 groups of 33 patients per group. The allocation ratio was 1:1 by simple randomization. The random sequence list was manually generated by the table of random numbers and concealment by recruiting sequentially numbered opaque sealed envelopes (SNOSE). One group received a topical 85% formic acid solution (group 1) whereas the other group (group 2) received DuoFilm (topical 16.7% salicylic acid + 16.7% lactic acid; Stiefel Laboratories, Coral Gables, FL, USA). The 85% formic acid solution was prepared locally by the composition of formic acid (Merck®, Germany) and collodion (Merck®, Germany) at the School of Pharmacy of Shiraz University of Medical Sciences. Each patient received a 30 cc container of 85% formic acid.

The patients received detailed instructions. In addition, they were instructed to stop the medication if complete healing of the warts occurred. Patients were asked to apply petrolatum around the warts in order to prevent contamination of intact skin with the medication, followed by the application of either formic acid using a cotton-tipped swab or the DuoFilm solution using a thin brush. Because of the similarity in the shape of containers and method of consumption, both patients and care providers were blinded to the treatment assignment. The solutions were applied once per day for a maximum of 4 weeks. A dermatologist (outcome assessor) blinded to the treatment assignment examined the patients at 2 weeks post-treatment and at the end of the treatment course (after 4 weeks). We defined "partial cure" as shrinkage of the wart(s) and "complete cure" as complete disappearance of the wart(s). "No cure" was defined as no change in the wart(s).

We used SPSS statistical software (SPSS for Windows, version 16.0., SPSS, Inc., Chicago, IL, USA) to compare the results between the groups. In addition, the chi- square and gamma tests

were used for data analysis. A *P*-value ≤0.05 was considered statistically significant.

RESULTS

All 66 patients from both groups completed their specific interventions at the 4-week period and were assessed. There were 85 (71 on the hands and 14 on the feet) total warts treated with formic acid; 71 warts were treated with DuoFilm (60 on the hands and 11 on the feet).

In group 1 that received formic acid, 74.1% of the warts completely healed. Of the warts that completely healed, 77.5% were located on the hands and 57.1% on the feet. In group 2 that received DuoFilm, 40.8% of the warts completely healed. Of the warts that completely healed, 40% were located on the hands and 45.5% on the feet. We observed partial cure in 4.3% of warts on the hands in the formic acid group (group 1) while there was no partial change in foot lesions. However, 25% of the warts on the hands and 36.4% on the feet showed partial healing in the DuoFilm-treated group (Table 1). In the majority of cases that healed, the time to complete healing in the formic acid group (1 week) was much shorter than in the DuoFilm treated group (4 weeks).

Based on chi-square and gamma statistical analyses, the efficacy of formic acid in the treatment of warts on the hands was significantly higher than in the DuoFilm treated group (*P*<0.001). However, for the feet, this finding was not statistically significant. If we did not consider the treatment region we observed that formic acid was more effective compared to DuoFilm (*P*<0.001).

In the formic acid treated group, two patients developed secondary infection characterized by erythema and a pus-like discharge. We did not observe this adverse-effect in group 2. However, this difference was not statistically significant (*P*>0.05). In both cases, the secondary infection was relieved by topical mupirocin. Application of formic acid was associated with deep pain and a burning sensation which lasted for about 30 minutes. Hyperpigmentation at the site of treatment was another finding on the hands, but not the feet. In the DuoFilm treated group, the treatment was associated with some irritation, but no hyperpigmentation.

DISCUSSION

Warts are among the most common skin conditions, especially in children. Warts are viral, benign, self-limited lesions which can be irritating and embarrassing due to the lack of a suitable, effective treatment [18]. Many treatments have been suggested in order to hasten the healing process as well as lessen scar formation that may follow, however the choice of the best treatment is still a challenge for physicians.

One of the treatments suggested for warts is the use of kearolytics. Salicylic acid with its keratolytic property can cause destruction to the epidermal layer [16,19,20]. In addition, the pain caused by this medication seems to stimulate the immune system which can be helpful for wart removal [16]. According to a Cochrane review, topical salicylic acid alongside cryotherapy is a safe, effective treatment for warts [21]. However, Bacelieri and Johnsson have not totally supported this finding and criticized the methodology of that review. Nevertheless, this author has agreed that salicylic acid is one of the most effective drugs for treatment of warts, especially non-genital ones [2]. A review by Kwok *el al.* has reported that in most instances, salicylic acid is a safer, more effective therapy than cryotherapy with less pain and scar formation [8]. Dall'Oglio *et al*. have shown that the combination of cryotherapy and salicylic acid leads to higher rate of cure and should be considered one of the first choices for the treatment of warts [5]. However, another study by Bedinghaus and Niedfeldt demonstrated no significant differences between

Table 1. Treatment outcomes using topical formic acid 85% and DuoFilm for warts.

Location	Formic acid group			DuoFilm group			*P*
	Complete cure*	Partial cure†	No cure	Complete cure	Partial cure	No cure	
Hands	55 (77.5%)	3 (4.3%)	13 (18.3%)	24 (40%)	15 (25%)	21 (35%)	<0.001
Feet	8 (57.1%)	0 (0%)	6 (42.9%)	5 (45.5%)	4 (36.4%)	2 (18.1%)	>0.05
Total	63 (74.1%)	3 (3.5%)	19 (22.4%)	29 (40.8%)	19 (26.8%)	23 (32.4%)	<0.001

*Completely disappeared after the 4-week treatment. †Reduced in size but did not disappear after the 4-week treatment.

salicylic acid, cryotherapy, or the combination of both in the treatment of hand warts [22]. Rodriguez-Cerdeira and Sanchez-Blanco stated that glycolic acid plus salicylic acid could be considered a good choice as first line treatment of warts due to its high cure rate and decreased adverse effects [23].

Formic acid is a relatively new treatment for warts. There are an insufficient number of studies about its efficacy, however most studies to date introduce formic acid as a safe, effective topical addition to the current treatments available for warts [14,24,25]. Bhat *et al*. have shown that formic acid is a safe, economical drug with a significant cure rate compared to placebo. Their study used the puncture technique to administer formic acid, which was safe, inexpensive, and resulted in a complete cure rate of 93% [25]. In another study, Yoon *et al*. compared cryotherapy with formic acid and concluded that cryotherapy was more effective than formic acid [14]. Others suggested that formic acid was stronger than salicylic acid [15,25].

In this study we observed that topical formic acid had a higher cure rate compared to DuoFilm in the treatment of warts, particularly on the hands. According to the data, we have suggested that topical formic acid can be considered an effective, economical drug for the treatment of warts, especially since it is readily available and does not need specific equipment to administer.

Although post-inflammatory hyperpigmentation as well as a burning sensation and pain were among the adverse effects, the transient nature of these effects alongside a more vigorous patient-education session on self-administration of this medication could be helpful for its wider use by patients. Decreasing the formic acid concentration might be of benefit. However this suggestion should be investigated in order to determine efficacy at lower concentrations. The time to healing in the majority of patients was within 1 week, hence, this could be regarded as an advantage in treatment of children who have lower compliance and decreased cooperation.

One of our study limitations was the maximum time which we assessed the outcome because partially cured warts might heal if the intervention were continued. Hence, a study with a longer follow up time would be recommended. Another limitation was the gelatinization of the formic acid solution which we observed when patients did not refrigerate or properly seal the solution. We have investigated the efficacy of our proposed treatment on hands and feet. The next studies should consider other areas of the body. Despite the positive findings in this study that favor the use of topical formic acid as treatment of warts, more studies are still needed to determine the exact mechanism of action, the most suitable method of administration, and ways to minimize adverse effects.

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