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RESEARCH ARTICLE

An open, comparative clinical study on the efficacy and safety of 10% trichloroacetic acid, 25% trichloroacetic acid and cryotherapy for verruca plana

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Abstract

Objective: Although there are several methods to treat Verruca plana, warts do not respond well to the common therapeutic options. In this study, we compared the safety and efficacy of 10% trichloroacetic acid, 25% trichloroacetic acid, and cryotherapy for the treatment of warts caused by Verruca plana.

Methods: Ten percent and 25% trichloroacetic acid were applied to warts weekly until all lesions cleared. Cryotherapy was performed by liquid nitrogen spray for 5–10 seconds for each lesion per week until the lesions cleared. The number of Verruca plana lesions and adverse effects were evaluated five times during the treatment (the initial visit, week 2, week 4, week 6, and week 8).

Results: The number of lesions decreased through week 8 for all three treatments, and the reductions in the mean numbers of lesions were statistically similar ($p > 0.05$). Those in the cryotherapy group exhibited more erythema, pain, erosions, bullae, and hyperpigmentation ($p < 0.001$, $p < 0.001$, $p < 0.001$, $p < 0.05$, and $p = 0.001$, respectively) than those in either TCA group. Itching was more common among those in the trichloroacetic acid groups than in the cryotherapy group ($p < 0.05$). Additionally, hyperpigmentation, erythema, pain, and itching were more frequent in the 25% trichloroacetic acid group than in the 10% trichloroacetic acid group ($p < 0.001$), ($p < 0.05$), ($p < 0.05$), ($p < 0.05$).

Conclusion: Ten percent trichloroacetic acid, 25% trichloroacetic acid, and cryotherapy are effective methods to treat Verruca plana. 10% trichloroacetic acid offers a safer and easier treatment than either 25% trichloroacetic acid or cryotherapy.

Keywords

Cryotherapy, trichloroacetic acid, Verruca plana

History

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Introduction

Verruca plana (VP) is a common, benign viral infection of the skin caused by human papilloma virus[1] (HPV) types 3 and 10. VP often occurs on the face as flat, slightly raised, skin-colored or coffee-colored papules. VP warts are usually numerous and may appear in a line because of autoinoculation. VP may induce cosmetic and social problems and effective treatments are limited despite the existence of a variety of treatment methods. Conventional treatments for VP include cryosurgery, electrocautery, topical agents such as cantharidin, podophyllin, tretinoin, salicylic acid, imiquimod, and laser surgery[2]. All methods are associated with pain, post-inflammatory pigmentation, and recurrence of infection. Factors that influence selection of treatment include the size, number, and location of the wart(s), participant preference, cost, convenience, adverse effects, and provider experience with the treatment.

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Cryotherapy is a commonly used treatment because of its short preparation time, low-risk of infection, and low cost. Cryotherapy destroys warts by thermal-induced cytolysis. Use of cryotherapy in children is restricted because they cannot tolerate pain and recalcitrant warts often persist despite the repeated treatments. Post-inflammatory pigment alterations and scarring are other common side effects of cryotherapy.

Trichloroacetic acid (TCA) and monochloroacetic acid are caustic agents that destroy warts by chemical coagulation of proteins. Although these preparations are widely used, they have not been investigated thoroughly. TCA can spread rapidly if applied in excess; therefore, it can damage healthy tissues. TCA must be applied to the wart only and allowed to dry until a white frost develops at the site of the wart. The purpose of this study was to compare the efficacy and safety of 10% TCA, 25% TCA, and cryotherapy in the treatment of VP.

Materials and methods

This prospective, comparative, randomized, multi-center, clinical trial was conducted to evaluate the safety and efficacy

of TCA for treatment of VP. Eighty-five participants with VP seen at the dermatology outpatient clinics of our hospitals between April 2013 and October 2013 were enrolled in this study. The study was approved by the Local Ethics Committee and signed informed consent was obtained from participants and parents of the participants if a child was younger than 18 years old.

The exclusion criteria were immunosuppression, pregnancy, breastfeeding, secondary infection, receiving systemic treatments within the previous six months or topical treatments within the previous two weeks. Patients with a minimum of five lesions who were willing to return for follow-up visits were included. For each participant, age, sex, site of lesion, disease duration, and color of lesion were recorded. Clinical examination was performed for all participants. The diagnosis of VP was confirmed by dermatological examination. Of 85 participants, 30 participants were randomly assigned to the 10% TCA group, 30 were assigned to the 25% TCA group, and the others were assigned to the cryotherapy group (25).

Ten grams of TCA crystals was dissolved in 100 ml of distilled water (weight-plus-volume) to prepare a 10% TCA solution. Twenty-five grams of TCA crystals was dissolved in 100 ml of distilled water to prepare a 25% TCA solution. For group A, 10% TCA was applied only to the warts by a physician once a week and allowed to dry. The participants were advised not to wash the TCA off for four hours after application. For group B, 25% TCA was applied only to the warts by a physician once a week and allowed to dry and the participants were advised not to wash the TCA off for four hours after application. For group C, cryotherapy was performed by a physician using liquid nitrogen spray for 5–10 seconds applied to each lesion each week. Patients were evaluated at the first visit and at the end of week 2, week 4, week 6, and week 8. The number of lesions was recorded and lesions were photographed at each visit. At week 8, local adverse events such as erythema, itching, pain, vesicles/bullae and pigmentary alterations were assessed.

SPSS 15.0 (SPSS Inc., Chicago, IL) was used in the statistical analysis with a statistical significance of $p < 0.05$. The Kruskal–Wallis test was used to compare the efficacies of the three treatment methods, and the Friedman test was used to compare the number of lesions found each week.

Results

Of 85 participants, 80 completed the clinical trial after being assigned to one of three treatment groups. Twenty-eight participants were in the 10% TCA treatment group, 27 were in the 25% TCA treatment group, and 25 were in the cryotherapy treatment group. The mean age of participants was 16.68 ± 7.42 years (ranging from 2 years to 58 years). The mean ages of participants in the 10% TCA group, 25% TCA group, and cryotherapy groups were 10.35, 14.10, and 12.10 years, respectively.

There were no significant differences in age or sex among participants in the three groups. The duration of disease varied from one month to 24 months (mean: 10.6). The number of lesions ranged from 5 to 33 in the 10% TCA group (mean: 10.8), six to 51 in the 25% TCA group (mean: 11.7), and five to 25 in the cryotherapy group (mean: 12.2). Of the 80 participants, 64 had VP lesions on the face, 13 had VP lesions on the dorsum of the hand, and three had VP lesions on the genitals. Before they were enrolled in the trial, 34 participants had been treated with topical retinoids while 19 participants had been advised to ''wait and see'', and, the number of lesions was increased in that group relative to the treated participant group. The remaining participants underwent dermatological examination for the first time.

We observed total remission of lesions in 24 (85.7%) of 28 participants treated with 10% TCA. Of these 24 participants, two were cleared of lesions by two weeks (initial lesion count: 5, 8), eight were cleared of lesions by 4 weeks (initial lesion count: 5, 6, 6, 8, 9, 10, 10, 11), ten were cleared of lesions by six weeks (initial lesion count: 7, 7, 8, 11, 12, 12, 15, 15, 15, 16), and four were cleared of lesions by eight weeks (initial lesion count: 11, 10, 22, 23). However, four participants showed no response to treatment until week 8. Eighteen of 28 participants had skin-colored lesions and ten participants had coffee-colored lesions. Fewer skin-colored lesions than coffee-colored lesions remained at the end of week 8 ($p < 0.01$).

Among those treated with 25% TCA, 25 (92.6%) of 27 participants were cleared of lesions: six participants were cleared of lesions by two weeks (initial lesion count: 6, 8, 9, 9, 9, 11), 13 were cleared of lesions by four weeks (initial lesion count: 6, 6, 7, 7, 7, 9, 9, 9 12, 12, 14, 16, 18), three were cleared of lesions by six weeks (initial lesion count: 8, 20, 23), and three were cleared of lesions by eight weeks (initial lesion count: 10, 11, 31). One participant showed partial remission by week 8 and one participant showed no response until week 8. Fifteen of 27 participants had skin-colored lesions and 12 participants had coffee-colored lesions. Fewer lesions remained at the end of week 8 among those with skin-colored lesions than among those with coffee-colored lesions ($p < 0.05$).

After eight weeks of cryotherapy, there was complete clearance of lesions in 23 (92%) of 25 participants: seven participants were cleared of lesions by two weeks (initial lesion count: 8, 8, 10, 11, 11, 12, 12), 13 were cleared of lesions by four weeks (5, 6, 10, 11, 13, 13, 13, 15, 17, 18, 19, 20, 21), two were cleared of lesions by six weeks (initial lesion count: 5, 14), and one was cleared of lesions by eight weeks (initial lesion count: 13). Two participants had a partial response to cryotherapy by week 8. Thirteen of the 25 participants had skin-colored lesions and 12 had coffee-colored lesions. There were fewer lesions at the end of week 8 among those with skin-colored lesions than among those with the coffee-colored lesions ($p < 0.05$).

Among the three treatment groups, the mean number of lesions decreased throughout the eight weeks of the clinical trial (Table 1, Figure 1). The reductions in the number of lesions at the end of week 2, week 4, week 6, and week 8 were statistically significant ($p < 0.05$) ($p < 0.05$) ($p < 0.01$) ($p < 0.001$). The differences in the numbers of lesions among the three groups at week 2, week 4, week 6, and week 8 were not statistically significant ($p > 0.05$) ($p > 0.05$) ($p > 0.05$) ($p > 0.05$) (Table 1).

All the treatments were tolerated without any systemic adverse effects. The most common local symptoms due to

Table 1. Comparision of the number of lesions between treatment groups.

	Number of lesions (Mean ± SD)			
	10% TCA	25% TCA	Cryotherapy	*p* Value
Week 0	10.82 ± 6.84	11.70 ± 11.27	12.28 ± 5.57	0.813
Week 2	6.28 ± 5.89	7.22 ± 6.84	8.52 ± 4.04	0.373
Week 4	3.97 ± 3.10	4.37 ± 3.35	5.56 ± 3.01	0.053
Week 6	2.74 ± 1.32	2.04 ± 1.77	3.08 ± 2.36	0.058
Week 8	1.34 ± 0.46	1.69 ± 0.44	1.87 ± 1.00	0.392

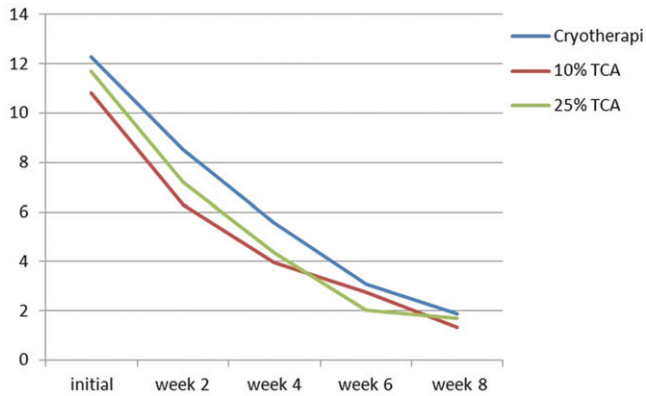

Figure 1. A graph showing number of lesions at different weeks between group A, group B and group C patients.

cryotherapy included pain during treatment in 24 (96%), erythema in 18 (72%), itching in seven (28%), erosions in 14 (56%), and bullae in three participants (12%). The most frequent local side effect of TCA was itching during application in 14 participants (50%) of the 10% TCA group and in 21 participants (77.8%) of the 25% TCA group. Pain was observed in one participant (3.6%) of the 10% TCA group and in seven participants (25.9%) of the 25% TCA group. Erythema occurred in two participants (7.1%) of the 10% TCA group and in ten participants (37%) of the 25% TCA group (Table 2).

At week 8, hyperpigmentation developed in three participants (10.7%) in the 10% TCA group, in 13 participants (48.1%) in the 25% TCA group, and in 16 participants (64%) in the cryotherapy group. Erythema, pain during treatment, erosions, and development of bullae were significantly higher in the cryotherapy group than in the 10% TCA group or the 25% TCA group ($p<0.001$), ($p<0.001$), ($p<0.001$), ($p<0.05$). Hyperpigmentation was more common in the cryotherapy group than in the 10% TCA group or 25% TCA group ($p=0.001$). Itching was more common in the TCA treatment groups than in the cryotherapy group ($p<0.05$). Additionally, hyperpigmentation, erythema, pain during treatment, and itching were more frequent in the 25% TCA group than in the 10% TCA group ($p<0.001$), ($p<0.05$), ($p<0.05$), ($p<0.05$). Hyperpigmentation disappeared four to seven months after the clinical trial in all participants of the 10% TCA group and the 25% TCA group. Persistent hyperpigmentation occurred in two participants (8%) of the cryotherapy group. There were fewer lesions at the end of week 8 among those with skin-colored lesions than among those with the coffee-colored lesions ($p<0.05$). Skin-colored lesions were more responsive to either TCA or cryotherapy treatments than coffee-colored lesions. Response to treatment did not differ by participant gender, location of the warts and duration of the disease ($p>0.05$) ($p>0.05$) ($p>0.05$). In addition, there were no significant differences in the response to the treatments among participants in the retinoid therapy taken group and ''wait and see'' group ($p>0.05$). Among the 23 participants in the cryotherapy group, relapse occurred in two (8.6%) participants after seven months, while no relapse occurred among participants in either of the TCA treatment groups.

Table 2. Comparison of adverse effects seen in treatment groups.

	10% TCA	25% TCA	Cryotherapy	*p* Value
Painful Sensation	1 (3.6%)	7 (25.9%)	24 (96%)	$p<0.001$
Erythema	2 (7.1%)	10 (37%)	18 (72%)	$p<0.001$
Itching	14 (50%)	21 (77.8%)	7 (28%)	$p<0.05$
Erosions	–	–	14 (56%)	$p<0.001$
Bulla	–	–	3 (12%)	$p<0.05$
Hyperpigmentation	3 (10.7%)	13 (48.1%)	16 (64%)	$p=0.001$

Discussion

Methods to treat VP include cryotherapy, electrocautery, topical agents such as cantharidin, podophyllin, tretinoin, salicylic acid, or imiquimod, and laser surgery. Liquid nitrogen is the most commonly used cryogen for cryotherapy. Development of ice during cryotherapy causes irreversible tissue damage. Inflammation occurs within 24 hours after cryotherapy, which causes separation of the dermis and epidermis. The advantages of cryotherapy include fast application, low risk of infection, and no requirement for local anesthesia. The disadvantages of cryotherapy are the pain during treatment, development of vesicles or bullae after application, the need for repeated treatments, and the high risk of scarring or hyper- or hypo- pigmentation[3].

Electrocauterization is the process of destroying tissue using heat from a metal probe. This procedure is used in surgery to remove warts. Despite the high rate of complete clearance of lesions, the risks of this procedure are bleeding, infection, pain, and scarring. Cantharidin is an extract of the green blister beetle that causes epidermal necrosis and blistering. Aminolevulinic acid (ALA) is a photosensitizer that has been successfully used topically in combination with blue light to treat flat warts[5]. Topical retinoids are effective treatments for VP and result in proliferation and reduced keratinisation of skin cells independent of their functions as vitamins. The advantages of topical retinoids are easy administration, no requirement for repeated visits to the doctor, and no pain[6]. However, excessive use of retinoids can irritate the skin, causing redness, swelling, peeling, and blistering. Retinoids may aggravate eczema and trigger koebnerization and the development of new lesions[7]. TCA is a chemical that is commonly used for cosmetic skin peels and removal of warts. Because these caustic medications are liquids, it is necessary to apply them carefully to avoid contact with unaffected skin. TCA solutions are commonly used to treat genital warts.

Despite the numerous methods available to treat VP, the results are unsatisfactory. We chose to compare the effectiveness of 10% TCA, 25% TCA, and cryotherapy because they are easy to obtain in Turkey. Using a pulsed dye laser, Grillo et al.[8] achieved complete clearance of multiple VP lesions in 14 participants (44%) and an excellent response was observed in an additional 18 participants (56%) at the 1-year follow-up examination. They reported that the advantages of using a pulsed dye laser to treat VP were the low-risk of complication, better and faster responses in recalcitrant VP lesions, and low recurrences of VP after treatment. The only side effect they observed was an intense transitory purpuric response. The treatment efficacy of 10% TCA was similar to the results reported using the pulsed dye laser, but the laser yields faster results. However, the pulsed dye laser is an expensive treatment method, which is an important drawback.

Li et al. found that photodynamic therapy with 10% aminolevulinic acid was superior to photodynamic therapy with 5% aminolevulinic acid in the treatment of VP and that hyperpigmentation was less common with the 10% aminolevulinic acid treatment than with the 20% aminolevulinic acid treatment[9]. They observed that skin-colored lesions were more responsive to the treatment than coffee-colored lesions regardless of the aminolevulinic acid concentrations, and reported complete clearance of VP lesions in 33.3% of lesions treated with 10% aminolevulinic acid at week 12. Hyperpigmentation was observed in 12.9% of participants at week 12. Hyperpigmentation was more common in the 10% aminolevulinic acid group than in the 10% TCA group, however, 10% aminolevulinic acid was as effective as 10% TCA.

Good results were reported for treatment of VP using topical imiquimod (5%) with complete clearance of all flat warts after three weeks of therapy[10]. Glycolic acid (15%) plus salicylic acid was applied to the face once daily for two months. Complete clearance of VP was observed in all participants before 8 weeks of treatment. No noticeable side effects were recorded[11]. Both of the treatment methods were more effective and safer than the 10% TCA treatment, however, they are more expensive than 10% TCA.

Pezeshkpoor et al. compared the efficacies of 80% TCA and 35% TCA in the treatment of the common warts[12]. At the end of week 6, they observed a mild response in ten participants (33.3%), a moderate response in six participants (20%), and a good response in 14 participants (46.7%) in the 80% TCA group. They observed a mild response in 16 participants (64%), a moderate response in six participants (24%), and a good response in three participants (12%) in the 35% TCA group. They reported that the response rates of participants in the 80% TCA group were statistically higher than those of participants in the 35% TCA group.

To our knowledge, this is the first clinical trial to compare the efficacies and safety profiles of using TCA (10% or 25%) and cryotherapy in the treatment of VP. Both TCA and cryotherapy were effective in the treatment of VP, with no statistically significant differences between the complete clearance of lesions among the three groups at eight weeks. The decrease in the number of lesions at weeks 2, 4, and 6 were similar among the groups, therefore, the effect of each of these treatments begins at approximately the same time. Two participants (8.6%) in the cryotherapy group developed a relapse of VP, however, no participant in either of the TCA treatment groups experienced this. TCA can be applied to very small lesions, and we conclude that the rate of relapse among those in the TCA treatment group is less than among those in the cryotherapy treatment group.

More local side effects were observed among those in the cryotherapy treatment group than in the TCA groups. Erythema, pain, erosions, bullae, and hyperpigmentation were significantly higher among those in the cryotherapy group than among those in the TCA groups. Itching during application was the only symptom that was more common among participants in the TCA groups than cryotherapy group. Despite the similar effectiveness of either of the TCA solutions, adverse effects were more frequent among those in the 25% TCA group. Itching may be more acceptable to participants than erythema, pain, erosions, bullae, or hyperpigmentation. TCA appears to be better tolerated by participants than cryotherapy. Limitations of the study are the exclusion of spontaneous clearing of VP lesions and the small sample size.

Conclusion

TCA solutions are easily available and inexpensive treatment options for VP. We found that 10% and 25% TCA solutions were as effective as cryotherapy in the treatment of VP and had fewer adverse effects. Despite the similar efficacy of both 10% and 25% TCA, 10% TCA caused the fewest side effects. In conclusion, 10% TCA offers a safer and easier treatment for VP than 25% TCA or cryotherapy. The easy and painless application and better cosmetic results obtained using 10% TCA are attractive features of this treatment for VP.

Declaration of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of this article.

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