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Comparing the Effect of 20% Zinc Oxide Ointment With 80% Trichloroacetic Acid Solution in the Treatment of Genital Warts: A Single-Blind Randomized Clinical Trial

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Abstract

Objectives: There are several treatment options for genital warts, but many can cause skin sensitivities or lead to a recurrence of lesions. This study seeks to compare the effectiveness of 20% zinc oxide ointment with 80% trichloroacetic acid (TCA) solution for treating genital warts.

Materials and Methods: In this single-blind randomized clinical trial, 88 women with genital warts were divided into two groups of 44. Group A received treatment with zinc oxide, while group B was treated with TCA. Patients were followed up three times, at the end of the fourth, eighth, and twelfth weeks after the start of treatment, to assess the effectiveness of the treatments for genital warts.

Results: The number, thickness, and diameter of genital warts decreased significantly in both groups during 12-week period (P=0.0001). However, the reduction in the number, thickness, and diameter of warts was significantly greater in the TCA group compared to the zinc oxide group (P=0.001). After 12 weeks, the TCA group achieved complete clearance of lesions in 84.1% of patients, while the zinc oxide group had a 31.7% clearance rate (P=0.001).

Conclusions: Given the significantly higher rate of complete clearance of lesions achieved with TCA compared to zinc oxide, it may be a more effective treatment option and preferable in the management of genital warts.

Keywords: Genital warts, Trichloroacetic acid, Zinc oxide

Introduction

Genital warts are the most common sexually transmitted infection (STI) worldwide (1). This disease is caused by the human papillomavirus (HPV), which has approximately 100 types, among which about 40 types are known to cause genital infections. Genital warts are usually caused by HPV types 6 and 11 (2). The prevalence of HPV infection among women has been estimated between 10% and 24.4% in various studies (2). Today, a high prevalence of infection with human papillomavirus is observed, which is considered the cause of warts, especially genital warts (3). The highest number of new HPV infections occurs before the age of 24 in women and between the ages of 25 and 29 in men (2). In a review study conducted by Patel et al in 2013, the annual prevalence of genital warts in the world was reported to be 160-289 per 100,000 in men and women, respectively (4). However, there is no accurate information on the prevalence of genital warts in Iran.

The prevalence of cervical cancer is highest in developing countries and ranks as the second most common cancer affecting women across the globe (4). The relationship between HPV infection and cervical cancer is so strong that HPV is now recognized as the first cause of this type of cancer (1). Today, non-cancerous skin manifestations of the HPV virus, including common warts, are one of the most important reasons for visiting doctors (4).

Medications that are effective against HPV can be categorized into various groups, including destructive agents (such as cantharidin and salicylic acid), antivirals (like cidofovir and interferon α), antimitotic drugs (including bleomycin, podophyllotoxin, and 5-fluorouracil), immunotherapy options (such as Candida antigen immunotherapy and imiquimod), and miscellaneous treatments like trichloroacetic acid (TCA) and divided polyphenol E. Many of the current treatment approaches can lead to skin sensitivities, and in some cases, lesions may reappear after the treatment period ends (5).

TCA is a keratolytic agent categorized as a chemical cautery that induces the hydrolysis of cell proteins, ultimately resulting in cell death (6). Its application leads to chemical burns, effectively destroying old and infected epidermal cells, and promoting the growth of healthy, new cells (7). It has also been shown that zinc oxide ointment produces reactive oxygen species and by increasing membrane lipid peroxidation, it causes leakage of proteins and reducing sugars and eliminates skin irritants. Additionally, zinc oxide has been effectively

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Key Messages

- TCA demonstrates superior efficacy in treating genital warts compared to zinc oxide, as indicated by a significantly higher rate of complete lesion clearance (84.1% vs. 31.7%).
- This single-blind randomized clinical trial underscores the potential of TCA as a preferred and more effective therapeutic option for genital warts when compared to 20% zinc oxide ointment.

utilized in the treatment of viral warts, although the exact mechanism of action remains unclear (8). It is possible that this effect is due to the correction of zinc deficiency or the immunomodulatory properties of zinc.

Due to the limited research on the effects of TCA and 20% zinc oxide ointment on genital warts, this study aims to assess the effectiveness of 20% zinc oxide ointment compared to an 80% TCA solution for the treatment of genital warts. The study is structured to identify an optimal treatment approach in relation to accessibility, consumption, minimal side effects, and cost-effectiveness.

Materials and Methods

Research Methodology and Participant Demographics

This study is a single-blind randomized clinical trial. The study population includes women with genital warts who referred to the Gynecology and Obstetrics Clinic of Baath Hospital during 2022.

Sampling Method and Sample Size

The sample size for this study was determined through careful consideration of precision and the expected difference in waste reduction. To achieve a reliable level of accuracy, the researchers used OpenEpi software for sample size estimation, setting the anticipated effect size, or the expected difference in waste reduction, at 25%. This means that the researchers aimed to detect a 25% reduction in waste. Utilizing the software, the researchers calculated the sample size based on the effect size, statistical power, and significance level, resulting in a determined sample size of 44 individuals in each group, totaling 88 participants for both the experimental and control groups.

Additionally, to introduce an additional layer of randomness and balance potential confounding variables, the researchers opted for a random block sampling method with a block size of 4. This method ensures that each block, comprising four individuals, maintains a balanced representation of characteristics that might impact the study outcomes. This meticulous approach to sample size determination and sampling methodology aims to enhance the reliability and validity of the study's findings.

Inclusion and Exclusion Criteria

The inclusion criteria for the study required participants to be at least 18 years of age. Exclusion criteria encompassed pregnancy, patients with hypersensitivity to zinc oxide or TCA, and those using another treatment method at the time of referral.

Methodology

The study was a blinded randomized clinical trial that received approval from the Ethics Committee in Medical Research at the Faculty of Medicine of Kurdistan University of Medical Sciences (Approval ID: 2018.306.MUK.REC IR). All participants provided written consent by completing a complaint form. The study was also registered on the Iranian Registry of Clinical Trials (IRCT) website with the identifier IRCT20220816055716N1; https://www.irct.ir/trial/65401).

Participants were allocated to either the intervention or control group using a four random block sampling method. Group A received 20% zinc oxide ointment applied daily as a thin layer, while group B received TCA 80% solution through gentle pressure using swabs and medical Vaseline at five-day intervals. Demographic variables such as age, body mass index, and history of underlying diseases, smoking, or drug addiction were recorded during the initial visit.

Gynecologists and obstetricians conducted examinations during the first visit, clinically recording genital warts based on morphology, including number, diameter, and thickness. In cases of multiple warts, the average diameter and thickness were computed for evaluation.

The administration of drugs in both groups continued for 12 weeks or until the disappearance of all lesions, whichever occurred earlier. Evaluations took place at the end of the fourth, eighth, and twelfth weeks, where gynecologists assessed the response to treatment and recorded the number, thickness, and diameter of genital warts in both groups. This comprehensive approach provides a detailed understanding of the study design, treatment protocols, and assessment intervals (Figure 1).

Data Statistical

The analysis was performed using the t-test, Mann-Whitney U test, and repeated data analysis of variance with the SPSS version 22 software (SPSS, Chicago, IL, USA). A significance level of $P<0.05$ was considered statistically significant.

Ethical considerations

Participation in the study was entirely voluntary, and patients were fully informed before entering the study. They filled out a consent form to participate, ensuring their understanding of the study. Patient participation in the study did not result in any deprivation of treatment or additional costs. All patient information was treated as confidential, and the researcher was committed to maintaining the privacy of their information.

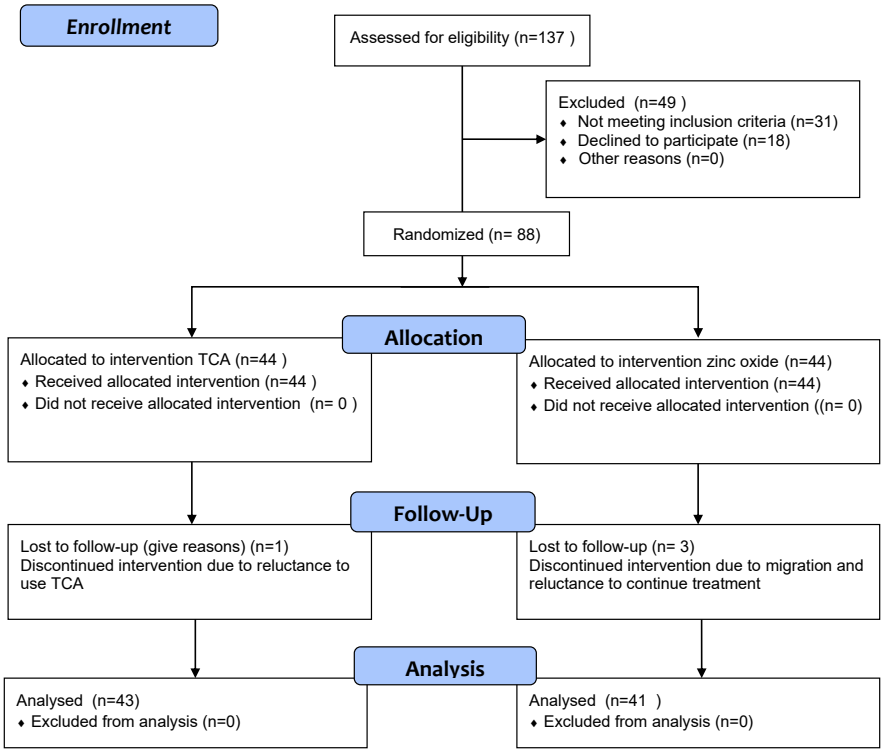

Figure 1. CONSORT Flow Diagram of the Study.

Results

The average age, body mass index, number of sexual activities per week, and duration of genital warts did not show statistically significant differences between the two studied groups of women. Similarly, there were no statistically significant differences in terms of place of residence, smoking, and number of sexual partners among the women (Table 1; $P<0.05$).

Based on the results (Table 2) and the repeated data analysis of variance, there was a significant reduction in the number of genital warts, thickness, and diameter of warts within each group over the 12-week period ($P=0.0001$). The number of warts in the TCA group women during the 12 weeks of follow-up was significantly lower than in the zinc oxide group women ($P=0.001$). The thickness of warts in the women of the TCA group during the study period was significantly less than that of the women in the zinc oxide group ($P=0.013$). Additionally, the diameter of warts in the women of the TCA group was significantly smaller than that of the women in the zinc oxide group during the study period ($P=0.012$).

In the fourth week, the TCA group had a frequency of 51.2% for complete cleansing of patients' lesions, while the zinc oxide group had 7.3%. In the eighth week, the TCA group had a frequency of 65.1%, compared to 14.6% in the zinc oxide group. By the twelfth week, the TCA group had a frequency of 84.1%, while the zinc oxide group had 31.7%. These differences between the two groups were statistically significant at all three time points ($P=0.001$; Table 3).

Regarding the examination of side effects caused by the consumption of zinc oxide and TCA, it was found that in the zinc oxide group, 22.7% experienced skin inflammation, 13.6% had skin ulcers, and 13.6% had scars. In contrast, in the TCA group, only 4.86% experienced skin inflammation, and this difference was statistically significant ($P<0.05$; Table 4).

The average duration of warts in patients who achieved

Table 1. Average Quantitative Variables in the Two Studied Groups

Variable	TCA 80%	Zinc Oxide 20%	*P* Value[a]
Age, Mean ± SD	36.4±9.2	38.4±10.5	0.35
BMI, Mean ± SD	27.4±3.9	27.1±4.3	0.82
Sexual activity per week, Mean ± SD	3.4±2.5	3.6±2.6	0.80
Duration of warts (months), Mean ± SD	19.8±17.8	24.5±23.4	0.29
Residence in the city, No. (%)	41 (93.2)	37 (84.1)	0.31
Smoking, No. (%)	12 (27.3)	10 (22.7)	0.80
Multiple sexual partners, No. (%)	15 (34.1)	11 (25.0)	0.24

[a] ANOVA.

Table 2. Average Number, Thickness, and Diameter of Lesions at the End of Weeks 4, 8 and 12

Variable	Group	Start Mean ± SD	Forth week Mean ± SD	Eighth week Mean ± SD	Twelfth week Mean ± SD	*P* Value[a]
Number	Zinc oxide 20%	4.3±2.7	3.2±2.2	2.5±2.5	1.8±2.3	0.001
	TCA 80%	3.7±2.3	1.5±1.5	0.7±1.2	0.4±0.9	
Thickness	Zinc oxide 20%	2.5±0.6	1.8±0.9	1.2±0.9	1.0±1.1	0.013
	TCA 80%	2.6±0.6	1.0±1.2	0.6±1.0	0.5±1.0	
Diameter	Zinc oxide 20%	2.9±0.7	1.9±0.9	1.4±1.0	1.0±1.1	0.012
	TCA 80%	3.1±0.8	1.1±1.3	0.7±1.1	0.5±1.0	

[a] ANOVA.

Table 3. Comparison of the Frequency of Complete Cleaning of Genital Warts in Weeks 4, 8 and 12

Complete Cleaning		Zinc Oxide 20% No. (%)	TCA 80% No. (%)	*P* Value[a]
Forth week	Yes	22 (51.2)	3 (7.3)	0.0001
	No	21 (48.8)	38 (92.7)	
Eighth week	Yes	28 (65.1)	6 (14.6)	0.0001
	No	15 (34.9)	35 (85.4)	
Twelfth week	Yes	37 (84.1)	13 (31.7)	0.0001
	No	7 (15.9)	28 (68.3)	

[a] ANOVA.

Table 4. Comparison of the Frequency of Inflammation, Scar and Wound

Complications	Groups	Yes No. (%)	No No. (%)	*P* Value[a]
Inflammation	Zinc oxide 20%	10 (22.7)	34 (77.3)	0.001
	TCA 80%	38 (86.4)	3 (13.6)	
Wound	Zinc oxide 20%	6 (13.6)	38 (86.4)	0.014
	TCA 80%	17 (38.6)	27 (61.4)	
Scar	Zinc oxide 20%	6 (13.6)	38 (86.4)	0.001
	TCA 80%	20 (45.5)	24 (54.5)	

[a] ANOVA.

complete clearance was 14.5 ± 13.0 months, whereas in patients who did not fully recover, it was 24.5 ± 15.6 months (P=0.003; Figure 2).

Discussion

Genital human papillomavirus infection is the most prevalent sexually transmitted disease, with 1 million new patients diagnosed with genital warts annually, of which two-thirds are women. There are numerous treatment options available for treating genital warts, including both destructive and non-destructive methods such as surgical removal, cryotherapy, electrocautery, carbon dioxide laser, imiquimod, podophyllin, podophyllotoxin, and interferons (9). TCA is a caustic agent that chemically cauterizes anogenital warts and is considered to be the safest treatment option during pregnancy (9,10). Although TCA treatment is relatively inexpensive and somewhat effective, it can cause side effects such as irritation, pain, and peeling (11).

The number of genital warts, thickness, and diameter of warts in 12 weeks significantly decreased in each of the TCA and zinc oxide groups. However, the number, thickness, and diameter of warts in women in the TCA group were significantly reduced more than in the zinc oxide group. It is worth noting that during the first 4 weeks of treatment, there was a greater reduction in the number, thickness, and diameter of warts in each group compared to the 8th and 12th weeks. This difference could be attributed to the varying forms and mechanisms of the drugs used to eliminate the lesions. In a study conducted by Layeh et al in 2001, a significant correlation was observed between the number of lesions and the response to treatment, with a faster response seen in patients with a smaller number of lesions (12).

The frequency of complete patient recovery at the end of the 12th week was 84.1% in the TCA group and 31.7% in the zinc oxide group. Qayum et al found TCA to be effective in treating 82.2% of subjects in a 6-month evaluation after the last visit (13). Lotfabadi et al reported a higher recovery rate (94.1%) in patients treated with TCA than those treated with cryotherapy (85.3%) (14). Taner et al recorded 100% clearance in 6 months after TCA treatment (15). Abdullah et al compared liquid nitrogen and topical TCA on 43 patients and reported a

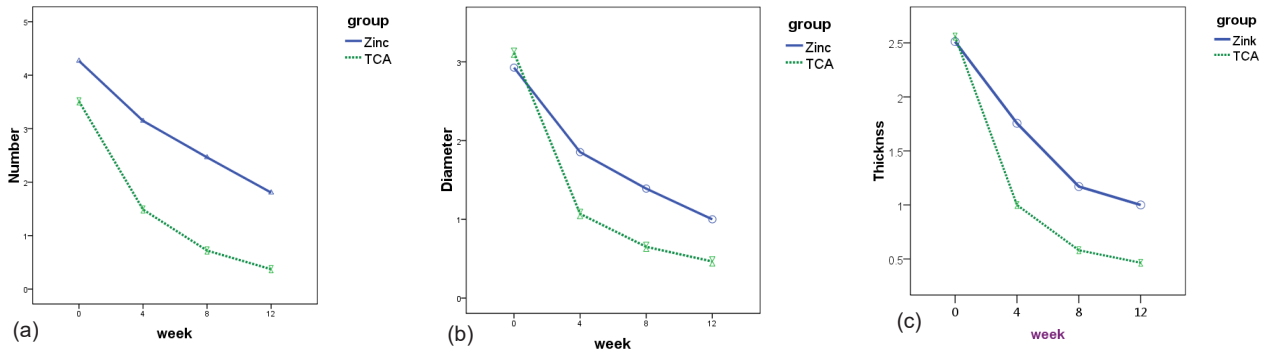

Figure 2. The Average Number of Genital Warts. (a) The average number of genital warts at the time of measurement in two groups. (b) The average size of genital warts during the measurement times in two groups. (c) The average thickness of genital warts during the measurement times in two groups.

genital wart clearance rate of 70% with a recurrence rate of 36% (16). Damstra et al found that TCA resulted in 96% clearance after six months (17). In Schwart et al.'s study, TCA resulted in a clearing rate of 97% in pregnant women with anogenital warts (18). Layeh and colleagues study reported an 88% success rate for TCA treatment in patients with genital warts (12). These findings are consistent with our study regarding the high therapeutic effect of TCA, although small differences in therapeutic effects may exist due to variations in skin types and subtypes of the papillomavirus.

In our study, the frequency of complete patient recovery at the end of the twelfth week in the zinc oxide group was 31.7%. Khattar et al employed 20% zinc oxide as the active drug and salicylic acid as a placebo in treating genital warts among 44 patients, resulting in a clearance rate of 50% after a 12-week treatment period (19). Differences in the frequency of treated patients may be due to variations in the number, thickness, and diameter of warts among the study participants.

In a systematic review study that investigated the effectiveness of local and ablative treatments in the treatment of anogenital warts, it showed that among the compared treatment options, carbon dioxide laser therapy is the most effective treatment to achieve complete removal of genital warts in the end of the treatment. Among the topical treatments used by the patient, 0.5% podophyllotoxin solution was the most effective solution in achieving complete clearance, and surgical removal was the most effective in minimizing the risk of recurrence (20).

The findings of our research showed that the complete clearing of genital wart lesions had an inverse relationship with the duration of infection so patients with long duration of infection were less likely to recover completely.

In our study, the side effects of skin inflammation and scarring in the TCA group were significantly higher than those in the zinc oxide group. In the study of Layeh et al, the highest complication of erosion (96.7%) was reported in the group treated with TCA (12). In Khattar's study, the skin complications of patients receiving zinc oxide were minimal and included erythema, scaling, and swelling (19).

Study Limitations

- Limited generalizability: The study focused exclusively on women, which restricts the generalizability of the findings to a broader population that includes men with genital warts. The exclusion of male participants limits the applicability of the results to the entire affected population.
- Short-term follow-up: The 12-week follow-up period, although suitable for assessing short-term outcomes, may not capture the long-term efficacy and recurrence rates of TCA and zinc oxide treatments. A more extended follow-up duration would provide a comprehensive understanding of the sustained effects of the treatments.
- Absence of placebo group: The study design did not include a placebo group, which could have provided a stronger basis for comparison and controlled for potential placebo effects. The absence of a placebo group introduces some uncertainty in attributing treatment effects solely to TCA or zinc oxide.

Conclusion

The findings of this study indicate that both zinc oxide and TCA treatments are effective in treating genital warts caused by the human papillomavirus. However, considering the higher percentage of complete lesion removal in the TCA group and the lower cost of the drug compared to similar treatments, TCA appears to have a more favorable effect than zinc oxide and may be preferred in treatment. Zinc oxide ointment can be used as an adjunctive treatment for lesion elimination but is not recommended as a standalone treatment.

Clinical Implications and Future Directions

In conclusion, the study's findings support the superior effectiveness of TCA over zinc oxide in treating genital warts among women. The comprehensive analysis of treatment outcomes, side effects, and wart duration

provides valuable insights for clinicians. Future research could explore individual patient characteristics that may influence treatment responses and further investigate the long-term effects and recurrence rates associated with TCA and zinc oxide interventions.

This study serves as a valuable contribution to the field of genital wart management, providing clinicians with evidence-based information to make informed decisions regarding treatment options based on efficacy and safety considerations.

Authors' Contribution

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Formal analysis: Leila Safar Bakhshayeshi,Khaled Rahmani, Fariba Seyedoshohadaei.
Funding acquisition: Leila Safar Bakhshayeshi.
Investigation: Rehane Yosefi Sharam, Fariba Seyedoshohadaei.
Methodology: Rehane Yosefi Sharam, Leila Safar Bakhshayeshi.
Project administration: Leila Safar Bakhshayeshi.
Resources: Fariba Seyedoshohadaei.
Software: Leila Safar Bakhshayeshi, Khaled Rahmani, Fariba Seyedoshohadaei.
Supervision: Leila Safar Bakhshayeshi.
Validation: Leila Safar Bakhshayeshi.
Visualization: Fariba Seyedoshohadaei.
Writing–original draft: Fariba Seyedoshohadaei, Rehane Yosefi Sharami.
Writing–review & editing: Leila Safar Bakhshayeshi,:Rehane Yosefi Sharami.

Conflict of Interests

None declared.

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