



ORIGINAL ARTICLE

## Comparison of efficacy of cryotherapy plus oral zinc sulphate versus cryotherapy alone in treatment of viral warts.

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**ABSTRACT... Objective:** To evaluate the efficacy of combining oral zinc sulphate with cryotherapy versus cryotherapy alone in the treatment of cutaneous warts. **Study Design:** Randomized Controlled Trial. **Setting:** Department of Dermatology, PNS Shifa Hospital, Karachi. **Period:** October 2023 to June 2024. **Methods:** Patients aged 18–65 years with cutaneous warts and no prior treatments were included. Exclusions were patients with systemic illnesses or hypersensitivity. Group A received oral zinc sulphate (10 mg/kg/day for 8 weeks) combined with weekly cryotherapy, while Group B underwent cryotherapy alone. Efficacy was assessed after 12 weeks based on complete wart resolution. Chi-square tests compared efficacy, and descriptive statistics were used for demographic analysis. **Results:** Significantly higher efficacy (58.7%) was observed in Group A compared to Group B (36%;  $p = 0.004$ ). Both groups were demographically similar with no statistical differences in age, gender, or disease duration. **Conclusion:** The combination of oral zinc sulphate with cryotherapy significantly improves treatment outcomes for cutaneous warts compared to cryotherapy alone, highlighting zinc's potential as an effective, accessible, and cost-efficient adjunct therapy. Further research is recommended to establish broader clinical guidelines.

**Key words:** Cutaneous Warts, Cryotherapy, Combination Therapy, Dermatology, HPV, Immunomodulatory Therapy, Oral Zinc Sulphate, Randomized Controlled Trial, Skin Lesions, Viral Wart Treatment.

### INTRODUCTION

Warts are a common skin condition that do not pose any significant health risks and typically disappear on their own after a few weeks or months. However, they have the potential to be annoying and unattractive. Additionally, they might be painful, particularly when worn on the feet. There are a variety of treatments available that may hasten the removal of warts. When it comes to treating cutaneous warts, there are a few different home remedies that people might find helpful. However, it is essential to keep in mind that these treatments might not be effective for everyone. Before attempting any home remedy, it is always best to discuss your condition with a qualified medical professional first.<sup>1</sup> Many DNA viruses cause warts, including papillomaviruses. A few human papillomaviruses cause cutaneous warts. “Common warts” are the most common cutaneous warts, with a 20% prevalence in school

children and a decline with age.<sup>2</sup>

Regarding its usefulness, studies have produced a wide range of findings. Because of its ease of use and generally high rate of success, cryotherapy is frequently regarded as a treatment option that should be tried first. On the other hand, you might need to go through a few different sessions, and it can be quite uncomfortable. On the other hand, the efficacy of zinc sulphate taken orally along with cryo is somewhat up for discussion. While some research points to its potential usefulness, particularly in circumstances where the immune system is already compromised, other studies point to its limited benefits. While managing the patients of cutaneous warts, it appears that there is inconsistent evidence regarding the efficacy of cryotherapy compared to that of oral zinc sulphate. This was discovered after reviewing the results of the search.

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Some studies suggest that oral zinc sulphate may be effective in treating warts<sup>3,4</sup>, while others have found no benefit when compared to cryotherapy or placebo.<sup>3</sup>

Additionally, the use of combination therapy with oral zinc sulphate and other treatments, such as imiquimod, podophyllin, or cryotherapy, has been investigated and found to be effective by a number of studies.<sup>5</sup> In general, it appears that additional research is required in order to determine which treatment for cutaneous warts is the most effective. It is essential to confer with a qualified medical practitioner in order to ascertain the most appropriate mode of therapy for particular patients.

## METHODS

This was a randomized controlled trial conducted in the Department of Dermatology, PNS Shifa Hospital, Karachi after the approval from the ethical review committee of the Hospital (letter no. ERC/2023/DERM/77). Data collection was done during October, 2023 to June, 2024. Patients enrolled were those with cutaneous warts and it was ensured that all of the patients who participated in the study gave us their written informed consent. We used a method of sampling that did not involve probability and was sequential.

All those patients who presented with cutaneous warts with no history of any treatment related to warts in the dermatology OPD during the duration of the study mentioned above were recruited, ranging in age from 18 to 65 years old and including patients of both sexes. Patients who suffered from hypersensitivity reactions, genital warts, cardiac disease, hepatic disease, or renal disease; hypercholesterolemia; or had high cholesterol levels were excluded from the study.

Each participant was given a comprehensive dermatological examination after first having their medical history thoroughly documented. After obtaining the patients' informed consent, we divided them into two groups, plantar wart sufferers and common wart sufferers, based on the location of their warts. Patients, who had warts

on the palms of their hands or in other locations were classified as having common warts, while patients whose warts were located on the soles of their feet were classified as having plantar warts. Patients who had both plantar and common warts were separated into two groups, one for each site on their body where the majority of their warts were located.

Patients were divided at random into two groups of the same size using the lottery method. These groups were designated as A and B. Following the distribution of patients into the two groups, the doctor who was in charge of giving the treatment and the doctor who was in charge of collecting the results both pretended to be unaware of the randomization status of the patients they were treating. Patients in group A were given zinc sulphate in the form of an oral solution at a dose of 10 mg/kg/day and given the medication half an hour before each meal for a period of eight weeks. Cryotherapy was administered to patients in both groups once every week for a total of eight weeks of treatment. During each treatment session, the warts were treated with three separate applications of liquid nitrogen, which were applied with the assistance of a wad of cotton wool.

Continued applications of liquid nitrogen were made until a frozen halo measuring 2 millimeters in diameter appeared around the base of the lesions. A dermatologist with more than 5 years of experience acted as the patient's supervisor throughout the treatment and periodic examinations. At the end of the 12th week, the clinical response was measured in terms of complete resolution of warts on clinical examination (restoration of skin color and skin lines). Patients who continued to have warts after receiving treatment for a period of 12 weeks were considered unsuccessful treatment cases.

We analysed the data to calculate mean and standard deviation for quantitative variables such as age, and the duration of symptoms and frequency and percentages of variables like gender, location, laterality, and effectiveness of treatment. The Chi-square test was used to

analyze the data and draw conclusions regarding the relative effectiveness of both groups.

## RESULTS

**Age Distribution:** Within Group-A, consisting of 75 individuals, 54 individuals (72%) are in the 18-40 age group, while 21 individuals (28%) belong to the 41-65 age group. This age distribution is not significantly different from Group-B (n=75), where 68% are in the 18-40 age group, and 32% are in the 41-65 age group, with a non-significant p-value of 0.361, mean age in Group A was  $33.47 \pm 11.96$  and in Group B  $34.37 \pm 11.99$  years.

**Gender Distribution:** Group-A includes 50 Male individuals (66.7%) and 25 Female individuals (33.3%). In contrast, Group-B comprises 49 Male individuals (65.3%) and 26 Female individuals (34.7%). The gender distribution is not significantly different between the two groups, with a p-value of 0.500.

**Disease Duration:** In Group-A, 61 individuals (81.3%) have a disease duration of less than 3 months, while 14 individuals (18.7%) have a disease duration of more than 3 months. Group-B has 80% of individuals with disease duration of less than 3 months and 20% with duration of more than 3 months. The difference in disease duration between the two groups is not statistically significant, as indicated by a p-value of 0.500. Mean duration of disease in Group A was  $2.53 \pm 0.88$  whereas in Group B  $2.57 \pm 0.86$ .

**Site Affected:** Within Group-A, 52 individuals (69.3%) have the Plantar site affected, while 23 individuals (30.7%) have the Common site affected. In Group-B, this distribution is similar, with 69.3% having the Plantar site affected and 30.7% having the Common site affected. The difference in site distribution is not statistically significant, with a p-value of 0.570.

**Efficacy:** In terms of treatment efficacy, 44 individuals (58.7%) in Group-A experienced efficacy, while 31 individuals (41.3%) did not. In contrast, 27 individuals (36%) in Group-B experienced efficacy, while 48 individuals (64%) did not. The difference in treatment efficacy

between the two groups is statistically significant, with a p-value of 0.004.

In summary, Group with Oral Zinc Sulphate plus cryo and Group Cryotherapy-alone are compared across various variables, including age, gender, disease duration, site affected, and treatment efficacy. While there are no significant differences between the groups in terms of age, gender, disease duration, and site affected, there is a significant difference in treatment efficacy, with Group-A showing higher efficacy compared to Group-B.

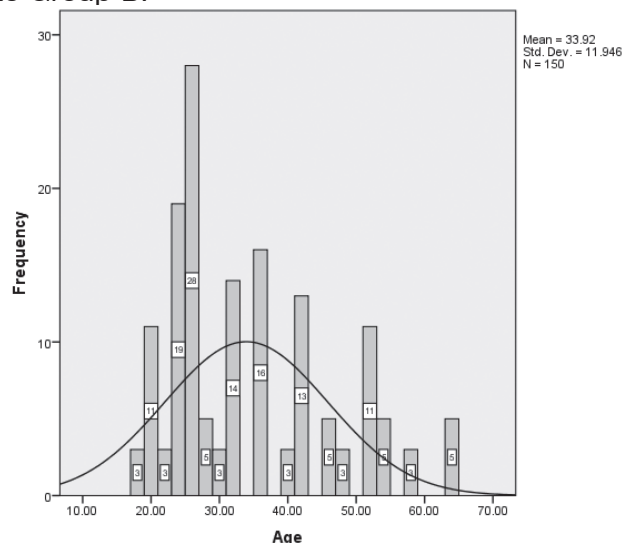


Figure-1. Age distribution of study participants

## DISCUSSION

Zinc is likely one of the most crucial trace mineral for the functioning of the immune system, and it is currently utilised for managing a number of skin problems as an immune-modulator. Kitamura et al. postulated that dendritic cell activity is influenced by TLR-mediated control of zinc maintenance.<sup>6</sup>

Zinc insufficiency has been linked to lowered immunity against infections of the skin.<sup>7,8</sup> It also has unique anti-viral action, first by connecting the two-stranded structure of viral DNA, preventing it from participating in the splitting process required for the replication of viruses, and subsequent by eliminating viral outside glycoproteins, preventing viral permeation into a vulnerable host cell. Oral zinc sulphate along with cryo therapy is also a successful cure for warts.

Variables		Group-A (n=75)		Group-B (n=75)		P-Value
Age	18-40	54	72%	51	68%	0.361
	41-65	21	28%	24	32%	
Gender	Male	50	66.7%	49	65.3%	0.500
	Female	25	33.3%	26	34.7%	
Duration of disease	<3 months	61	81.3%	60	80%	0.500
	>3 months	14	18.7%	15	20%	
Site	Plantar	52	69.3%	52	69.3%	0.570
	Common	23	30.7%	23	30.7%	
Efficacy	Yes	44	58.7%	27	36%	0.004
	No	31	41.3%	48	64%	

Table-I. Demographics of the patients

Variable		Efficacy	Group-A (n=75)	Group-B (n=75)	Total	P-Value
Age (years)	18-40	Yes	33 (64.7%)	18 (35.3%)	51 (100.0%)	0.007
		No	21 (38.9%)	33 (61.1%)	54 (100.0%)	
	41-65	Yes	11 (55.0%)	9 (45.0%)	20 (100.0%)	0.242
		No	10 (40.0%)	15 (60.0%)	25 (100.0%)	
Gender	Male	Yes	30 (60.0%)	20 (40.0%)	50 (100.0%)	0.044
		No	20 (40.8%)	29 (59.2%)	49 (100.0%)	
	Female	Yes	14 (66.7%)	7 (33.3%)	21 (100.0%)	0.034
		No	11 (36.7%)	19 (63.3%)	30 (100.0%)	
Duration of Disease	<3	Yes	35 (61.4%)	22 (38.6%)	57 (100.0%)	0.18
		No	26 (40.6%)	38 (59.4%)	64 (100.0%)	
	>3	Yes	9 (64.3%)	5 (35.7%)	14 (100.0%)	0.97
		No	5 (33.3%)	10 (66.7%)	15 (100.0%)	
Site	Plantar	Yes	30 (61.2%)	19 (38.8%)	49 (100.0%)	0.024
		No	22 (40.0%)	33 (60.0%)	55 (100.0%)	
	Common	Yes	14 (63.6%)	8 (36.4%)	22 (100.0%)	0.070
		No	9 (37.5%)	15 (62.5%)	24 (100.0%)	

Table-II. Comparison of Efficacy in Group A and B according to demographics

Zinc sulphate is the most well-tolerated and bioavailable component. GI effects including nausea and vomiting are most common adverse reactions along with moderate to severe epigastric pain.

Cryotherapy is one of the most widely utilized treatments for warts. It entails freezing the wart with an extremely cold chemical known as cryogen. The cryogen most usually used is liquid nitrogen, which has a temperature of  $-196^{\circ}\text{C}$ .<sup>9</sup> Cryotherapy leads to change in the appearance of the lesion in terms of pigmentation, along with some injuries to the muscle tendon or nerve when treated excessively, and annular relapse surrounding the surgically removed wart if scorching is significant. Patients with weak perfusion ought to be handled with caution as well.<sup>9</sup>

Our study showed that oral zinc sulphate with cryo had an efficacy of around 58.5% while cryotherapy

was effective in 41.3% cases. This in line with the study done by Riaz et al., in which they showed that added oral zinc sulphate was successful in 63.8% of individuals whereas cryotherapy was beneficial for 37.2% of cases. They came to the conclusion after analysis of the results that giving oral zinc can be a better alternate of cryotherapy in treating viral warts.<sup>10</sup>

Al-Ghurair et al.<sup>11</sup>, observed a substantially greater eradication rate of 87% when using oral zinc sulphate tablets for 2 months in the management of warts along with cryo. Our findings were close to those of Waqas et al.<sup>12</sup>, who did a study in 2017 and reported that the success rate of eradication of warts using zinc orally used for 60 days was around 62%, and Hassan et al.<sup>13</sup> did a similar study in 2013, and showed this eradication rate of 60.9%. Mun et al. showed this to be around fifty percent.<sup>14</sup>

In terms of cryotherapy, our investigation observed an efficacy rate of 37.2%, which was close to the findings of Kwok et al.'s meta-analysis, which indicated a mean cure rate of 49%.<sup>15</sup> Our findings were likewise similar to those of Bruggink et al, with an estimated eradication rate of 37%.<sup>16</sup> Similarly, Mahmoudi et al reported it to be around 64% using, which is considerably greater than the reported cure rate of our study.<sup>3</sup> Cryotherapy has been documented to be a painful technique, and adherence to cryotherapy treatments is low due to the negative side effects.<sup>17</sup>

Zinc sulphate supplementation was proven to be an improved remedy choice for widespread warts in our investigation. The shortcomings of this study include a lower sample size and the absence of long-term subsequent follow-up visits. Additional study procedures, including randomised controlled trials and meta-analysis, are advised to be done in the local community in order to further assess the beneficial effects of different therapies for viral warts in the present era of evidence-based practises.

## CONCLUSION

The combination of oral zinc sulfate and cryotherapy significantly improves the treatment efficacy for cutaneous warts compared to cryotherapy alone. This approach provides a cost-effective, accessible, and safe adjunct therapy for better clinical outcomes.

## CONFLICT OF INTEREST

The authors declare no conflict of interest.

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#### AUTHORSHIP AND CONTRIBUTION DECLARATION

1	<b>Aroosa:</b> Data collection, Analysis and paper writing.
2	<b>Seemab Khan:</b> Data collection and paper writing.
3	<b>Hafiz Muhammad Fahad:</b> Discussion writing and review of manuscript.
4	<b>Syed Arbab Shah:</b> Data analysis and Discussion writing.
5	<b>Muhammad Umair Memon:</b> Discussion writing and review of manuscript.
6	<b>Rehana Batool:</b> Data collection and Review of manuscript.
7	<b>Muhammad Ahsan:</b> Data analysis and Manuscript writing.