

## COMPARISON OF EFFICACY OF CRYOTHERAPY VERSUS ORAL ZINC SULPHATE IN THE TREATMENT OF CUTANEOUS WARTS

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### ABSTRACT

**Objective:** To compare the efficacy of oral zinc sulphate with cryotherapy in the treatment of viral warts.

**Study Design:** Quasi-experimental study.

**Place and Duration of Study:** Department of Dermatology, Combined Military Hospital Malir, from Nov 2018 to Apr 2019.

**Methodology:** A total of 210 patients (105 in each group) were included in this study. We randomized the patients into two equal groups, A and B by lottery method. Patients of both genders with cutaneous warts between the ages of 18 to 65 years. Patients with genital warts, cardiac, hepatic and renal disease, and hypercholesterolemia were excluded. Patients in group A were given oral zinc sulphate 10mg/kg/day for 8 weeks. Patients in group B were treated with cryotherapy after every 2 weeks for 8 weeks.

**Results:** Mean age of the patients was  $39.30 \pm 11.35$  years and  $38.92 \pm 10.32$  years in group A and B, respectively. In group A, 63 patients (60%) and in group B, 62 patients (59%) were males while 42 patients (40%) of group A and 43 patients (41%) of group B were females. Oral zinc sulphate was found to be effective in 67 patients (63.8%) and cryotherapy in 39 patients (37.2%). Statistically significant difference was observed between the two groups ( $p < 0.001$ ).

**Conclusion:** The results suggested that oral zinc sulphate is more effective than cryotherapy in the treatment of viral warts.

**Keywords:** Cutaneous warts, Cryotherapy, Oral zinc sulphate.

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### INTRODUCTION

Viral Warts are one of the commonest dermatological infections which have been reported to affect about 7-12% of the population at any given time. They tend to be more common amongst the younger age groups. Human papilloma virus (HPV) is the causative agent responsible for viral warts in majority of the cases, of which there are some 150 different genotypes<sup>1</sup>. The prevalence varies from 2.4% to 33% among school children, with equal frequency in both males and females. Risk factors for the development of warts include lower socio-economic class, large family size, and rearing household animals<sup>2</sup>.

Viral warts have been notorious for recurrence and they are often found to be quite

resistant to therapy. The need for therapeutic intervention can be highlighted from the fact that the rate of spontaneous clearance of warts has been painstakingly low. Sinha *et al* reported that spontaneous clearance rate was only 23% after 2 months, 30% after 3 months and up to 78% after 2 years<sup>3</sup>. Many treatment options are available to treat warts, which include salicylic acid (SA) dressings, cryotherapy, bleomycin, 5-fluorouracil (5-FU), dinitrochlorobenzene (DNCB), interferons (IFN), photodynamic therapy (PDT), pulsed-dye laser, duct tape and combinational therapy such as SA and cryotherapy<sup>4</sup>. Various systemic agents such as cimetidine, levamisole, and zinc sulphate have also been tried in cutaneous warts with variable results<sup>5</sup>.

Zinc has been found to be a useful treatment modality in common warts. This essentially vital nutrient of the human body is a prime component of more than 300 metalloenzymes and more

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than 2000 transcription factors. Zinc regulates the activities of both DNA and RNA polymerases, ribonucleases and thymidine kinase enzymes thereby helping in wound healing, repair and maintenance of the baseline immune response<sup>6</sup>. The dermatological applications of zinc has boomed over the past decade. It has been successfully employed in the treatment of infections such as cutaneous leishmaniasis, pigment disorders such as melasma, inflammatory dermatoses such as acne vulgaris and skin neoplasias like basal cell carcinoma<sup>7</sup>. Studies have reported variable results regarding efficacy of zinc in treating warts. Hassan *et al*<sup>8</sup> reported that oral zinc sulphate was successful in the treatment of warts in 60.9% patients, whereas efficacy was reported to be 50% in another open-label clinical study by Mun *et al*<sup>9</sup>.

Cryotherapy with liquid nitrogen is a viable therapeutic option in patients who are able to tolerate it. Extremely low temperature of liquid nitrogen (-20°C to -25°C) leads to rapid freezing of cellular matrix resulting in the production of ice crystals and causes the disruption of cell membrane. As thawing follows there is rapid influx of water into cells which ultimately proves fatal for the cell<sup>10</sup>. The reported efficacy of cryotherapy in terms of complete resolution of warts was reported to vary between 50-70% in one study and while other research protocols have reported the efficacy of cryotherapy to be 49% and 39%.

There is a wide range of disparity between the results of existing body of literature. Despite the fact that zinc sulphate and cryotherapy are two of the most commonly employed treatment modalities for viral warts, studies comparing these two treatment options are limited in number in the local population. In the current era of evidence based medical practices, studies and research protocols are a way to enhance and improve the existing treatment options and to find the better modality for improving patient care. Therefore study on this topic was designed with the aim of comparing the efficacy of oral

zinc sulphate with cryotherapy in the treatment of viral warts.

## METHODOLOGY

After approval from the ethical review committee of Combined Military Hospital (CMH) Malir, a quasi-experimental study was conducted from November 2018 to April 2019 in the Department of Dermatology, CMH Malir on patients presenting with cutaneous warts who fulfilled the sample selection criteria. We took an informed consent from all the patients included in the study. Sample size was calculated to be 105 patients in each group taking anticipated population proportion in group A,  $P_1 = 60.9\%$ <sup>8</sup> i.e., efficacy of oral zinc sulphate and anticipated population proportion in group B,  $P_2=39\%$ <sup>4</sup> i.e. Efficacy of cryotherapy in the treatment of warts, with 95% confidence interval and 90% power of the test. Consecutive non-probability sampling technique was employed.

Patients with cutaneous warts were enrolled with age range between 18 to 65 years and of both sexes. Patients with genital warts, cardiac, hepatic and renal disease, hypercholesterolemia and those with hypersensitivity reactions were not included in the study. A detailed history followed by complete dermatological examination was performed on each participant. After taking the informed consent, we stratified the patients according to the location of the warts into plantar or common warts. Patients having warts on the soles of feet were labelled as having plantar warts while patients having warts on the hands or other locations were labelled as having common warts. Those patients who had both plantar and common warts were grouped according to the site where most of their warts were located. Stratification was also done according to the number (<5 warts versus  $\geq 5$  warts) and duration (<3months versus 3 months or more).

Patients were randomly placed into two equal groups namely, A and B by employing the lottery method. After allocation of patients into the two groups, the doctor administering the treatment and the doctor collecting the results

were both blinded to the randomization status of the patient. Patients in group A were given oral zinc sulphate in a dose of 10 mg/kg/day half an hour before meals for a duration of 8 weeks. Patients in group B were treated with cryotherapy after every 2 weeks for 8 weeks. In every session, liquid nitrogen was applied on the warts with the help of a wad of cotton wool three times. Each application of liquid nitrogen was continued until a frozen halo of 2mm appeared around the base of the lesions. The treatment and periodic examination was supervised by a dermatologist with more than 5 years of experience. Clinical response was determined in terms of complete resolution of warts on clinical examination (skin colour and skin lines are restored) at the end of 12th week. After 12 weeks of therapy, patients having persistent warts were declared as cases of treatment failure.

Statistical analysis was done by using SPSS-25. Mean and standard deviation was calculated for quantitative variables specifically age, number of warts and duration of symptoms. Qualitative variables like gender, location, laterality and efficacy of treatment were recorded in terms of frequency and percentages. Chi square test was applied to compare the efficacy of both the groups. The *p*-value of  $\leq 0.05$  was considered as statistically significant.

## RESULTS

A total of 210 patients were enrolled in the study and divided into two equal groups comprising of 105 patients each. The mean age of the patients was  $39.30 \pm 11.35$  years in group A and  $38.92 \pm 10.32$  years in group B, respectively. The age distribution of patients is shown in table-I. In group A, 63 patients (60%) and in group B 62 patients (59%) were males, while 42 patients (40%) of Group A and 43 patients (41%) of Group were females.

Fifty five patients (52.2%) in group A and 43 patients (41%) in group B had plantar warts while 50 patients (47.6%) in group A and 62 patients (59%) in group B were having common warts. The duration of disease was less than 3 months in

57 patients (54.3%) of group A and 69 patients (65.7%) of group B while the duration of disease was  $\geq 3$  months in 48 patients (45.7%) of group A and 36 patients (34.3%) of group B respectively. Regarding the number of warts, less than 5 warts were present in 55 patients (52.4%) of group A

**Table-I: Distribution of patients by age.**

Age (years)	Group-A (Oral Zinc Sulphate)	Group-B (Cryotherapy)
	No (%)	No (%)
20-40	55 (52.4%)	59 (56.2%)
41-60	50 (47.6%)	46 (43.8%)
Mean $\pm$ SD	$39.30 \pm 11.35$	$38.92 \pm 10.32$

**Table-II: Distribution of patients by efficacy.**

Efficacy	Group-A (oral zinc sulphate)		Group-B (Cryotherapy)		<i>p</i> -value
	No.	%	No.	%	
Yes	67	63.8	39	37.2	<0.001
No	38	36.2	66	62.8	

**Table-III: Summary of comparison of stratified groups.**

Variable	Stratification	Group	Efficacy		<i>p</i> -value
			Yes	No	
Age (years)	20-40	A	38	17	0.001
		B	23	36	
	41-60	A	29	21	0.023
		B	16	30	
Gender	Male	A	39	24	<0.001
		B	18	44	
	Female	A	28	14	0.096
		B	21	22	
Site	Plantar	A	40	15	<0.001
		B	16	27	
	Common	A	27	23	0.074
		B	23	39	
Duration	<3 months	A	40	17	<0.001
		B	22	47	
	$\geq 3$ months	A	27	21	0.412
		B	17	19	

while 87 patients (82.9%) of group B presented with less than 5 warts, whereas  $\geq 5$  warts were found in 50 patients (47.6%) of group A and 18 patients (17.1%) of Group B respectively.

Oral zinc sulphate was found to be an effective treatment modality in 67 patients (63.8%)

while cryotherapy was successful in 39 patients (37.2%). Statistically significant difference was observed between two groups in terms of efficacy of both treatment options ( $p < 0.001$ ).

Age stratification showed significant difference between oral zinc sulphate ( $p = 0.001$ ) and cryotherapy ( $p = 0.023$ ) regardless of the age group. Stratification of gender showed significant difference between the two groups in the males ( $p < 0.001$ ), while in the female patients, there was no significant difference ( $p = 0.096$ ). Statistically significant difference was observed for patients undergoing cryotherapy ( $p < 0.001$ ) in plantar warts group, while in common warts group there was no significant difference ( $p = 0.074$ ). A statistically significant difference was also observed between the two treatment modalities ( $p < 0.001$ ) in <3 months duration group, while there was no significant difference ( $p = 0.412$ ) in the group with duration of warts of 3 or more months. The results of stratified groups were summarised in table-III.

## DISCUSSION

Viral warts are one of the commonest benign dermatological pathologies which is caused by infection of keratinocytes. The causative organism is the human papillomavirus (HPV). Hands, feet and face are the most common sites of infection in the body<sup>11-13</sup>. Because of the fact that no single treatment modality is effective universally for the management of viral warts, a number of options are available with variable cure rates. A few of the commonly employed therapeutic strategies include oral zinc sulphate, oral cimetidine, intralesional injection of antigens, cryo-therapy, topical immunotherapy, electrosurgery, use of antimetabolic agents, carbon dioxide laser, photodynamic therapy, and use of topical immune response modifiers<sup>14</sup>.

Zinc is an essential element in the human body that is vital to the functionality of more than 300 enzymes. Due to its role in the immune modulation, the importance of zinc in immune response can't be emphasized enough. Studies have reported that the deficiency of zinc leads to

impairment of the function of both the macrophages and T lymphocytes. Both mechanisms of immune response i.e. antibody-mediated and cell-mediated immune response take a hit with almost 50% decrease in the number of T lymphocytes and up to 70% reduction in the antibody mediated immune response thereby predisposing the body to infections<sup>15,16</sup>. Zinc has been added to different culture systems for polyclonal activation and stimulation of lymphocytes to enhance the immune response to various pathogens<sup>17</sup>.

Zinc has been employed successfully for its role as an immunomodulator in the treatment of a wide array skin conditions. Erythema nodosum, leprosum and dissecting cellulitis of the scalp are two of the dermatological diseases which responded effectively to treatment with zinc<sup>18</sup>. Going through the available literature, the present study was done to compare the efficacy of oral zinc sulphate with cryotherapy in the treatment of viral warts since no randomized controlled trials have been held in the country comparing the two treatment modalities. Oral zinc sulphate was effective in 63.8% patients in our study.

Al-Ghurair *et al*<sup>19</sup> reported a significantly higher cure rate of 87% as compared to our study with the use of similar dose of 10mg/kg oral zinc sulphate tablets given for two months in the treatment of warts. Our result was however comparable to the studies by Waqas *et al*<sup>20</sup> in 2017 who reported a cure rate of 62.22% with oral zinc sulphate with the same dosage for two months and Hassan *et al*<sup>8</sup> who reported a cure rate of 60.97% in 2013. Mun *et al* in 2010 from Korea reported a cure rate of 50% with oral zinc sulphate<sup>9</sup>.

As regards cryotherapy, our study found a success rate of 37.2% which was comparable to the result of the meta-analysis by Kwok *et al* who reported an average cure rate of 49%<sup>12</sup>. Our finding was also comparable to the study by Bruggink *et al* who reported a care rate of 37% with cryotherapy<sup>21</sup>. Mahmoudi *et al* in 2018

reported a higher cure rate of 63.9% with cryotherapy for cutaneous warts which was much higher than our findings<sup>22</sup>.

Cryotherapy has been reported to be a painful procedure and compliance to treatment with cryotherapy is less because of the adverse effects profile ranging from haemorrhagic blisters formation, infection, dyspigmentation, recurrence and erythema<sup>23</sup>. Our study found zinc sulphate to be a better treatment option for the treatment of common warts. The limitations of this study are that this study had a smaller sample size while the long term follow up was not done. In the current era of evidence based practices, further research protocols including randomized controlled trials and meta-analysis is recommended to be conducted in the local population to further validate the efficacy of different treatments of viral warts.

## CONCLUSION

The results suggested that oral zinc sulphate is more effective than cryotherapy in the treatment of viral warts.

## CONFLICT OF INTEREST

This study has no conflict of interest to be declared by any author.

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