Comparative Efficacy and Safety of Oral zinc Sulphate Versus Cryotherapy in the Treatment of Viral Warts.

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Abstract

Viral warts are a common problem in dermatology. Viral warts have a considerable negative effect on a patient's quality of life ; although the rate of spontaneous recovery is high, it usually takes a long time and some patients might not show this spontaneous healing.A clinical trial was carried out to evaluate and compare the efficacy of oral zinc sulphate and cryotherapy in patients with viral warts. The study was conducted in the Department of Dermatology and Venereology, Bangabandhu Sheikh Mujib Medical University, Dhaka, Bangladesh for duration of July 2015 to December 2015. Total sixty patients were enrolled and divided into group A and group B. Thirty of group A patients was treated by cryotherapy and thirty of group B patients was treated by oral zinc sulphate.Improvement rate was highest for the lesions on the finger, which is 18 (34.6%) and lowest for scalp 03 (5.8%). Improvement rate for palm 17 (32.7%); for foot 10 (19.2%) and toe04 (7.7%). Out of all respondents from Group-A, the mean size of the lesions were 8.17mm, 5.90 mm, 4.32 mm and 3.57 mm at before treatment and 1st visit, 2nd visit and 3rd visit after treatment respectively. In Group-B, the mean size of the lesions were 7.50 mm, 4.92 mm, 3.00 mm, and 4.75 mm at before treatment and 1st visit, 2nd visit and 3rd visit after treatment respectively. Among the respondents of group-A & B, 27 (90%) and 25 (83.3%) were improved respectively. No statistical significant difference was observed between the two groups. Both cryotherapy and oral zinc sulphate when used individually were found to be equally effective in the treatment of viral warts but cryotherapywas found to be superior in efficacy.

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Introduction

Cutaneous warts (verrucae) are benign epidermal proliferations caused by human papillomavirus (HPV) infection.[1,2] Their causative agent, the human papillomavirus (HPV), usually spread via person-to-person contact or indirectly by fomites.[3,4]The diagnosis of verrucae is based upon clinical appearance.[5] Although they may be benign and self-limited for the most part, warts can be the root of significant morbidity at times: beyond their unsightly appearance, in one study over half of patients reported moderate to severe discomfort from their warts.[6]The type and aggressiveness of therapy for verrucae will depend upon the type of wart, its location, the degree of symptoms, the patient's cooperation, the patient's desires, and the underlying immune status.[7,8] Cryotherapy is commonly used for treatment of warts and is also available over the country. Liquid nitrogen can freeze the tissue to a temperature of 321 F (196 C).[9,10] Common adverse effects of cryotherapy include pain; blistering; hypo- or hyperpigmentation, particularly in dark skin; tendon or nerve damage with aggressive therapy and onychodystrophy following treatment of periungual warts.[11,12] It is important to remember that after treatment, the wart may recur. [13]

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Zinc has an important effect on the immune system and it has been used as an immunomodulator to treat a variety of skin disorders.[14]It maintains macrophage and neutrophil functions, natural killer cell activity, and complement activity. It inhibits the expression of integrins by keratinocytes and modulates the production of TNF-□ and IL-6 and reduces the production of inflammatory mediators like nitric oxide. It is also proposed that it is toll-like receptors mediated regulation of zinc homeostasis which influences dendritic cell function and immune processes.[15-17]Zinc can be a useful oral treatment modality in warts as many studies have demonstrated efficacy of oral zinc in treating warts without significant adverse effects.[18,19]Various modalities have been used to treat warts, but none are uniformly effective or directly antiviral.[20]High quality studies of therapeutic interventions for cutaneous warts are limited, complicating definitive recommendations on the best approach to therapy. Besides this, considering the lack of availability of facility of cryotherapy in every corner of Bangladesh for warty conditions, this study evaluated the efficacy of oral zinc sulfate and compared the efficacy of oral zinc sulfate with commonly using cryotherapy in the treatment of viral warts.

Methods

Aclinical trial was carried out with patients with viral warts from Department of Dermatology and Venereology, Bangabandhu Sheikh Mujib Medical University (BSMMU), Dhaka from July 2015 to December 2015.Simple random samplingtype of probability sampling technique was followed.Inclusion criterias were patients with viral warts with any age and sex; presence of multiple cutaneous or recalcitrant warts, that is, patients who submitted to two or more treatment approaches by destructive methods without resolution of clinical presentation were selected for oral zinc sulphate therapy; whose last treatment course finished at least two months before the study start; absence of chronic diseases like bronchial asthma, bronchiectasis, diabetes mellitus, hypertension etc; commitment not to use other drugs during treatment and patient who will give informed consent and willing to comply the study procedure.Exclusion criterias were presence of immunodeficiency like malignancy, chemotherapeutics treated patients, HIV infected patients etc; pregnancy and lactational period; use of immunosuppressant drugs like steroid, azathioprine, mycophenolate mofetil etc; medication to inhibit activity of cytochrome P450 like propranolol, amitriptyline, diazepam, omeprazole, diclofenac, ibuprofen, isoniazide, phenytoin etc; patients suffering from wart but those have contra-indications for cryotherapy likecold urticaria, abnormal cold intolerance, cryoglobulinemia, cryofibrinogen-emia, raynaud's phenomenon etc and patients who were unwilling to give informed consent to take part in the study.

Procedures of collecting data

Total sixty (60) patients with multiple recalcitrant cutaneous warts were recruited from Department of Dermatology and Venereology of Bangabandhu Sheikh Mujib Medical University (BSMMU) for a period of six months. Patients were randomly selected for group A and group B by lottery method. Thirty of group A patients was treated by cryotherapy and thirty of group B patients was treated by oral zinc sulphate. Group A was treated with cryotherapy and another group B was oral zinc sulphate 10 mg/Kg/day (maximum 600mg/day) for a total duration of six weeks. The cryotherapy treatment protocol were as follows: EMLA cream were applied to the wart 1 hour before treatment. The centre of the wart were sprayed with liquid nitrogen from a distance of 1 cm from the skin until the field were frozen. Patients were receive cryotherapy at weekly intervals using hand held cryosurgical unit, for a maximum of six sessions. Patients were given two freeze thaw cycles of 15 seconds freeze time each using spot freeze technique. In case of larger lesions, the field were divided into overlapping circles of 2 cm each. Each circle were treated separately, treating not more than 16-18 mm^2 area at a time. The parameters of the

assessment included size of wart (measured using measuring tape), and symptomatic improvement. No improvement when no flattening or <25% flattening and improvement were considered, when more than 25% flattening develoved. Patients were assessed the cosmetic appearance and the symptomatology for grading of the improvement. During each visit, the size of the wart were recorded in milimeters using the measuring tape. Patients were examined after every four weeks for sign and symptoms of regression of the warts, observing number of warts and side effects of the medication. Assessment were made 4 weekly after each treatment sessions.

Informed consent were obtained from all of the enrolled patients. Patient's age, sex, diagnosis, family history, presenting complaints and history related to the wart, predisposing factors, medications and present cutaneous status were noted. Detailed history and thorough physical examination were done in each patient to find out different arrays of skin manifestations. Routine investigation of patients were done to exclude the patients according to exclusion criteria and to assess the baseline status of the patients. The evaluation were applied at baseline and 4 weeks after the end of treatment periods.

Data were collected and recorded in a proforma. After collection, data were checked for inadequacy, irrelevancy, and inconsistency. Irrelevant data were discarded. Data were analyzed by computer with the help of SPSS (Statistical Package for the Social Sciences) windows 16 software package. Descriptive statistics were calculated, including mean, standard deviation (SD).To compare the proportion of clinical response, chi square test (x^2) and t test were applied. Statistical significance were set at 0.05 level and confidence interval at 95% level.

Ethical issues

The researcher was duly careful about ethical issues related to this study. In this study the following criteria was set to ensure maintaining the ethical values:

1. All patients were given an explanation of the study including the potential risks and obtainable benefits.
2. All patients were included in the trial after taking their informed written consent.
3. The researcher also explained them that they have the right to refuse or accept to participate in the study and they have the right to refuse during study period, if he or she desire.
4. The patients were not gain financial benefit from this study.
5. All data obtained during study period from the patients remained confidential.

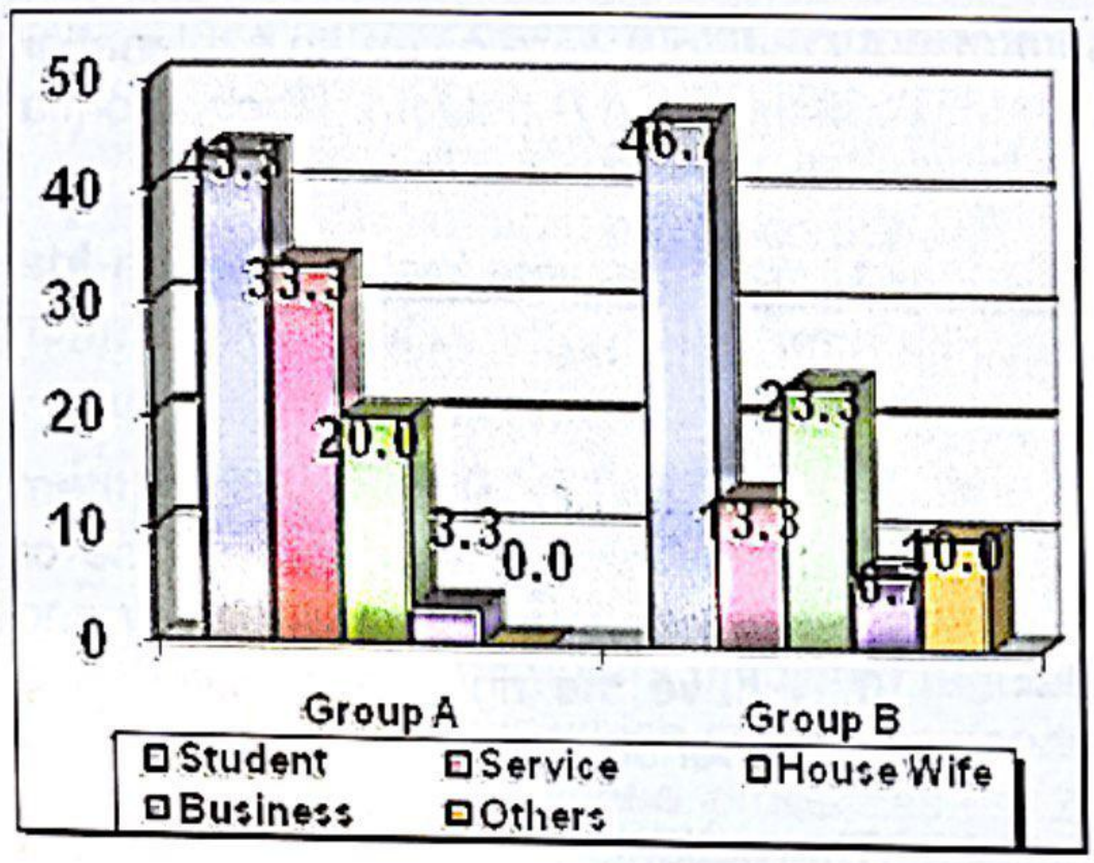
Results

Total sixty patients were enrolled and divided into group A and group B. Thirty of group A patients was treated by cryotherapy and thirty of group B patients was treated by oral zinc sulphate.

Table 1: Distribution of study groups by age.

Age in groups	Study groups				Total	
	GROUP A		GROUP B			
	n	%	n	%	n	%
≤15 Years	08	26.7	07	23.3	15	25.0
> 15 Years	22	73.3	23	76.7	45	75.0
Total	30	100.0	30	100.0	60	100.0
x^2 value = 0.089. df = 1. P = 0.766. Not Significant (> 0.05)						

The table 1 shows age distribution of two groups; one for ≤ 15 years and another for > 15 years. For Group- A, ≤ 15 years was 08 (26.7%) and > 15 years was 22 (73.3%). For Group- B, ≤ 15 years was 07 (23.3%) and > 15 years was 23 (76.7%). x^2 value = 0.089. df = 1. P = 0.766. The table shows that there was no statistically significant difference in two groups (> 0.05).



x^2 value = 6.019. df = 4. P = 0.198. Not Significant (> 0.05)

Figure I: Distribution of study groups by occupation (n=60).

Figure I shows that there was no statistically significant difference between patients of both groups in term of occupation. ^{2} value = 6.019. df = 4. P value= 0.198 (> 0.05). The maximum patients for both Group-A and B were students which was 43.3% and 46.7% respectively. The lowest incidence for both groups was business man which was 3.3% & 6.7% respectively.

Table 2: Distribution of study groups by duration of illness (n=60)

		N	mean	± sd	median	range	Sign.
Duration of Illness (Months)	GROUP A	30	10.00	7.24	08	2-36	t =1.010 P =0.316 NS
	GROUP B	30	8.20	6.54	06	1-24	
	TOTAL	60	9.10	6.90	06	1-36	

Table 2 shows that out of all respondents of Group-A, the duration of illness ranging from 2 months to 36 months, with an average of 10 months. In group-B, the duration of illness ranging from 1 month to 24 months, with an average of 8.20 months. No significant difference was observed. (p value = 0.316)

Table 3: Distribution of recovery pattern among site of lesion(n=60)

Site of lesion	Recovery pattern				Total	
	IMPROVED		NOT IMPROVED			
	n	%	n	%	n	%
Finger	18	34.6	00	0.0	18	30.0
Palm	17	32.7	05	62.5	22	36.7
Foot	10	19.2	00	0.0	10	16.6
Toe	04	7.7	03	37.5	07	11.7
Scalp	03	5.8	00	0.0	03	5.0
Total	52	100.0	08	100.0	60	100.0
x2 value = 8.670. df = 4. P = 0.070. Not Significant (> 0.05)						

Table 3 shows the recovery pattern according to the site of distribution of lesions. Improvement rate was highest for the lesions on the finger, which is 18 (34.6%) and lowest for scalp 03 (5.8%). Improvement rate for palm 17 (32.7%); for foot 10 (19.2%) and toe, 04 (7.7%). No improvement was found for the lesions on the palm and toe, which was 5 (62.5%) and 3 (37.5%) respectively. No statistical significant difference was observed between two groups. P value = 0.070 (> 0.05)

Table 4: Distribution of clinical responses among the study groups(n=60)

Size of lesion (mm)	Study groups	mean	± sd	median	range	Significance
Before Treatment	GROUP A	8.17	3.11	08	3 – 15	t = 0.779 P = 0.439 NS
	GROUP B	7.50	3.51	07	1 – 20	
After Treatment / 1st Visit at 4th Week	GROUP A	5.90	3.78	06	0 – 14	t = 0.104 P = 0.918 NS
	GROUP B	4.92	4.55	05	0 – 18	
After Treatment / 2nd Visit at 8th Week	GROUP A	4.32	4.34	05	0 – 12	t = 0.104 P = 0.918 NS
	GROUP B	3.00	5.52	00	0 – 18	
After Treatment / 3rd Visit at 12th Week	GROUP A	3.57	5.03	00	0 – 12	t = 0.104 P = 0.918 NS
	GROUP B	4.75	7.45	8.50	0 – 18	

Table 4 shows the clinical responses among the study groups. Out of all respondents from Group-A, the mean size of the lesions were 8.17mm, 5.90 mm, 4.32 mm, and 3.57 mm at before treatment and 1st visit, 2nd visit and 3rd visit after treatment respectively. In Group-B, the mean size of the lesions were 7.50 mm, 4.92 mm, 3.00 mm, and 4.75 mm at before treatment and 1st visit, 2nd visit and 3rd visit after treatment respectively. No statistical significant difference is observed between two groups.

Table 5: Distribution of recovery rate among the study groups(n=60)

Recovery Rate	Study groups				Total	
	GROUP A		GROUP B			
	n	%	n	%	n	%
Improved	27	90.0	25	83.3	52	86.7
Not improved	03	10.0	05	16.7	08	13.3
Total	30	100.0	30	100.0	60	100.0
x^2 value = 0.577. df = 1. P = 0.448. Not Significant (> 0.05)						

Table 5 shows the recovery rate after treatment. Among the respondents of group-A & B, 27 (90%) and 25 (83.3%) were improved respectively. The numbers of failure were 03 (10%) & 05 (16.7%) for Group-A and Group-B respectively. No statistical significant difference was observed between the two groups. P value = 0.448 (> 0.05).

Discussion

In our study, regarding age distribution of two groups-majorities were more than 15 years of age, similar to the study findings of Iffat Hassanet aland Sharquie KA.[21,16]Iffat Hassanet al conducted a study with 100 patients with viral warts over a period of one year. Of the 50 patients included in Group A, 41 patients completed the 6 weeks trial of zinc sulphate whereas in Group B only 33 patients completed the clinical trial. The mean age of participants in the placebo group was 30.28 ± 7.15 years and in the treatment group was 32.15 ± 8.10 years.[21]Sharquie KAconducted a study with one hundred patients aged 4-45 years (mean+/-SD 19.93+/-7.92) and diagnosed with multiple verruca vulgaris (common warts). [16]Out of all respondents of Group-A, the duration of illness ranging from 2 months to 36 months, with an average of 10 months. In group-B, the duration of illness ranging from 1 month to 24 months, with an average of 8.20 months.No significant difference was observed. (p value = 0.316). Sharquie KAconducted a study with viral warts with the duration of the viral warts ranged from 0.1-17 years (mean+/- SD 1.87+/-2.73).[16]

Out of all respondents from Group-A, the mean size of the lesions were 8.17mm, 5.90 mm, 4.32 mm, and 3.57 mm at before treatment and 1st visit, 2nd visit and 3rd visit after treatment respectively. In Group-B, the mean size of the lesions were 7.50 mm, 4.92 mm, 3.00 mm, and 4.75 mm at before treatment and 1st visit, 2nd visit and 3rd visit after treatment respectively. No statistical significant difference is observed between two groups.Among the respondents of group-A & B, 27 (90%) and 25 (83.3%) were improved respectively. The numbers of failure were 03 (10%) & 05 (16.7%) for Group-A and Group-B respectively. No statistical significant difference was observed between the two groups. P value = 0.448 (> 0.05). Mun et al conducted a study with thirty-one patients with multiple, non-genital viral warts. The patients were treated with oral zinc sulfate (10 mg/kg to a maximum dose of 600 mg/day) for 2 months and followed up with assessments for the resolution of their warts and for any evidence of recurrence after treatment. Of 26 patients who completed the study (84%), 13 (50%) showed complete resolution of their warts after 2 months of treatment. Complete responders remained free of lesions at 6-month follow-up. [22]

Iffat Hassan et al conducted a study with 100 patients with warts over a period of one year. Fifty patients were given oral zinc sulphate at the dose of 5mg/kg/day in two divided doses for a total duration of six weeks. Another 50 patients were given an oral placebo for the same period. Patients were examined after every two weeks for signs and symptoms of regression of the warts. A total of 26 patients (60.97%) showed complete resolution of the warts; 6 (14.6%) patients showed partial response; there was no response to treatment in 10 (24.3%) patients. In the placebo group there was partial response in 2 (6.45%) patients while 29 (93.5%) patients showed no response to placebo. [21]

Al-Gurairi FT conducted a placebo-controlled clinical trial to assess whether oral zinc was effective in treating viral warts of patients. Forty patients were treated by oral zinc sulphate at a dose of 10 mg kg(-1) daily up to 600 mg day(-1) and followed-up for resolution of their warts and for any evidence of recurrence for 2-6 months. Another 40

patients were given a placebo oral treatment in the form of glucose, and followed-up for the same period. Only 23 patients of the first group (zinc treated) and 20 patients of the second group (placebo treated) completed the study. In the zinc-treated group, the overall response was complete clearance of warts observed in 20 patients (86.9%) after 2 months of treatment. Fourteen patients (60.9%) showed complete disappearance of their warts after 1 month. Three patients (13.3%) failed to respond to the treatment after 2 months of therapy. No patient of the placebo-treated group showed any response. They concluded that zinc sulphate at a dose of 10 mg kg(-1) daily seems to be a highly efficacious therapeutic option for recalcitrant viral warts.[17]Sharquie KAconducted a study to verify the efficacy of the intralesional injection of 2% zinc sulphate as compared to an injection of 7% hypertonic sodium chloride solution in the treatment of viral warts. A total of 623 lesions were included in the study (mean+/- SD of lesions, 10.8+/-8.05). The treated number of lesions were 316 (mean+/- SD 4.78+/-5.09), with the untreated 307 lesions left as control. In 53 patients (30 females, 23 males), 173 lesions were treated with 2% zinc sulphate intralesionally, while 176 lesion were left untreated as control. The total clearance rate of the treated lesions were 98.2% within 6 weeks of follow-up (80.92% of lesions needed a single injection and showed total clearance within 2 weeks), while none of the control lesions showed any spontaneous clearance within the same period. In 47 patients (27 females, 20 males), 143 lesions were treated with 7% hypertonic sodium chloride solution intralesinally, with the remaining 131 lesions left untreated as control. Only 8.3% of treated lesions showed total clearance within 10 weeks of follow-up. Two percent zinc sulphate can be recommended as a new and effective local mode of therapy of viral warts, especially for the recalcitrant form. [16]

Mariane Stefaniconducted a random double-blind prospective study to compare the efficacy of cimetidine and zinc sulphate in the treatment of multiple and recalcitrant warts. Eighteen patients with multiple warts were divided into two groups: one took 35mg/Kg/day of cimetidine (maximum 1200 mg/day) and the other 10 mg/Kg/day of zinc sulphate (maximum 600 mg/day) for three months. Among the 18 patients who participated in the study, nine took cimetidine and nine zinc sulphate. Five patients who were treated with zinc sulphate were cured and only one did not show modifications in lesions. Among the group who was treated with cimetidine, five did not show modifications in lesions and four showed decrease from baseline below 30%. They concluded that 10 mg/Kg/day zinc sulphate dose seems to be more effective than cimetidine for the treatment of children and adults with multiple and difficult-to-handle warts.[18]

Conclusion

Both cryotherapy and oral zinc sulphate when used individually were found to be equally effective in the treatment of viral warts, but cryotherapy was found to be superior in efficacy. Further multicenter, randomized, double-blind study should be conducted with large sample size.

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