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RESEARCH ARTICLE

ORAL ZINC SULPHATE IN MULTIPLE AND RECALCITRANT WARTS

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ABSTRACT

Introduction: Cutaneous Warts are viral infection caused by human papilloma virus (HPV). In multiple warts or recalcitrant warts most of the destructive methods are painful therefore it is inappropriate.

Materials and Methods: All patients clinically diagnosed as having multiple or recalcitrant warts were included in the study. Digital photographs were taken and all data recorded in the predesigned proforma.

Results: There were total of 50 patients. Commonest age group of presentation was seen between 15 and 25years (should be deleted). Commonest age group of presentation was seen between 15 and 25years, 27(53%) patients, mean years of presentation was 36 years. Females were 60%. Commonest site of lesions was seen over face in 32%. 10 to 20 lesions were seen in 36% and more than 40 in 6%.Most common morphology of lesions were papules in 38%. In three month follow-up mild (25%) improvement was seen in 8%, moderate (50%) improvement in 34%, good (75%)improvement in 28% and excellent (100 %) improvement in 3(6%). Mild gastrointestinal side effects were seen in 4%.Drop out rate was 8%.

Conclusion: Oral Zinc sulphate is a novel therapeutic option for treatment of multiple and recalcitrant wart with fewer side effects compared to other surgical modality.

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INTRODUCTION

Warts are viral infection caused by human papilloma virus (HPV). The prevalence of warts is around 10% (Shanker, 2008). It is commonly seen in children and adolescents but can occur in any age. Most of the warts disappear in two years but in 35% they become recalcitrant (Massing, 1963). Various modalities of treatment options are available like electrocautery, cryosurgery, lasers and others but none are uniformly effective or directly anti-viral (Proietti *et al*., 2011). In multiple warts or recalcitrant warts most of the destructive methods are painful therefore it is inappropriate in respect to morbidity, psychological concern of the patients. Therapeutic options aimed at modulating the immune system as HPV infection doesn't evoke any inflammatory cytokines (Yaghoobi *et al*., 2009). Oral Zinc has immunomodulatory properties and been tried with patients having warts. There is paucity of literature on use of Oral Zinc for treatment of warts in Nepal. So with this study we want to know the clinical efficacy and side effects of the drug for the treatment of multiple and recalcitrant wart.

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MATERIALS AND METHOD

This study was designed as a Non randomized quasi experimental study including all patients above 15 years of age, who visited Dermatology outpatient department of Nepal Medical College and Teaching hospital and clinically diagnosed as having multiple warts (which is presence of ten or more warts) or recalcitrant wart (which is defined as patients who have been submitted to two or more treatment approaches by destructive methods without resolution of clinical presentation, whose last treatment course had finished at least two months prior to study). Consent was sought to be included in the study. Patients with mucosal warts or taking other drugs for warts or for any systemic disease for last two months prior to study or suffering with systemic illnesses or pregnancy and lactating were excluded for the study. The study period was between Jan 2017 to June 2017. All patients were clinically examined thoroughly to rule out any systemic disease. Digital photographs were taken at baseline and at the outcome assessment. All data including demographic profile, clinical, response of treatment and side effects was recorded in a predesignedproforma. All patients were given Oral Zinc sulphate 10mg/kg/body weight (maximum of 600mg) daily for 3months.

Baseline investigations were carried out to rule out any systemic disease. Statistical analysis was done using SPSS statistical software version 16 and descriptive analysis and Friedman test was used to study the significant association. p value less than 0.05 was considered significant.

RESULTS

A total of 50 patients were studied in this study. Mean years of presentation was 36 years. Commonest age group of presentation was seen between 15 and 25years, 27(53%) patients (See table 1). Thirty (60%) patients were females. For the profession, 18(36%) patients were students, 16(32%) employed, 10(20%) were housewives, and 6(12%) unemployed. Commonest site of presentation was seen over face in 16(32%) patients, followed by upper limbs 13(26%), scalp six (12%), soles six (12%), lower limbs two (8%), palms one (2%) and trunk one (2%).

DISCUSSION

Viral warts are skin (keratinizing) or mucosal (non keratinizing) proliferations caused by Human papilloma virus. Clinically divided into cutaneous warts, genital warts, oral warts and laryngeal warts. The cutaneous warts are further divided into verruca vulgaris, filiform, palmoplantar, periungual and flat. There are about 100 types recognized and characterized till date (Parton, 1994). The most common type causing cutaneous wart are 1,2 and 57.HPV 4 and 7 are rare and refractory to treatment observed mainly in butchers and dairy workers. Few lesions can be treated with treatment like surgical excision, electrocautery, cryotherapy, lasers, intralesionalbleomycin, topical keratolytics or 5% imiquimod. In multiple warts photodynamic therapy, topical sensitizer like dinitrochlorobenzene are found to be effective Sterling *et al*., 2001).

Table 1. Age distribution of the cohort

Age in years	Number of patients	Percentage
15-25	27	53
26-40	15	30
41-59	5	10
> 60	3	7

Table 2. Follow up of patients

Clinical Improvement	1 month follow up No.(%)	2 months follow-up No.(%)	3months follow-up No.(%)
None	11 (22)	3(6)	0
Mild (25%)	32 (64)	26(52)	12(24)
Moderate (50%)	5(10)	15(30)	17(34)
Good (75%)	2(4)	5(10)	14(28)
Excellent (100%)	0	0	3(6)
Drop out	0	1(2)	3(6)

Ten to twenty lesions were seen in 18(36%) patients, followed by 21-30 in 14(28%),31-40 in 11(22%),and more than 40 in 3(6%) patients. Size of the lesion was less than 1cm in 26(48%) patients, 1-5 cm in 20(40%) and more than 5cm in 6(12%) patients. Mostly lesions were papules in 19 (38%) followed by papule and plaques in 15(30%), plaques in 10(20%) and combinations of nodules, papules and plaques in 6(12%).In about 22(44%) patients, lesions were firm, smooth in 21(42%) with regular margin in 27(54%).General examination of all patients were unremarkable. Laboratory tests were normal in 48(96%) except for two patients with urine abnormality like pus cells and positive urine albumin. They were treated accordingly before start of treatment. During follow-up of one month no improvement was seen in 11(22%), 25% improvement was seen in 32(64%), 50% improvement in five (10%) and 75% improvement in two (4%) patients. Side effects like nausea and mild abdominal pain was seen in four (8%) patients (See Table 2). Follow-up in two months showed 25% improvement in 26(52%), 50 % improvement in 15(30%) and 75% improvement in 5(10%). Dropout rate was 2%. Side effect was seen in one (2%) patient who had gastrointestinal upset. Follow-up in three month showed 25% improvement in 4(8%), 50% improvement in 17(34%), 75% improvement in 14(28%) and 100 % improvement in 3(6%) patients. This improvement over 3 months was statistically significant ($p< 0.05$). Age of the patients was statistically significantly associated with clinical improvement ($p<0.05$). However, there was no significant association between sex and clinical improvement. No side effects were noticed dropout rate over 3 months was 8%.

In some cases due to large number of warts destructive methods are not feasible due to associated pain, scar and psychological trauma (particularly with recalcitrant type). Despite of different treatment modalities, the treatment of warts has not always been successful because of lack of antiviral medications against HPV.HPV infection being non-lytic, antigen presentation occurs very slowly. HPV infection doesn't induce inflammatory cytokines therefore therapeutic options aimed at modulating the immune system and facilitating the production of cytokines has been proposed (Parton, 1994). One of the immunomodulatory approaches involves treatment with Oral Zinc sulfate.

Zinc is micronutrient which is important for humans as an essential component of more than 300 metalloenzymes and over 2000 transcription factors that are necessary for regulation of lipid, protein and nucleic acid metabolism, and gene transcription. It is involved in gene transcription at various levels, via participation in his tone deacetylation reactions and via factors possessing the zinc-finger motifs. Kitamura *et al* proposed that Toll-like receptors mediated regulation of zinc homeostasis influences dendritic cell function. It regulates macrophage and neutrophil functions, natural killer cell activity, and complement activity. It activates natural killer cells and phagocytic function of granulocytes and stabilizes the plasma subcellular membranes like the lysosomes. The expression of integrins by keratinocytes is inhibited and modulates the production of TNF-α and IL-6 and decrease the production of inflammatory mediators like nitric oxide. Zinc also has antioxidant property and has been found useful in

preventing UV-induced damage and reducing the incidence of malignancies. It has also been demonstrated to possess anti-androgenic properties as it causes modulation of 5α-reductase type 1 and 2 activity (Kitamura *et al*., 2006; Nitzan, 2006; Brocard, 2007; Sharma, 1985; Gupta *et al*., 2014; Thappa, 2016). Oral Zinc sulfate is well established for the treatment of acrodermatitisenteropathica. In other zinc deficiency conditions like alcohol abuse, gastrointestinal affection, pancreatic failure, cirrhosis, poor absorption syndrome, burns, neoplasm, renal disease has been acknowledged. Some studies report therapeutic efficacy of Zinc sulphate on alopecia areata, cutaneous lesimaniasis, perifolliculitis capitis abscendens et sufodiens and inflammatory acne (Gupta *et al*., 2014; Nitzan, 2016). It has been shown that there is a deficiency of zinc in patients with multiple or recurrent warts (Raza *et al*., 2010). Zinc has been proven efficaci ous as with both topical and oral treatment modalities in common warts without significant adverse effects. Gurairi *et al.* in a placebo controlled trial found that oral zinc sulfate in a dose of (10 mg/kg/day) in common warts resulted in complete clearance in 87% after two months of therapy. Mun *et al.* found clearance rate was 50% with the same dose of oral zinc sulphate after 2 months. In a patient of recalcitrant wart with epidermodysplasia verruci form is lesions disappeared in 12 weeks with oral zinc (Gupta *et al*., 2014; Gurairi *et al*., 2002; Mun *et al*., 2011; Sharma *et al*., 2014; Stefani *et al*., 2009). A Brazilian study by Stefani *et al* found oral zinc better than oral cimetidine in multiple warts (Stefani *et al*., 2009). In a placebo controlled trial, Sadighha found 76.9.% improvement in Zinc treatment group in comparison to placebo whereas Garcia *et al* found that the efficacy of oral placebo and zinc sulfate to be similar with significantly more gastrointestinal side effect and couldn't find any difference between control and zinc treatment group. In a study by Waqas *et al* treatment with oral zinc found to have complete clearance in 62.2% (Sadighha, 2009; Lopez Garcia *et al*., 2009; Waqas *et al*., 2017). In our study we found complete clearance in only 6% after 3months of treatment. However, 28% had good improvement (75%) after 3 months. Side effects like minor gastrointestinal symptoms were seen in 8% of patients similar to available literature.

Conclusion

Oral Zinc sulphate is a novel therapeutic option for treatment of multiple and recalcitrant wart with lesser side effects compared to other surgical modality. Further clinical and population based research should be conducted to consolidate these findings for treatment, long term follow-up and true prevalence of the disease in the community.

Conflict of Interest: None

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