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Original Research

Cryotherapy plus oral zinc sulfate versus cryotherapy plus placebo to treat common warts: A double blind, randomized, placebo-controlled trial☆,☆☆

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ABSTRACT

Background: Cutaneous warts are caused by a small group of specific types of human papillomaviruses. Cryotherapy is a highly effective treatment for patients with viral warts; however, it is a painful method and usually requires several treatment sessions. Zinc is a trace element with many proven effects on the immune system.
Objective: Our aim was to assess the efficacy and safety of oral zinc sulfate in the treatment and recurrence rate of common warts.
Methods: Eighty-three patients with common warts participated in this double-blind, randomized, placebo-controlled trial. In both groups, three sessions of liquid nitrogen cryotherapy were performed for up to 2 months with 3-week intervals. The treatment group (n = 45) received oral zinc sulfate capsules in a dose of 10 mg/kg per day up to 600 mg day. The control group (n = 38) was provided with placebo of similar appearance. Treatment continued for 2 months and the follow-up period lasted up to 6 months.
Results: Warts completely resolved in 26 patients in the treatment group (68.4%) and 23 patients in the placebo group (63.9%; $p = .68$). Three patients (7.9%) in the treatment group and six patients (16.6%) in the placebo group has a recurrence of the warts ($p = .19$).
Conclusion: According to our study, the addition of zinc to cryotherapy was not beneficial in the treatment of patients with common warts nor did it prevent recurrences.

Introduction

Papillomaviruses are a large group of DNA viruses that induce warts (zur Hausen, 1996). Cutaneous warts are caused by a small group of specific types of human papillomaviruses. "Common warts" are the most frequent clinical presentation of the cutaneous warts (Plunkett et al., 1999) with an overall prevalence of 20% in school children and a decline thereafter with patients' increasing age (Massing and Epstein, 1963).

No specific antiviral therapy is available to cure warts. Although spontaneous recovery often occurs, it usually takes a long time, even years, for warts to resolve (Kirnbauer et al., 2008). There are several therapies for warts, but none that is uniformly effective in the elimination of the lesions and all have different adverse effects (Micali et al., 2004). Existing modalities focus primarily on the destruction or removal of visible lesions or induction of the immune system against infected cells. Cryotherapy with liquid nitrogen is one of the most effective treatments and destroys the warts by freezing the infected tissues. Treatment that is repeated every 3 weeks gives a 30% to 70% cure rate after 3 months for warts on the hands (Bourke et al., 1995).

Zinc is a trace element with a proven effect on the immune system and a deficiency causes reduced immune capacity and lymphopenia (Fraker, 1987). Zinc is considered an immunomodulator and has been used successfully to treat patients with skin diseases who have an altered immune response such as cutaneous leishmaniasis (Sharquie et al., 2001), erythema nodosum leprosum (Mahajan et al., 1994), alopecia areata (Lutz and Kreysel, 1990), and perifolliculitis capitis (Bern et al., 1985).

The role of oral zinc in the treatment of patients with cutaneous warts is controversial. A number of previous clinical reports have suggested that oral zinc sulfate can successfully treat cutaneous warts

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(Al-Gurairi et al., 2002; Mun et al., 2011; Yaghoobi et al., 2009). On the other hand, one study questioned this role (López-García et al., 2009). In this study, we used a combination of zinc sulfate and cryotherapy to evaluate any additive effect of zinc in the treatment and recurrence rate of common warts.

Methods

This study was a double-blind, randomized, placebo-controlled trial that was performed at Razi Hospital in Tehran, Iran from September 2011 to November 2012. Eighty-three patients were enrolled in the study.

The inclusion criteria for the study were patient age >7 years, more than two common warts, no history of systemic or iatrogenic immunosuppression, no use of medication or procedures for the treatment of warts within 6 months of the study, and not pregnant or currently breastfeeding. Patients were assigned to either the treatment or placebo group by simple randomization. All patients included in the study were informed of the treatment protocol and asked to sign an informed consent form. In the case of patients who were not of legal age, parents provided the consent on their behalf. The treatment was blinded to the patients, investigators, and pharmacist. Both products were similar in color, shape, and smell. The study was conducted in accordance with the Declaration of Helsinki.

Full patient history including age, sex, past medical and family history of disease, time since the warts first appeared, any previous treatment and/or systemic illnesses, sites and distribution of the warts, and any signs of zinc deficiency were recorded for each patient with a questionnaire.

Serum zinc was measured in all patients both at the beginning of the trial (baseline) and after discontinuation of the treatment (final) using the atomic absorption spectrophotometer assay method (Hitachi 902, Seoul, South Korea).

Patients in the treatment group received oral zinc sulfate in the form of 220 mg capsules (Al-havi, Tehran, Iran) in a dose of 10 mg/kg per day in three divided doses up to 600 mg/day. Patients in the placebo (control) group were given capsules of similar appearance that were filled with starch.

In both groups, liquid nitrogen cryotherapy was administered with a saturated, cotton-tipped applicator until an ice-ball formation had spread from the center to a margin of 2 mm around each wart with a double freeze-thaw cycle. Cryotherapy was repeated at intervals of 3 weeks for up 2 months. Cryotherapy and clinical assessments were performed by the same physician for all patients.

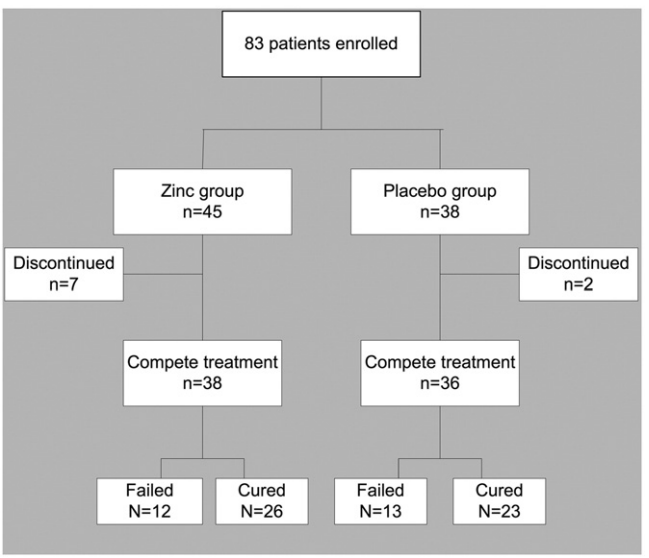

Fig. 1. Flowchart of study design and results

Due to the common digestive adverse effects of zinc sulfate, patients were recommended to take the drug with food and one glass of water or juice. If any drug adverse effect occurred, patients were recommended to stop the drug intake for 2 to 3 days. If the patient showed an adequate drug tolerance afterward, they were advised to keep taking the medication. Otherwise, they were told to discontinue the drug and excluded from the study.

The treatment trial lasted for 2 months and the follow-up period was up to 6 months. A cure was defined as the total elimination of all lesions and the appearance of any new warts in any location was considered a recurrence. With a statistically significant level of 0.05 and a statistical power of 80%, 40 patients in each group were needed.

The data analysis was performed with IBM SPSS Statistics for Windows (IBM Corp., Armonk, NY) Version 19. Standard deviation (SD) was calculated for means, and the comparisons were done by χ^2, paired T-test, and ANOVA tests for rates, means, and groups, respectively. A p-value <.05 was considered statistically significant. A logistic regression test was used to calculate odds ratio.

Results

Eighty-three patients (40 male; 43 female) participated in the study. A total of 38 of 45 patients in the treatment group and 36 of 38 patients in placebo group completed the study (Fig. 1). The demographic and clinical data of patients are shown in Table 1. The patients were assigned randomly to the groups, and there were no significant difference between the two groups with regard to age, sex, location, mean number of warts, and duration of the disease. No symptoms or signs of zinc deficiency were observed.

At the end of the study, the serum zinc level had increased significantly in patients in the treatment group ($p < .001$) but the change in the placebo group was not significant (Table 1). Twenty-six patients (68.4%) in the treatment group and 23 patients (63.9%) in the placebo group showed a complete resolution of their warts with no significant difference ($p = .68$). There was no difference in the cure rate in each session of the cryotherapy between the two groups (Table 3). Local side effects such as hyperpigmentation, hypopigmentation, and scar formation were seen in both groups with no significant difference.

In the treatment group, there was a high frequency of gastrointestinal adverse effects such as nausea (68.89%), vomiting (17.77%), and epigastric pain (17.77%) in comparison with the placebo group. Seven patients (15.56%) in the treatment group discontinued the drug because of severe nausea, vomiting, and epigastric pain. In the placebo group, 2 patients (5.13%) discontinued the treatment due to gastrointestinal adverse effects and acute appendicitis (1 patient each).

The mean duration of the disease was 16.84 ± 12.91 months in patients who were cured and 24.17 ± 15.97 months in patients with treatment failure ($p = .03$). The mean counts of the lesions in patients who were cured were 6.55 ± 5.49 and 9.75 ± 4.19 in patients with treatment failure ($p = .04$).

Only three patients in the study had a zinc deficiency (i.e., below 72 μg/dl in male and 70 μg/dl in female patients). One patient was completely cured without any significant rise in serum zinc levels, another patient had treatment failure, and another patient did not complete the study. No significant differences were observed between the basic and final serum zinc levels in patients who were cured and those with treatment failure (Table 2). Nine patients had a recurrence during the 6-month follow-up period including three patients (7.9%) in the treatment group and six patients (16.6%) in the placebo group. The recurrence rate was higher in the placebo group although the difference was not significant ($p = .19$; Table 3).

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