

ORIGINAL ARTICLE

A RANDOMIZED DOUBLE-BLIND PLACEBO-CONTROLLED CLINICAL TRIAL OF TWO STRENGTHS OF TOPICAL ZINC SULFATE SOLUTION AGAINST RECURRENT HERPES SIMPLEX

Fariba Iraji MD, Gita Faghihi MD*

Department of Dermatology, Isfahan University of Medical Sciences, Isfahan, Iran

Background and Objective – Recurrent herpes simplex is one of the most common infections in humans, but there is not yet an effective treatment to prevent recurrence. Topical zinc sulfate 0.5% to 20% was recently used to reduce recurrence of the infection, but the high concentrations caused severe irritation. In this study, the efficacy of topically administered zinc sulfate in reducing the frequency of herpes simplex attacks was assessed.

Methods – Sixty-four patients with recurrent herpes simplex referred to educational dermatology centers in Isfahan during 1999 – 2000 were enrolled in a double-blind clinical trial. Patients were randomized to treatment with topical zinc sulfate 0.05% or 0.025% or placebo for 6 months. No other drugs were permitted during the study. Patients were followed for possible side effects. Data analysis was performed using χ^2 (Chi-squared) and SPSS software.

Results – There was a statistically significant reduction (60% reduction from pre-treatment number of attacks) in the group receiving zinc sulfate 0.05% ($p < 0.01$) compared with the groups receiving zinc sulfate 0.025% (25% reduction) and placebo (16% reduction). There was no significant difference between the frequency of recurrence in patients receiving placebo or 0.025% zinc sulfate at the end of 4 months of follow-up. After 6 months, the recurrence rate in patients treated with zinc sulfate 0.05% was much lower than that in the other two groups.

Conclusion – Topical zinc sulfate 0.05% was an effective therapeutic modality against recurrent herpes simplex compared with either a lower concentration or placebo.

Keywords herpes simplex topical therapy zinc sulfate

Introduction

Recurrent herpes simplex is a very common viral infection worldwide, for which many treatment modalities have been proposed. Orolabial herpes simplex virus (HSV) infection is caused most commonly by serotype HSV1, which affects more than 85% of adult populations worldwide. HSV2 is the most common cause of genital herpes and accounts for an estimated 20 – 50% of genital lesions.¹

In the past, topical zinc sulfate solution 0.5% to 20% was used for recurrent herpes simplex,

especially for herpetic keratoconjunctivitis, but it was soon discontinued because of severe irritation and dryness of skin and mucous membranes caused by the drug.²

The main objective of the current study was to determine the efficacy of low concentrations of topical zinc sulfate solution in reducing recurrent HSV infection and reducing the possibility of local cutaneous or mucosal side effects.

Materials and Methods

Sixty-four patients (48% male and 52% female; aged 2–56 years, mean 22.5 years); presenting at the educational dermatology clinics in Isfahan between October 1999 and May 2000 were enrolled in a simple randomized double-

* Correspondence: G. Faghihi MD, Department of Dermatology, Isfahan University of Medical Sciences, Isfahan, Iran.
P.O. Box: 81668 – 13671, E-mail: yaldarad22@yahoo.com.

Topical Zinc Sulfate for Recurrent Herpes Simplex

Table 1. The prevalence of different anatomic sites of HSV involvement in patients.

Anatomic site	Prevalence rate
Orofacial	69%
Genital	18%
Limbs	12.5%
Trunk	11%

blind placebo-controlled clinical trial. All fulfilled following criteria:

- 1- At least one attack of herpes infection during the past two months and recurrent HSV infection;
- 2- No history of drug hypersensitivity, pregnancy and breast-feeding (at the time of study); and
- 3- No medications other than the study drug.

Patients were randomly divided into three treatment groups. In the first group, lesions were compressed with 0.025% zinc sulfate solution (Alhavi Pharm Co, Iran) made by dissolving the salt in 0.9% saline solution. The dressing remained in place for ten minutes once daily during the acute phase, for ten minutes once weekly for one month, and for ten minutes every two weeks until the end of the follow-up period (total 6 months). In the second group, lesions were compressed with 0.05% zinc sulfate solution. The treatment protocol was the same as that for the first group. In the last group, a placebo compress was applied according to the same protocol. Zinc sulfate was not applied to oral mucosal lesions due to side effects such as irritation and nausea.

All patients were visited at 14-day intervals for one month and then at monthly intervals to the end of the 6 months. At each visit, the number of attacks, patient tolerance, any complications and subjective symptoms were recorded. Data were analyzed using χ^2 and SPSS software. The statistical power was $\hat{\alpha} = 0.9$ and the probability of first-degree error was $\hat{\alpha} = 0.05$.

Results

A total of 20 patients (31.3%) were immunocompromised due to diabetes mellitus,

immunosuppressive therapy, leukemia or HIV infection. The most prevalent anatomic sites of HSV involvement are shown in Table 1.

The results are summarized in Table 2. At the end of the 4th month of follow-up, there were no significant differences in the recurrence rate of HSV among the three groups of patients. At the end of the 6-month follow-up period, there was a statistically significant reduction (60% compared to pre-treatment number of attacks) in the group treated with zinc sulfate 0.05% ($p < 0.01$) compared with the groups treated with zinc sulfate 0.025% (25% reduction) and placebo (16% reduction).

No serious complications occurred in any of our patients during treatment. There was no difference in the results with zinc sulfate 0.025% and placebo in our patients ($p > 0.05$).

Discussion

Zinc ions inhibit the activity of HSV-specified DNA polymerase, like other well-known therapeutic agents (e.g. acyclovir), but the hypothesis that zinc might block HSV replication by selective intranuclear inhibition of viral DNA polymerase appears to have lost its validity.³ It is thought that zinc binds to sulfhydryl groups of viral glycoprotein B and that when zinc accumulates in the virion, glycoprotein functions are inhibited, leading to the dramatic antiviral effect.⁴ The daily topical application of zinc sulfate 0.1% was apparently successful in long-term prevention of HSV reactivation.⁵ In a small controlled trial, ten-minute soaking with zinc sulfate solution (0.025 – 0.05% in water) on the expected site of herpes simplex reactivation (repeated two to four times monthly) did not show any therapeutic response.²

In another study, however, topical application of zinc sulfate 0.05% reduced the frequency of herpetic attacks during a period of 16 – 23 months.⁶ A third report showed that topical treatment with zinc sulfate 0.5% gave the same results, but the 10-fold rise in concentration again

Table 2. The results of treatment in three different groups of patients.

Groups of patients	Reduction rate	Total number of attacks		
		Baseline	4 months	6 months
Placebo	16%	77	70	65
Zinc sulfate 0.025%	25%	61	50	46
Zinc sulfate 0.05%	60%	62	48	25

Comparing the results of placebo and zinc sulfate 0.025%: $p > 0.05$. Comparing the results of zinc sulfate 0.05% with the other groups: $p < 0.01$.

caused some irritation.⁷

Humoral and cell-mediated immunity do not fully protect against recurrent herpes simplex, but where immunity is deficient, recurrent herpetic infection may be more frequent and more severe.^{8, 9} In our study, 31.3% of patients had some degree of immunodeficiency. These patients responded less to treatment than immunocompetent individuals. Mild uncomplicated eruptions of herpes simplex require no treatment, but frequent recurrences and any associated erythema multiform should be suppressed by safe and cost-effective long-term treatment.^{10, 11}

Zinc can also regulate human DNA and RNA polymerases and thymidine kinase, so plays an important role in normal immunological functions.¹²⁻¹⁴

Zinc ions have been reported to be antiviral to HSV. Long-term topical application of zinc salts appears to greatly reduce or eliminate recurrence of genital herpetic infections.¹⁵ Zinc ions can precipitate protein, and Sharquie et al clearly showed that zinc sulfate causes very high inhibition of growth of amastigotes of *Leishmania* spp.¹⁶ Thus, zinc sulfate has been used to treat oriental sores. Zinc monoglycerolate is also effective against oral herpetic sores.¹⁷

Further studies must be carried out to determine the mechanisms of the response of HSV infection to zinc ions, which could be through enhancement of the host's cellular immunity.

Acknowledgments

We wish to thank Dr. M.R. Radan MD, for his assistance in drafting the manuscript. Our regards also go to the Research Council of Isfahan University of Medical Sciences and the Head of the Dermatology Department and the Manager of International and Foreign Affairs of Isfahan University of Medical Sciences, School of Medicine.

References

- 1 Nahmias AJ. Sero-epidemiological and sociological patterns of herpes simplex virus infection in the world. *Scand J Infect Dis Suppl.* 1990; **69**: 19 – 36.
- 2 Graham RM, James MP, Bennett S. Low concentration zinc sulphate solution in the management of recurrent herpes simplex infection. *Br J Dermatol.* 1985; **112**: 123 – 4.
- 3 Kumel G, Schrader S, Zentgraf H, et al. The mechanism of the antiherpetic activity of zinc sulfate. *J Gen Virol.* 1990; **71**: 2989 – 97.
- 4 Kumel G, Schrader S, Zentgraf H, et al. Therapy of banal HSV lesions: molecular mechanisms of the antiviral activity of zinc sulfate [in German]. *Hautarzt.* 1991; **42**: 439 – 45.
- 5 Highet AS, Kurtz J. Viral infections. In: Rook A, Wilkinson DS, Ebling FJG, et al, eds. *Textbook of Dermatology.* Oxford: Blackwell Scientific; 1998: 2892.
- 6 Brody I. Topical treatment of recurrent herpes simplex and post herpetic erythema multiform with low concentrations of zinc sulphate solution. *Br J Dermatol.* 1981; **104**: 191 – 4.
- 7 Arens M, Travis S. Zinc salts inactivate clinical isolates of herpes simplex virus *in vitro.* *J Clin Microbiol.* 2000; **38**: 1758 – 62.
- 8 Goldgeier MH, Cohen SR, Braverman IM, et al. An unusual and fatal case of disseminated cutaneous herpes simplex infection in a patient with cutaneous T-cell lymphoma (mycosis fungoides). *J Am Acad Dermatol.* 1981; **4**: 176 – 80.
- 9 Greenberg MS, Friedman H, Cohen SG, et al. A comparative study of herpes simplex infections in renal transplant and leukemic patients. *J Infect Dis.* 1987; **156**: 280 – 7.
- 10 Huff JC. Acyclovir for recurrent erythema multiform caused by herpes simplex. *J Am Acad Dermatol.* 1988; **18**: 197 – 9.
- 11 Mindel A, Faherty A, Carney O, et al. Dosage and safety of long-term suppressive acyclovir therapy for recurrent genital herpes. *Lancet.* 1988; **1**: 926 – 8.
- 12 Lonnerdal B, Stanislawski AG, Hurley LS. Isolation of a low-molecular-weight zinc binding ligand from human milk. *J Inorg Biochem.* 1980; **12**: 71 – 8.
- 13 Lutz G, Kreysel HW. Selective changes in lymphocytic differentiation antigens in the peripheral blood of patients with alopecia areata treated with oral zinc [in German]. *Z Hautkr.* 1990; **65**: 132 – 4, 137 – 8.
- 14 Tong TK, Andrew LR, Albert A, et al. Childhood acquired immunodeficiency syndrome manifesting as acrodermatitis enteropathica. *J Pediatr.* 1986; **108**: 426 – 8.
- 15 Eby GA, Halcomb WW. Use of topical zinc to prevent recurrent herpes simplex infection: review of literature and suggested protocols. *Med Hypotheses.* 1985; **17**: 157 – 65.
- 16 Sharquie E, Najim RA, Farjou IB, et al. A comparative controlled trial of intralesionally-administered zinc sulfate, hypertonic sodium chloride and pentavalent antimony compound against acute cutaneous leishmaniasis. *J Clin Exp Dermatol.* 1997; **22**: 69 – 73.
- 17 Apisariyakulm A, Buddhasukh D, Apisariyakul S, et al. Zinc monoglycerolate is effective against oral herpetic sores. *Med J Aust.* 1990; **152**: 54.