

A RANDOMIZED CLINICAL TRIAL ON THE TREATMENT OF ORAL HERPES WITH TOPICAL ZINC OXIDE/GLYCINE

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Context • A zinc preparation that provides a higher concentration of solubilized zinc in a minimally irritating formulation allowing controlled absorption would be of great clinical value for treating oral herpes.

Objective • To determine the effect of zinc oxide/glycine cream as a treatment for facial and circumoral herpes infection by measuring duration and intensity of signs and symptoms and assessing adverse effects.

Design • Double-blind, placebo-controlled, randomized clinical trial.

Setting • Subjects were enrolled from the general community through advertisements.

Patients • Forty-six subjects with facial or circumoral herpes infections.

Intervention • Application of a zinc oxide/glycine cream or a placebo cream every 2 hours until cold sore resolved or 21 days elapsed.

Main Outcome Measures • Duration of cold sore lesions, severity of signs and symptoms, and frequency of adverse effects.

Results • Subjects who began treatment with a zinc oxide/glycine cream within 24 hours of onset of signs and symptoms experienced a significantly shorter duration of cold sore lesions (mean, 5.0 days) than did subjects treated with a placebo cream (mean, 6.5 days). Subjects treated with the zinc oxide/glycine cream also experienced reduction in overall severity of signs and symptoms, particularly blistering, soreness, itching, and tingling. Side effects among subjects treated with zinc oxide/glycine cream were those expected from an ionic zinc salt solution. All were completely reversible and of short duration.

Conclusion • Zinc oxide/glycine cream is an effective treatment for facial and circumoral herpes infection with predictable adverse effects that are completely reversible. (*Altern Ther Health Med.* 2001;7(3):49-56)

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The value of zinc in tissue growth and repair is well documented. When applied to herpetic lesions, zinc decreases viral load and markedly improves healing rates, relieving the symptoms of herpes as healing occurs.^{1,2} It has been postulated that the delivery of a high concentration of the virucidal agent to the site of infection may prevent retrograde spread of virus along involved ganglia.³

ZINC PHYSIOLOGY

Zinc is essential for the function of at least 70 enzymes critical to human metabolism and is a limiting factor in the regulation of RNA and DNA production through zinc-dependent enzymes such as RNA and DNA polymerases, deoxythymidine kinase, and reverse transcriptase. Diminished zinc availability slows protein synthesis, thereby slowing the replication of cells and inhibiting tissue repair. Even though the skin boasts a higher zinc concentration than most tissues (10 µg/g of tissue), this concentration is quickly depleted during the regeneration process.⁴ It has been shown experimentally that the activity of deoxythymidine kinase in rapidly regenerating connective tissue decreases as early as 6 days after animals are placed on a zinc-deficient diet,⁵ demonstrating that an external supply of zinc for use in tissue repair is essential. In fact, zinc supplementation has been shown to markedly improve wound healing in zinc-deficient persons,⁶ and topical zinc improves wound healing regardless of whether the patient is zinc deficient.^{7,8}

ZINC SAFETY

The safety of zinc supplements in excess of the amounts found in a normal diet is well documented. Although excessive zinc produces signs and symptoms of poisoning, such as nausea and vomiting, these signs and symptoms are rare. With topical application of zinc salts, no significant increase in serum levels of zinc or evidence of toxic effects have been noted.⁷ Reports of zinc poisoning are relatively rare. Except for extremely large doses (more than 150 mg/day for extended periods), zinc is nontoxic.

Whereas some prescription medications have been clinically proven to alleviate the discomfort of circumoral herpes and to effect small reductions in lesion duration,^{9,10} this study was undertaken and designed to take advantage of the antitherpetic effects of ionic zinc. The goal was to provide a simple, effective,

nonprescription medication capable of delivering ionic zinc to circumoral herpetic lesions.

OBJECTIVES

The purposes of this study were (1) to determine the effect of zinc oxide/glycine cream as a treatment for facial and circumoral herpes infection; (2) to investigate the latency (time between onset and recovery) of the signs and symptoms of facial and circumoral herpes sores as a function of treatment with zinc oxide/glycine cream or placebo; (3) to evaluate the safety of as many as 10 topical applications per day of ionic zinc at 2.7 to 3.1 mg/g (0.3%) in a cream base for up to 21 days, compared with placebo; and (4) to measure the amount of zinc oxide/glycine cream used by subjects to confirm compliance and estimate dosage requirements.

STUDY DESIGN

A total of 59 subjects were screened for entry into the study. Each subject signed the approved, written informed consent form before entering the study, consistent with the current regulations in Title 21, Code of Federal Regulations, Part 50. This study was reviewed and approved by the Southern California University of Health Sciences Internal Review Board.

Subjects were men and women aged 18 to 65 years, solicited by advertisement. Subjects had signs and symptoms consistent with herpes simplex virus (HSV) infection of no more than 24 hours' duration. They must previously have had an HSV infection diagnosed at the same facial or circumoral location.

Subjects were excluded if any of the following factors were present: (1) a history of any adverse response to oral or topical preparations of zinc, to cream base, or to glycine; (2) a history of immunodeficiency or a current condition or medication causing immunosuppression; (3) evidence of another dermatologic illness; (4) signs of disseminated HSV disease or of ocular involvement; (5) concurrent use of oral or topical antiviral medication or use in the week preceding entry into the study; or (6) pregnancy or lactation.

Following the protocol, treatment was discontinued during the active medication period of the study if (1) the subject had signs or symptoms inconsistent with a herpes infection or signs of a disseminated infection or ocular involvement developed, (2) either the investigator or the sponsor considered a subject to be unsuitable or medically compromised by an adverse reaction or therapeutic failure, (3) a protocol violation occurred during participation or was recognized after entry of the subject into the study, (4) the subject was noncompliant or failed to cooperate in following protocol requirements, and (5) the subject requested withdrawal from the study.

The subjects were evaluated by a physician or study nurse to confirm the presence of facial or circumoral herpes infection and to verify that none of the excluding conditions were present. Subjects were free of antiviral therapy for 7 days prior to entry into the study.

Jars of the zinc oxide/glycine cream and placebo cream were labeled with subjects' study numbers, which were assigned to either the experimental or the placebo group on the basis of a computer-generated randomization table created by using the

computer's timer as the seed and a blocking factor of 4. These jars were identical in appearance, smell, taste, and weight. They were supplied to the principal investigator by the sponsor, along with individual sealed, opaque envelopes for each study number so that the code could be broken for an individual subject without unblinding the study. Because no adverse effects warranting medical intervention were observed, none of these envelopes were opened during the study.

Qualified subjects were issued a 21-day supply of either zinc oxide/glycine cream or matching placebo cream at entry and were instructed to apply the cream, using a clean fingertip, to the site of infection at approximately 2-hour intervals during waking hours each day. Subjects made the first application at the clinic under supervision. They were observed for 20 minutes thereafter. A clinician instructed and assisted subjects to (1) rate signs and symptoms before the first application of the cream and (2) rate signs and symptoms 20 minutes after application of the cream.

Ratings were recorded in a subject diary. Symptoms were rated and recorded at 8 PM each day subjects were in the study. Signs and symptoms evaluated were tingling, itching, burning, tenderness, prickling, soreness, bump/swelling, small blister(s), oozing blister(s), and crusting. During the study, subjects were allowed to take Tylenol (acetaminophen) if needed (eg, to relieve a headache). Prescription medication unrelated to this study was left unchanged.

Subjects were telephoned once per week for midstudy interviews until a final study visit upon resolution of signs and symptoms, or on day 21 of the study. Subjects were asked, "How do you feel today?" No suggestive or leading questions were asked. Responses were recorded as part of the subject's record with attention to adverse effects. The side effect reasonably expected from the use of the study medications was an astringent or burning sensation immediately upon application.

Subjects were seen within 24 hours of resolution of signs and symptoms or on study day 21 to assess their status and to collect the subjects' diaries.

STATISTICAL ANALYSIS

A reduction of a least 1 day in the duration of the cold sore was considered necessary for the zinc/glycine cream to be considered of clinical value.⁹ Therefore, it was estimated that to see at least a 1-day reduction in duration, with an α error of no more than .05 and a β error of no more than .10 (ie, a power of .90), this preliminary study would have to yield at least 46 evaluable subjects.

For statistical analysis, the cold sore was considered resolved when only crusting remained.¹¹ The primary analysis was based on subjects who were determined to be evaluable at the data classification meeting before breaking the study code; that is, they met protocol entry and continuation requirements, had applied the cream substantially according to the protocol, had kept an adequate study diary, had not used any other medicinal or herbal treatment for their cold sores, and did not use antibiotics or antiviral agents while in the study.

Checks for kurtosis and skewedness indicated that parametric statistical analysis was appropriate. It was decided a priori

that if neither of these 2 values was significant, then parametric statistics would be used for the analysis of cold sore durations.

RESULTS

The total number of subjects enrolled in the study was 59. Eight subjects were dropped from the study due to protocol violations. Another 3 subjects stopped using the medication before the cold sore had resolved, and 1 subject was lost to follow-up. Protocol violations included 3 subjects who stopped and then restarted medications without consulting with the investigator; 1 subject (aged 70 years) who was outside the age span specified in the protocol; 1 subject who had signs and symptoms for almost 2 days before entry into the study (per protocol, subjects should have had signs or symptoms for less than 24 hours); 4 subjects who did not use the medication a minimum of 3 times a day; and 1 subject in whom a cold sore never developed after the onset of tingling. There were 46 evaluable subjects, of whom 24 received the zinc oxide/glycine cream and 22 received the placebo.

Returned medications for both groups were evaluated for the amount of cream used. Two subjects failed to return the medication as directed. Of the medications returned by subjects, the mean total amount of cream used in the active group was 3.93 ± 3.75 g, whereas the mean total amount of cream used in the placebo group was 5.35 ± 4.44 g.

The cold sore was considered resolved when only crusting remained.¹¹ An independent *t* test was used to compare the

results from placebo and zinc-treated subjects. However, before a *t* test was performed, both distributions of durations were checked for deviations from normality. Coefficients of skewedness and kurtosis were computed; both were insignificant.

For the zinc-treated subjects, the mean duration of the cold sore until resolution was 5.0 days (SD = 1.7 days), whereas the mean duration until resolution for subjects using placebo was 6.5 days (SD=2.5 days). This 23.6% reduction in cold sore duration is significant at the .05 level ($t=2.462$, $P=.018$) (Figure 1). From day 2 on, the percentage of the initial number of signs and symptoms experienced by the zinc-treated subjects averaged less than that of the placebo subjects (Figure 2).

Side effects included 1 subject using the active medication who dropped out because of a burning sensation when the cream was applied, and 1 subject using the placebo who dropped out because of lack of improvement of the sore and itching when the cream was applied. The subject in whom a blister never developed (who was using active medication) reported a tingling sensation with cream application.

Adverse effects (ie, effects that were to be expected from the action of ionic zinc on inflamed tissue), consisted of transient, mild to moderate sensations of burning, stinging, itching, and tingling that were more frequent in subjects using the zinc cream than in subjects using the placebo cream (see Table). All adverse effects resolved spontaneously. No unexpected effects of the treatment were noted in this study.

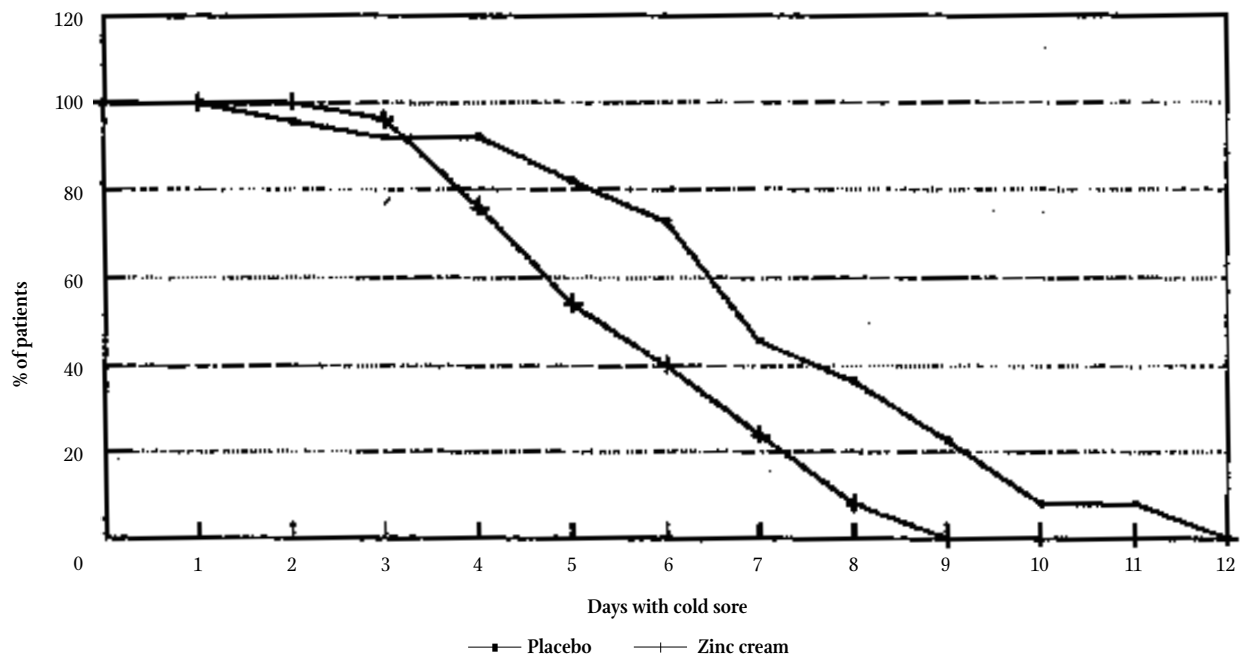


FIGURE 1 No. of days until all signs and symptoms of cold sore are resolved

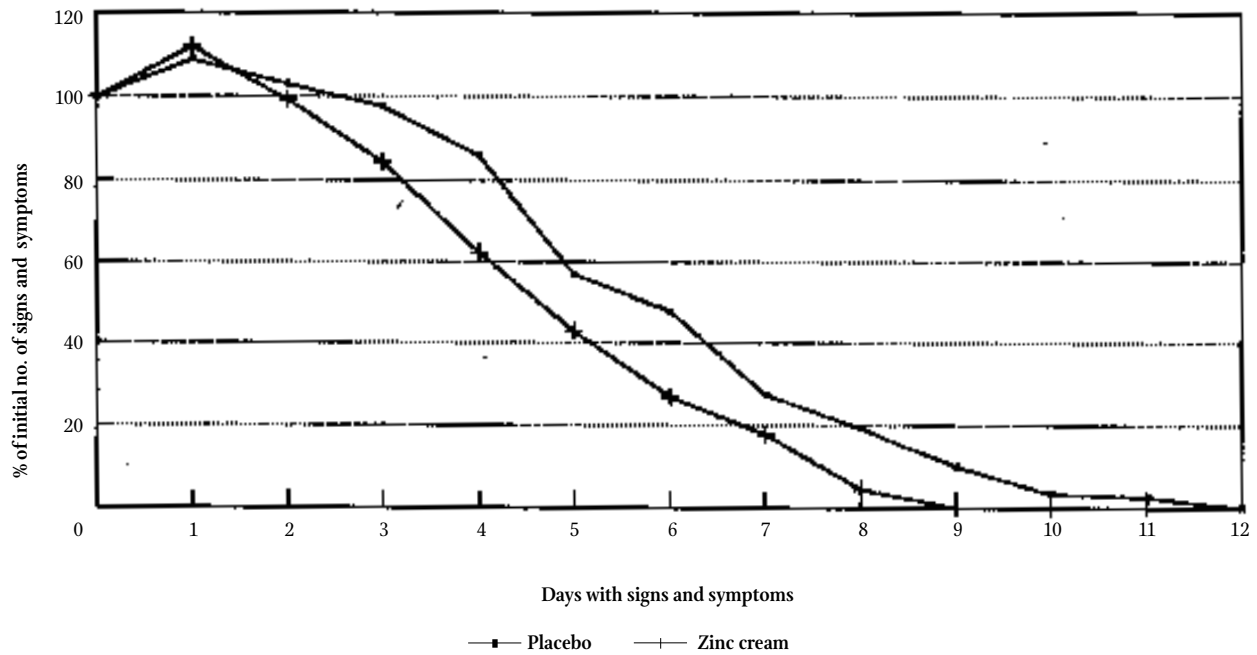


FIGURE 2 Percentage of the initial signs and symptoms of cold sores by day

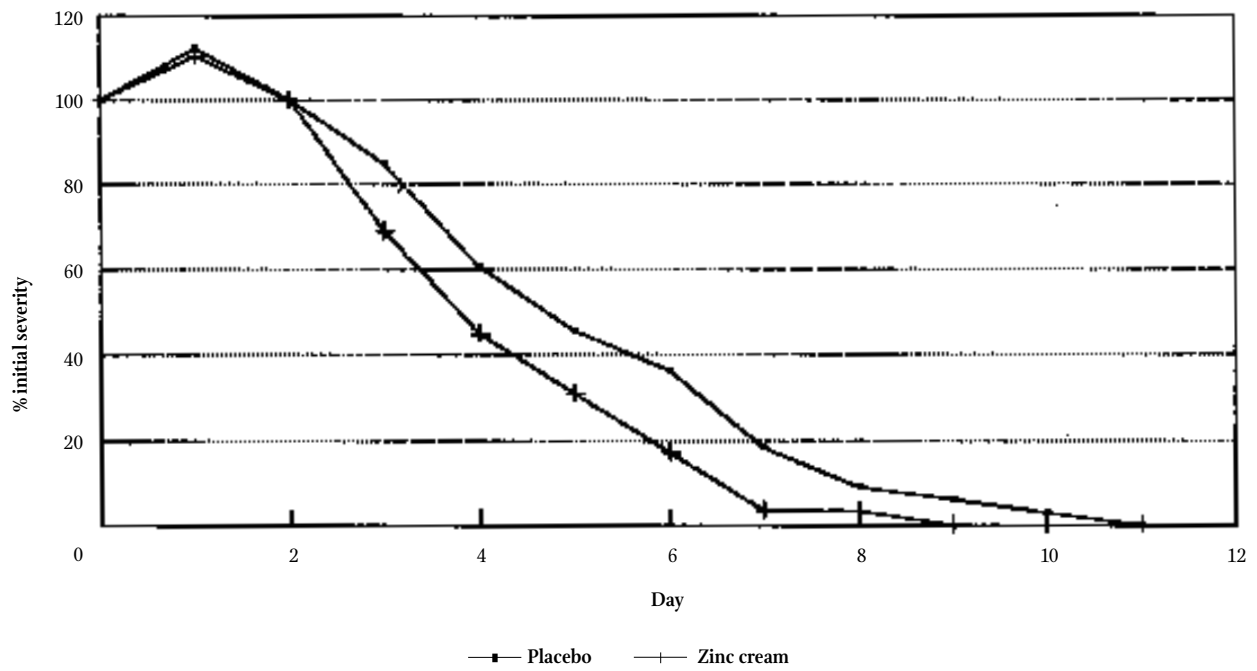


FIGURE 3 Percentage of initial severity of cold sore blisters by day

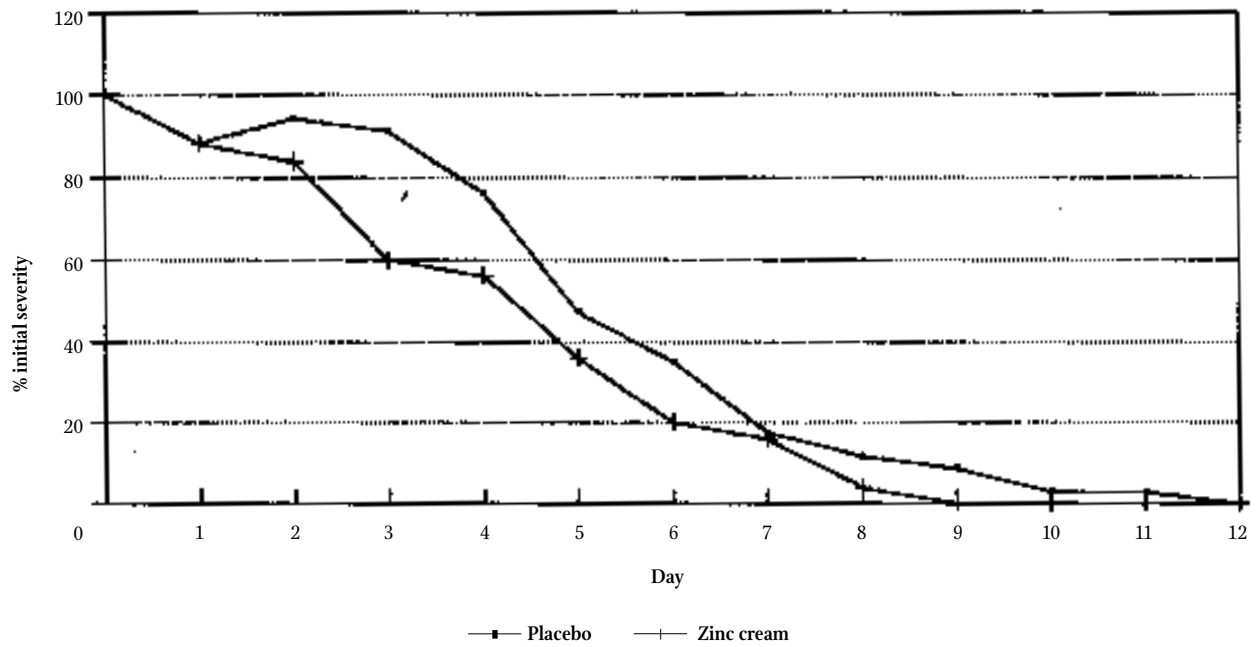


FIGURE 4 Percentage of initial severity of soreness of cold sores by day

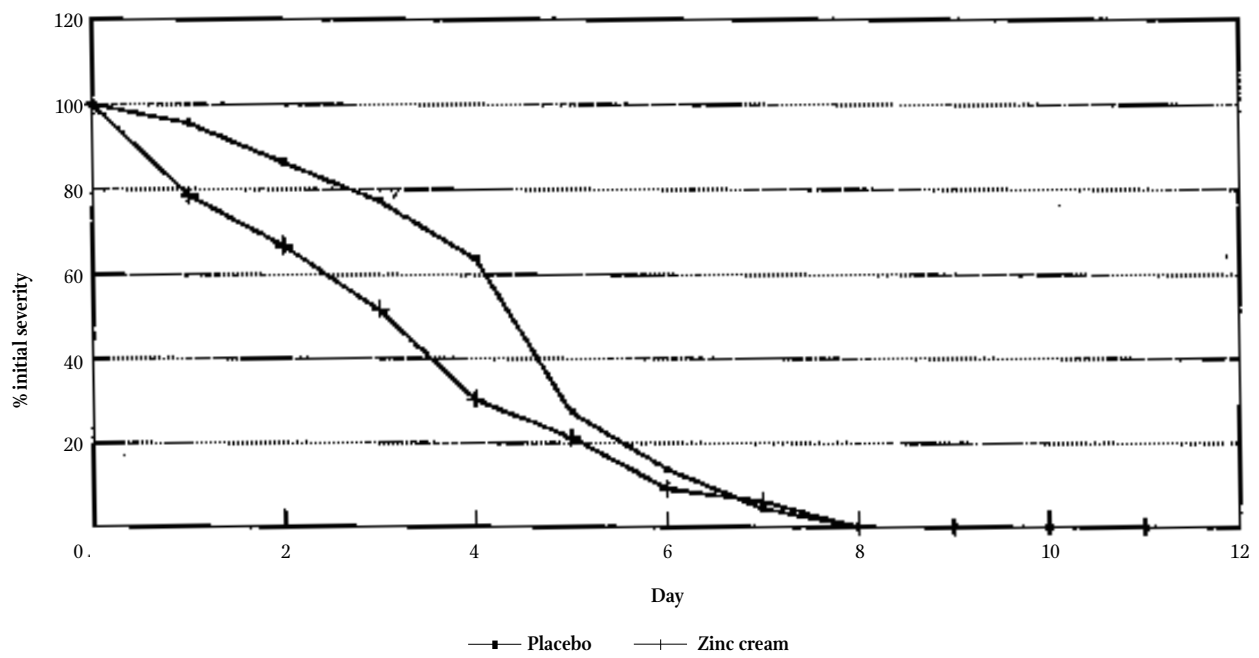


FIGURE 5 Percentage of initial severity of tingling of cold sores by day

This was the first study of its type designed by the investigators, so a broad range of signs and symptoms was considered. It was not known which signs or symptoms would be affected most by the treatment, or which signs and symptoms would overlap. In some cases, the descriptors used were too similar to be distinguishable by the subjects. It was planned that crusting would be listed with the signs and symptoms, but not evaluated as such; instead it would be used as a lesion end point. Also, it was decided a priori to combine all of the signs and symptoms (except for crusting, which was used only as an end point) to compute a total symptom severity score for each subject.

By the end point, all of the signs and symptoms showed improvement with the use of the zinc cream. Certain signs and symptoms, however, were more dramatically affected by the treatment than were others. In particular, the percentage of initial severity by day for small blister(s), for soreness, for tingling, and for itching experienced by zinc-treated subjects all showed a relatively steady decrease in severity compared with those percentages in the placebo-treated subjects (Figures 3-6).

DISCUSSION

Herpes of the lips occurs in 50% of the population,¹² and genital herpes is now one of the most common venereal diseases. The most common form of HSV disease is recurrent infection. After acute infection, the virus resides in the associated dorsal root ganglion and circulates along the endoneural sheath to the

skin if there is a breakdown in host defenses. The resulting self-limiting illness may begin with a prodrome of tingling, itching, or discomfort, as well as more generalized signs and symptoms such as nausea, fatigue, or fever. Although some subjects experience pain without rash, the characteristic maculopapular-vesicular eruption develops in most patients. Although silent shedding without evidence of rash can occur in 2% to 5% of subjects, shedding and risk of transmission is greatest in the first 96 hours after appearance of a rash.¹² Healing usually begins 7 to 10 days after onset of signs and symptoms and is complete by 21 days.¹¹ Zinc salts irreversibly inhibit herpes virus replication *in vitro* and are effective for treating herpes infections *in vivo*.¹³

Zinc salt solutions applied to herpetic lesions decrease viral load and markedly improve healing rates, relieving the signs and symptoms of herpes as healing occurs.^{1,2} Zinc ions irreversibly inhibit HSV glycoprotein functions by accumulating in the sulfhydryl groups of glycoprotein B in the viral membrane, blocking synthesis of DNA.^{14,15} In the closely related rhinovirus, it is theorized that free zinc ions also sequester in the convoluted surface of the virus, inhibiting viral binding with intercellular adhesion molecule receptor sites in mucous membranes.¹⁶ Long-term topical application of zinc salt solutions appears to greatly reduce or eliminate recurrence of genital herpetic lesions and prevent postherpetic erythema multiforme.¹⁷ The delivery of a high concentration of the virucidal agent to the infection site may prevent retrograde spread of virus along involved ganglia.³

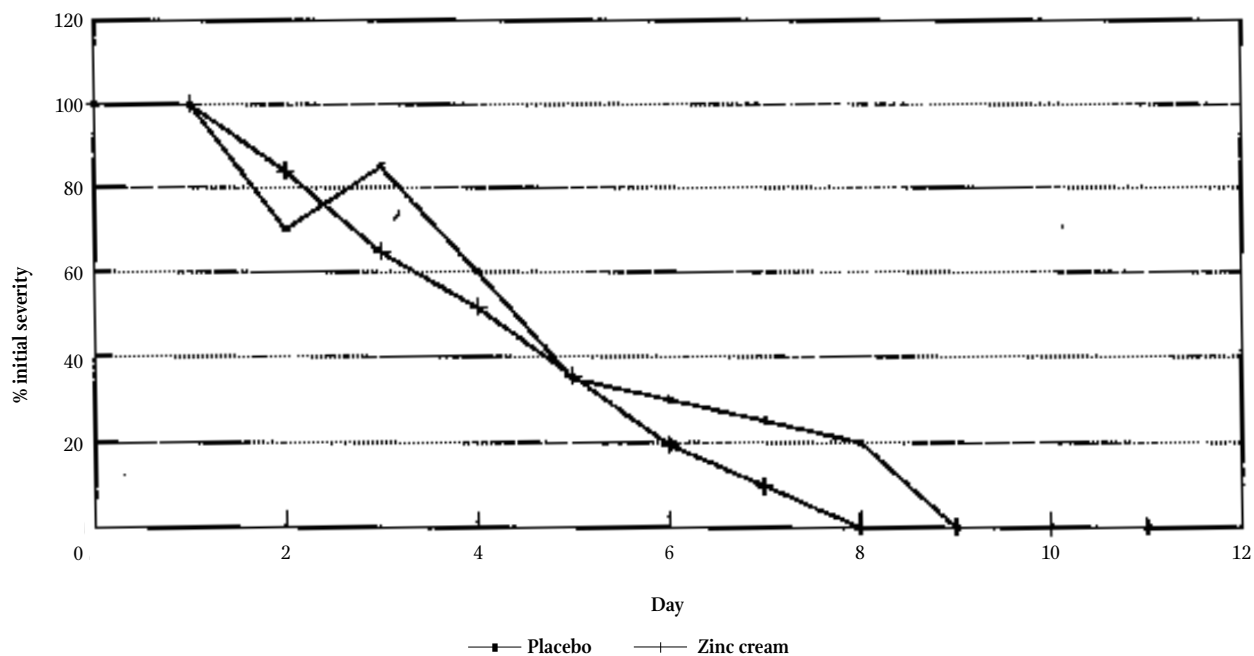


FIGURE 6 Percentage of initial severity of itching of cold sores by day

Other closely related viruses may similarly be affected by zinc ions. HSV has significant homology to varicella-zoster virus. In the United States alone, approximately 300 000 people per year are affected by herpes zoster. Most cases represent the reactivation of the varicella-zoster virus, with the primary infection having been chicken pox. It has been suggested that every person who has had chicken pox harbors latent virus, that 50% of all people who live to the age of 85 will have an attack of zoster, and that approximately 10% of those will have 2 attacks.¹³ Eruptions of herpes zoster are thought to be more frequent in the elderly, not because of immune dysfunction but due to slowed mobilization of the immune system.¹⁸ It follows that prompt treatment with a zinc salt would be extremely beneficial because it would markedly decrease viral load and painful lesions independent of immune system activation.

Unfortunately, topical application of some zinc solutions can cause painful or irritating adverse effects if not used in very low concentrations. Zinc sulfate solutions of 0.2% to 1% can cause severe irritation and unpleasant dryness and can stimulate the emetic reflex when applied circumorally.¹⁷

Zinc sulfate creams and occlusive ointments have shown limited effect in the treatment of herpes because of their low absorption. Application of zinc cream (Herpigon; 30% urea, 3% zinc sulfate, 2% tannic acid, 65% cream base) to genital herpes showed some effect in treating lesions in guinea pigs, but in human studies, ultrasound application of zinc ointment and cream was necessary to promote absorption and penetration.¹⁹ In prior studies, zinc solutions, particularly zinc sulfate, have not maintained constant local concentration levels when applied to the skin, because they are completely dissolved in a medium that evaporates. Zinc oxide creams provide for a constant level of absorption, but are highly insoluble, making the amount of free zinc ions available minuscule. A zinc preparation that would provide a higher concentration of solubilized zinc in a minimally irritating formulation allowing controlled absorption would be of great clinical value. The formulation used in this study does that, releasing a higher concentration of ionic zinc than zinc oxide alone. Such observations provided incentive for the present study.

CONCLUSION

Subjects who began treatment within 24 hours of onset of a facial or circumoral HSV infection and administered a zinc

oxide/glycine cream at the site of infection at least 4 times each day experienced a significantly shorter duration of cold sore lesions (mean, 5.0 days) than did subjects treated with a placebo cream (mean, 6.5 days). Subjects treated with zinc oxide/glycine cream also experienced reduction in overall severity of signs and symptoms, particularly blistering, soreness, itching, and tingling. These results were obtained without unexpected adverse experiences. Adverse effects occurred more frequently in subjects treated with the zinc oxide/glycine cream than in subjects treated with placebo, but all adverse effects were expected from an ionic zinc solution, of short duration, and completely reversible.

The signs and symptoms chosen for evaluation were the same as those sought by clinicians to diagnose a herpes infection. An inherent problem with such subjective terms as "tingling," "burning," "itching," "prickling," "tenderness," and "soreness" is that there is considerable overlap in subjects' perception of these sensations. Evaluation of the subjects' diaries led the investigators to conclude that in future studies signs and symptoms for subjects to evaluate should be limited to tingling, itching, burning, soreness, swelling, and blistering.

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Comparison of adverse effects between patients treated with zinc and patients treated with placebo

Adverse effect	No. (%) of patients	
	Zinc	Placebo
Burning	7 (22)	2 (7)
Itching	3 (9)	1 (4)
Stinging	1 (3)	1 (4)
Tingling	1 (3)	0 (0)