Title
Zinc cold therapy. Proof is still lacking. A review of key trials

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Introduction

Despite the vast information gleaned in medical research and the resulting major advances in medical treatment in the twentieth century, the cure for the common cold has remained elusive. Since 1984, however, a number of studies have sparked hope in the medical community by suggesting that zinc could accelerate the recovery from the common cold. Unfortunately, a near equal number of studies have suggested that zinc has no therapeutic effect in cold recovery. Nevertheless, the public has responded overwhelmingly to the positive studies and the result has been a vast array of cold fighting zinc products in drugstores around the globe. In an effort to aid clinicians in making decisions in patient care, this paper will present the findings and critique the study design of key studies of zinc cold therapy.

The Proposed Action of Zinc

Zinc has been found to inhibit the replication of a number of viruses (including the rhinovirus) in vitro at concentrations of 0.1 mmol/L by repressing the formation of viral capsid proteins. (9,13,14,21) Zinc has also been found to complex with rhinovirus surface canyons which prevents viral interaction with intracellular adhesion molecule 1. (19) Other studies report zinc salts play a role in stabilizing and protecting cell membranes against lysis by cytotoxic agents (e.g. microbial toxins and complement). (2,11,17,20,21) In vitro studies also describe an immunomodulation role for zinc, in which interferon-gamma production is stimulated in human leukocytes. (9,19,23) Zinc ions have also been found to inhibit human prostaglandin metabolites which may explain zinc's role in alleviating common cold symptoms. (12) It has also been proposed that heightened concentrations of intranasal zinc salts produce a "chemical clamp" on trigeminal and facial nerve endings and thus reduce the sneezing, nasal discharge and congestion which accompany colds. (19)

The biological plausibility of the above described mechanisms has been suspect since many of the described actions occur rather weakly in vitro (20) and further, zinc lozenges dissolved in oral saliva do not reach the nasal mucosa, the area infected by the rhinovirus. (22)

Conflicting Results of Eleven Double-Blinded Placebo-Controlled Studies of Zinc Cold Therapy

The past fifteen years have produced eleven double-blinded, placebo-controlled studies of zinc cold therapy (Table 1.). Five (1,5,10,18) of these found zinc salts to be therapeutically effective and the remaining (4,8,16,23,24) found zinc to be ineffective in the treatment of the common cold. These studies varied in zinc formulations and dosages and each had its design flaws.

The landmark study in 1984 by Eby et al., reported a 64% decrease in the duration of colds in the treatment group compared to the placebo group. (5) Further, 86% of the zinc-treated subjects were asymptomatic within seven days compared to 46% in the placebo group (P=0.0005). Weaknesses in this study include subjective outcome measures and the exclusion of a significant number of patients (55%, 81 of 126) from data analysis. Of equal concern is that the placebo and active medications tasted quite different, which may have resulted in inadequate blinding. Individuals who reported a bad taste in their mouth may have identified themselves (potential unmasking) as part of the true treatment group and may have expected an accelerated recovery. This may have been a source of differential bias in the study. For these reasons, the findings of this study are not persuasive with regard to the therapeutic effectiveness of zinc cold therapy.

In 1987, a prophylaxis study by Al-Nakib et al., reported a statistically significant reduction in the mean clinical score from 8.2 in the placebo group to 5.7 in the zinc treatment group. (1) In the therapeutic trial, Aŀ Nakib et al., reported a statistically significant reduction in the mean daily clinical score on the fourth and fifth day of medication. (1) Further, the mean daily nasal secretion weight and total tissue count were reduced and the reductions were statistically significant on days two and six and days and days four to six, respectively. Of particular concern in these two studies is the small sample size.

That same year, in a study by Douglas et al.,, zinc was claimed to have no therapeutic value in the treatment of colds. (4) This study, however, has been highly criticized for the formulation of zinc used in the study. For zinc to be effective, it must exist as the free ion Zn2+. (6,7) The effervescent zinc acetate

used by Douglas et al., may have delivered zinc in an inactive form. The issue of inactivation of zinc salts, however, remains controversial.

Farr et al., presented the findings of two studies in 1987. (8) Farr et al., found no reduction in the severity or duration of cold symptoms or the frequency or duration of viral shedding in either trial. Further, nasal mucus weights and numbers of paper tissues used were slightly higher in the treatment group compared to the placebo group. These findings suggest that zinc gluconate lozenges are ineffective in the treatment of colds. The formulation, zinc gluconate with 2% citric acid, used by Farr et al., has also been criticized as rendering zinc in the inactive form. This too remains controversial. These studies further suffer from small sample sizes, N=25 and N=29.

Three years later, Weismann et al., published their findings. (24) Much like the two studies before, Weismann et al., found no difference in the severity or duration of symptoms between the treatment and placebo groups. A key design flaw in this study was the low dosage of zinc, 4.5 mg, leading to adequacy of concentration concerns.

In 1992, Godfrey et al., presented their findings. (10) A disappearance of symptoms occurred 4.9 days after the first appearance of symptoms in the treatment group compared to 6.1 days for the placebo group ($P<.025$). The effectiveness of treatment was also observed to be enhanced by earlier treatment. Much like preceding zinc cold therapy studies with positive results, concerns in this study included poor comparability to placebo and subjective outcome measures.

Mossad et al., declared that the average time of coughing, headache, hoarseness, congestion, runny nose, and sore throat regression was 4.4 days in the zinc therapy group compared to 7.6 days in the placebo group. (18) Design flaws in the study by Mossad et al., include subjective outcome measures and poor comparability to placebo. Eighty percent of the treatment group reported that their lozenges had left a bad taste in their mouth; in comparison, 30% of the placebo group reported a bad taste in their mouth.

One of the most recent zinc cold therapy studies, performed by Macknin et al., in 1998, studied the time to resolution of cold symptoms in 580 children, aged 6 to 16, treated with zinc gluconate lozenges. (16) The median time to resolution of all cold symptoms in Macknin et al.,'s study was 9 days for both the intervention and control groups. The negative results in the study by Macknin et al.,, however, may have arisen from a low dose of zinc in the intervention group. The dose of zinc was based on the amount used in adult studies and corrected to account for the subject's smaller body surface area. Macknin et al.,'s study made an effort to make the lozenges in the placebo and intervention groups identical in taste and appearance. Nevertheless, a greater percentage of the intervention group reported a peculiar taste (56% vs 43%). Interestingly, negative results were obtained despite the potential unmasking. At this time, lozenges are not recommended for children. Further studies need be performed to hone in on effective dosages, if any, in children and adolescents.

The Adverse Effects of Zinc

Excess intake of zinc salts has been shown to result in a reduction of lymphocyte stimulation, a significant reduction in the concentration of high-density lipoproteins (HDLs), a slight increase in the concentration of low density lipoproteins (LDLs) and low neutrophil counts. (3) Additional side effects observed in key studies include bad-taste reactions, nausea, and mouth irritation. (5,8) Although little remains known of the outcome of acute overdoses of zinc, one report exists describing severe nausea and vomiting in a 17-year-old male after ingestion of 4g zinc gluconate (570 mg elemental zinc). (15) The long-term effects of zinc have yet to be determined.

Table 1. Eleven double-blinded, placebo-controlled zinc cold therapy studies. (Zinc Ion Availability (ZIA) not computed for studies after 1990.)

Investigators	N	Source of Cold	Dose(mg)/Formulation	Results	ZIA
Eby et al, 1984 [5]	28	Environmental	23/zinc gluconate	Therapeutically Effective	100
Al-Nakib et al, 1987 [1]					
Prophylactic trial	14	Innoculation	23/zinc gluconate	Therapeutically Effective	44
Therapeutic trial	12	Innoculation	23/zinc gluconate	Therapeutically Effective	44
Douglas et al, 1987 [4]	63	Environmental	10/zinc acetate	Therapeutically Ineffective	-55
Farr et al, 1987 [8]	25	Innoculation	23/zinc gluconate *with 2% citric acid*	Therapeutically Ineffective	-11
Farr et al, 1987 [8]	29	Innoculation	23/zinc gluconate *with 2% citric acid*	Therapeutically Ineffective	-11
Smith et al, 1989 [23]	140	Environmental	11.5/zinc gluconate	Therapeutically Ineffective	25
Weismann et al, 1990 [24]	130	Environmental	4.5/zinc gluconate	Therapeutically Ineffective	13.4
Godfrey et al, 1992 [10]	73	Environmental	23.7/zinc gluconate glycine	Therapeutically Effective	-
Mossad et al, 1996 [18]	100	Environmental	13.3/zinc gluconate glycine	Therapeutically Effective	-
Macknin et al, 1998 [18]	249	Environmental	10/zinc gluconate glycine	Therapeutically Ineffective	-

Resolving the Conflicting results

In 1997, Eby presented a study reanalyzing the results of the double-blind, placebo-controlled, clinical trials of zinc lozenges from 1984 to 1992. (5) Eby hypothesized that the conflicting findings were the result of major variations in the daily zinc ion availability (ZIA) between the chemically different lozenge formulations. Employing solution chemistry computations, Eby determined the bioavailability of Zn^{2+} at physiological pH for the zinc lozenges used in these studies. ZIA values were computed using Fick's law of diffusion in a electric field. Eby postulated that the efficacy of zinc lozenges could be predicted based upon the ZIAs. Eby found that formulations with a positive ZIA at physiological pH shortened colds, formulations with a negative ZIA lengthened colds and formulations having a zero ZIA had no effect on colds. Table 1 shows the ZIA values computed by Eby. The trend is clear. Large positive ZIA values were associated with positive results whereas small positive and negative values were associated with negative results.

Whether Eby's hypothesis explains the conflicting results in the zinc cold therapy studies remains controversial. In any case, there remain serious methodological flaws in studies with positive results and those with negative results. Design flaws including small sample sizes, subjective outcome measures, inadequate blinding, dosage, and treatment inactivation abound. Proof is still lacking. What is needed is better designed studies.

Suggested Modifications for Future Studies

First, study designs should guarantee adequate blinding by taste-matching tests on placebo and treatment medications before clinical trials begin. Second, an adequate concentration of zinc must be delivered.

Mossad el al (18) reported positive results with a 13.3 mg dose of zinc; this should be used as the lower limit of zinc dosage. Trials should also ensure sufficient sample sizes, standardized outcome measures and minimize subjects lost to follow-up. Finally, to further elucidate the safety of zinc, studies should closely monitor the short-term and long-term effects of zinc supplements. Persuasive results will follow only from studies whose design takes into the account the above suggestions.

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