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ZINC FOR THE COMMON COLD?

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## Original papers

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# Effect of zincum gluconicum nasal gel on the duration and symptom severity of the common cold in otherwise healthy adults

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## Summary

**Background:** Previous studies suggest that zinc salts may be effective in treating the common cold. Since rhinovirus infections occur primarily in the nasal cavity, an attempt to arrest the infection at the portal of entry seems logical.

**Aim:** To assess the ability of zinc nasal gel to shorten the duration and reduce the severity of the common cold in healthy adults.

**Study design:** Randomized, double blind, placebo-controlled study.

**Methods:** Of 1087 patients screened by telephone, 80 patients were enrolled, all presenting within 24–48 h of the onset of illness. They received one dose per nostril of a nasal gel spray containing either 33 mmol/l zincum gluconicum, or an identical

placebo four times daily until their symptoms resolved, for a maximum of 10 days.

**Results:** Median duration of cold symptoms in the zinc group was significantly shorter than in the placebo group (median [IQR] 4.3 days [2.5–5.5] vs. 6 days [5–8.5],  $p=0.002$ ). Nasal drainage, nasal congestion, hoarseness, and sore throat were the symptoms most affected. Significant reduction of total symptom scores started from the second day of the study. Adverse effects (mainly nasal stinging) were similar in both groups.

**Discussion:** Zincum gluconicum nasal gel shortens duration and reduces symptom severity of the common cold in healthy adults, when started within 24–48 h of the onset of illness.

## Introduction

The common cold is a mild, self-limited coryzal illness. However, with more than 1 billion colds occurring each year in the US alone, it is the leading cause of acute illness and health care visits.<sup>1</sup> Because adults develop 2–4 colds per year and children 6–8, nearly 5% of the US population is suffering from a cold at any given time.<sup>2</sup>

In the continuing search to find an effective treatment for the common cold, researchers have studied zinc salts, which have several properties

that make them potentially suitable agents. First, zinc combines with the carboxyl termini of rhinovirus coat proteins, thus preventing the virus from combining with surface proteins on the respiratory epithelium called intercellular adhesion molecules (ICAM-1).<sup>3</sup> Second, zinc prevents the formation of viral capsid proteins, thus inhibiting the replication of several viruses, including rhinovirus, which is the most common causative agent for the common cold.<sup>4</sup> Third, zinc stabilizes cell membranes<sup>5</sup> and

prevents histamine release.<sup>6</sup> Fourth, zinc potentiates the antiviral action of native human leukocyte interferon alpha ten-fold.<sup>7</sup> Fifth, zinc inhibits prostaglandin metabolism.<sup>8</sup> To date, none of these activities of zinc have been demonstrated to occur at clinically achievable concentrations of zinc in humans.

Fourteen controlled studies have evaluated the use of zinc to control symptoms of the common cold. Six of these studies showed that zinc had a beneficial effect<sup>9–14</sup> and eight did not.<sup>15–22</sup> A meta-analysis published in 1997 concluded that ‘despite numerous randomized trials, the evidence for effectiveness of zinc salts lozenges in reducing the duration of common colds is still lacking’.<sup>23</sup> A possible unmasking of the placebo, a small sample size, subjective outcome measures, differences in zinc formulations and doses, and the presence of different viruses may have caused these conflicting results. Zinc ion availability was identified as an important determinant of efficacy in zinc lozenge treatment of the common cold.<sup>24</sup>

There is considerable evidence that the nasal cavity is the portal of entry and site of initial replication for most viruses that cause the common cold.<sup>25</sup> Therefore, an attempt to arrest the infection at the portal of entry seems logical. Indeed, three groups of researchers have already studied the effects of a zinc nasal gel spray on the common cold.<sup>14,21,22</sup> Hirt *et al.*<sup>14</sup> found that zinc has a beneficial effect. However, they did not have any microbiological information, and did not comment on the onset of perceived improvement or on the severity of individual symptoms. Also, the season of the year during which the study was conducted was not indicated, so it is unclear whether the fall seasonal peak for rhinovirus infection was included. Finally, the blinding process was not evaluated in this study. The study by Belongia *et al.*<sup>21</sup> reported that zinc does not affect the duration of the common cold, although that could potentially be explained by the low dose (0.044 mg/day) of zinc sulphate they used. Turner<sup>22</sup> studied intranasal zinc gluconate for prevention of experimental colds, and concluded that it had no effect on the development of infection or clinical illness compared to placebo. Nevertheless, this study found a significant reduction in viral shedding of rhinovirus 39 with the use of zinc compared to placebo, on days 1 and 2 after virus challenge. Moreover, the population sample was of a size that would only detect moderately large effect size between groups. Lastly, blinding in this study may not have been adequate, since significantly more patients in the zinc group (44%) indicated that they could taste the study medication, compared to 12% only in the placebo group ( $p=0.008$ ).

The current study was performed to assess the ability of ionic zinc nasal gel (Zicam<sup>®</sup>, Gel Tech LLC) to shorten the duration and reduce the severity of symptoms of naturally acquired common cold in adults. Several measures were implemented to overcome the limitations of the studies by Hirt *et al.*<sup>14</sup> and Turner.<sup>22</sup> These included using a sample size adequate to detect a treatment effect size of 30%, collecting microbiological data, identifying the onset of perceived improvement, assessing the effect on individual cold symptoms, and ensuring and evaluating the blinding process. Unlike the experimental model used by Turner,<sup>22</sup> this was a pragmatic study designed to assess the efficacy of zinc nasal gel under conditions that simulated usual medical care for patients with the common cold. The current study used a different formulation and a higher dose than that used in the study by Belongia *et al.*<sup>21</sup>

## Methods

### Participants

Global Clinicals recruited patients at a single private practice clinic in Los Angeles, CA. The study was approved by the Institutional Review Board at Century City Hospital in Los Angeles, CA. Advertisements for the study appeared in the LA Times, college papers of the University of Southern California and the University of California in Los Angeles, and in physicians’ private practice offices in the surrounding area. Patients were enrolled during the fall and winter seasons between August 2000 and March 2001. They were informed of the double-blind, placebo-controlled nature of the study, and gave their written informed consent to participate after reviewing the consent form alone, and with the study coordinator. They were also informed of the potential to publish the results of the study in a scientific journal. They were compensated with a \$100 check, mailed to them 2–4 weeks after they completed the study.

### Assessment of eligibility

When patients who thought they had the common cold called the study coordinator to inquire about the study, a telephone pre-screen was performed to assess eligibility. A patient was deemed eligible if he or she was 18–55 years of age and had had symptoms of the common cold for 24–48 h. Common cold symptoms were designated as either major or minor. Major symptoms were nasal drainage and sore throat, and minor symptoms were nasal congestion, sneezing, scratchy throat,

hoarseness, cough, headache, muscle aches and fever (oral temperature  $>98.6$  °F). Presence of two major and at least one minor symptom, or one major and three minor symptoms were required for enrolment. Previous studies<sup>11–14,9–22</sup> defined common cold as having two or more of these ten symptoms. I chose more strict criteria for enrolment than these studies.

During the initial visit, patients completed a screening health questionnaire, were interviewed and examined by the same physician to confirm the presence of rhinitis (as noted by erythema of the nasal mucosa and excessive mucopurulent discharge) and to exclude other clinically obvious illnesses. Although there is a large variance in the signs associated with rhinitis, documenting their presence supported the diagnosis of common cold. Women also received a urine pregnancy test, which had to be negative for them to be included in the study.

Patients were excluded if they had common cold symptoms for  $>48$  h. Other exclusion criteria included: known immune system disorder (such as systemic lupus erythematosus or acquired immunodeficiency syndrome), diabetes mellitus, known uncorrected deviated nasal septum, or a history of recurrent sinusitis (more than two per year), bronchitis (more than six per year), or otitis. Patients who were receiving treatment for asthma or allergic rhinitis, those who were currently using decongestants, antihistamines, antibiotics, aspirin, or zinc products, and anyone who had ever used Zicam were also excluded. Lastly, all habitual smokers and women who were pregnant, lactating, planned to become pregnant within 30 days of enrolment or unwilling to use birth control measures were likewise excluded.

### Randomization and enrolment

An independent company, Botanicals International, prepared a computer-generated randomization code for the hand-held nasal pumps that remained concealed until the treatment assignment. This company was the only party that knew of the actual treatment assignment before enrolment. Randomization was performed in blocks of 10 (5 zinc and 5 placebo). The study coordinator enrolled the eligible patients and assigned them to their respective groups.

### Virus identification

Upon enrolment, all patients underwent testing to identify the viruses, if any, causing their illness. Nasal lavage samples were collected by instillation

of 3 ml 0.9% saline into each nostril. The samples were divided into three aliquots; two were frozen at  $-70$  °C, and one was used for viral isolation attempts. Tubes containing human fetal diploid lung cells and primary monkey kidney cells were inoculated, and cultures were rotated in a roller drum and incubated at 33 °C. Viral isolation and identification were performed by standard methods.<sup>26</sup> Rhinovirus growth was recognized by the characteristic cytopathic effects and confirmed by the acid lability assay. Polymerase chain reaction (PCR) for detection of rhinovirus was performed by standard methods<sup>27</sup> by Tsunami Biotechnology.

### Intervention

The zinc nasal gel consisted of 33 mmol/l of zincum gluconicum (Zenullose) in an emulsification of benzalkonium chloride, glycerin, hydroxyethylcellulose, sodium chloride, and sodium hydroxide (pH 7.2). Placebo was identical in appearance and content, except that it lacked the zinc component. Gel Tech LLC supplied both. Metered dose applicators delivered individual doses of 120  $\mu$ l.

All patients were instructed in scoring their cold symptoms and trained to use the hand-held nasal pump properly. The first dose was applied in each nostril at 9:00 pm on the day of enrolment. Patients were told to continue using the study drug four times per day (9:00 am, 1:00 pm, 5:00 pm, and 9:00 pm) thereafter until all their symptoms resolved (see Outcome measures) or for 10 days, whichever came first. Because one dose constituted two sprays, the total daily volume used was 960  $\mu$ l, giving a total daily dose of elemental zinc of about 2.1 mg.

Patients were instructed not to use cold remedies during the study period, including aspirin, decongestants, antihistamines, and other zinc products. They were, however, allowed to take acetaminophen (paracetamol) 500 mg every 6 h for temperature control only.

### Outcome measures

The primary outcome measure was the time to cold resolution, calculated as the number of days starting from the onset of symptoms till their complete resolution. The secondary outcome measures were the total daily symptom scores and the presence of adverse effects. Patients were asked to score the severity of the above mentioned ten symptoms, based on criteria initially developed by Jackson *et al.*<sup>28</sup> and validated in several subsequent studies.<sup>9,11–14,18–21</sup> Patients were instructed to score

their symptoms using a four-point scale (0 = none, 1 = mild, 2 = moderate, 3 = severe) twice daily at 9:00 am and 9:00 pm, just prior to the use of the study drug. Total symptoms scores were calculated by summing the scores of the ten symptoms every time they were scored.

Compliance was monitored by having the study coordinator telephone each patient daily to discuss their symptoms and review the symptoms scoring chart, and by weighing the nasal gel pumps on the day of enrolment and day of study completion. The average daily use of the pump was calculated as the starting weight of the pump minus the ending weight, divided by the number of days of usage; this was given the designation the 'weight factor'. Patients were instructed to enter their symptom scores on a daily basis, rather than from memory. The telephone calls also served to ensure that the patients were not developing a more serious illness.

Patients were asked about adverse effects during the daily telephone contacts and at the completion of the study, using an open-ended question, 'What side-effects did you have?' rather than asking them whether they developed certain pre-specified adverse effects. Patients were asked to return their used pumps and completed symptoms scores charts to the study site within 24 h of stopping use of the nasal gel.

## Maintenance of blinding

To ensure blinding of patients to treatment assignment, all pumps were identical in appearance except for the randomization numbers. The physician who examined the patients at enrolment and the clinical research coordinator that distributed the pumps were blinded to the treatment assignment. The investigator who assessed the outcomes was blinded to the treatment assignment until all patients were enrolled and returned their symptoms score charts. Asking patients on their first day of pump use whether they thought they were receiving an active agent or placebo assessed adequacy of the blinding procedure. This was done early in the process of the study rather than at the end, in order to decrease the possibility that a rapid improvement in symptoms would help patients in the zinc group correctly infer that they were receiving the active drug.

## Statistical analysis

Assuming a treatment effect size of 30% and significance level of  $\alpha = 0.05$ , the power to detect a significant difference between both groups with 80 total subjects was 70%. Fisher's Exact test

(two-tailed) was used to compare categorical variables, and Wilcoxon Rank Sum test (two-tailed) was used to compare continuous variables. Results were reported as median and interquartile range (IQR). A Kaplan-Meier curve was plotted for the resolution rates of common cold symptoms, comparing both groups. The data were positively skewed for days to resolution of all symptoms and total symptoms scores, with one or two outliers at each time point and within each treatment group.

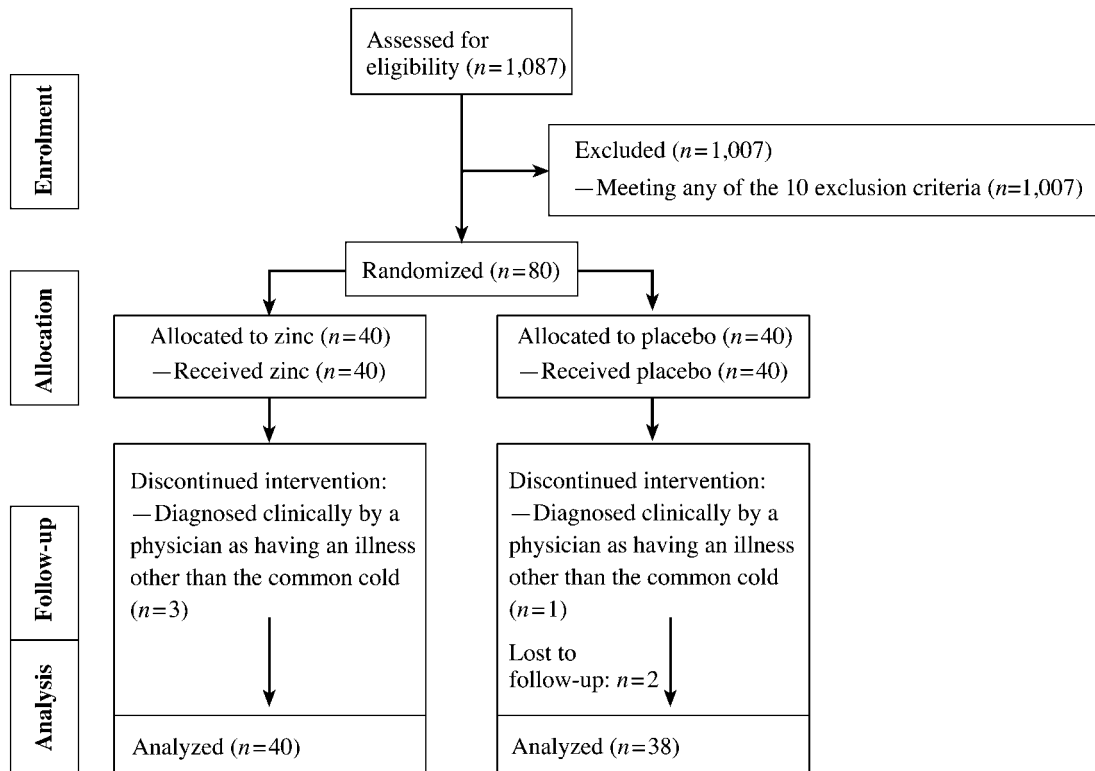
Analyses were performed for the patients with positive rhinovirus PCR and for the whole group. An intention-to-treat analysis of the primary outcome measure, the time to cold resolution, was performed for all enrolled patients, except two from the placebo group who were lost to follow-up and did not return their symptoms scores charts. Data for four patients who were diagnosed clinically by a physician as having an illness other than the common cold and one patient who was not compliant with the study drug were included in the intention-to-treat analysis of the primary outcome measure.

In a separate analysis, scores for nasal drainage and nasal congestion were combined and assessed as 'nasal symptoms' and scores for sore throat, scratchy throat and hoarseness were combined and assessed as 'throat symptoms'. Statistical analyses were performed using SAS.

## Results

### Demographic data

Of 1087 subjects screened by telephone, 1007 were not randomized, because they had one or more of the 10 exclusion criteria. Eighty patients were randomized to either the zinc ( $n = 40$ ), or placebo ( $n = 40$ ) (Figure 1). Of the 78 patients (40 in the zinc group, and 38 in the placebo group) who were included in the final analysis, 49 were women and 29 were men; the median age was 26 years. There were no statistically significant differences between the zinc and placebo groups in age, sex, total symptoms scores, or prevalence of individual symptoms of the common cold at the time of enrolment in the study (Table 1). Nine of the 78 patients (12%)—4 in the zinc group (10%), and 5 in the placebo group (13%)—had rhinovirus isolated on viral cultures. Eighteen of the 78 patients (23%)—7 in the zinc group (18%) and 11 in the placebo group (29%)—had rhinovirus identified by PCR ( $p = 0.29$ ). One patient in the zinc group had parainfluenza virus isolated, and two patients in the placebo group had influenza virus isolated.



**Figure 1.** Flow diagram for study participants.

**Table 1** Baseline demographic data, total symptom scores and prevalence of individual symptoms

	Zinc (n = 40)	Placebo (n = 38)
Age (years), median (IQR)	29 (22–39)	26 (21–40)
Sex (F/M)	24 (60%)/16 (40%)	25 (66%)/13 (34%)
Total symptoms scores, median (IQR)	12 (7–13.5)	12 (10–13)
Cough	26 (65%)	23 (61%)
Hoarseness	21 (53%)	22 (58%)
Scratchy throat	30 (75%)	32 (84%)
Sore throat	25 (63%)	28 (74%)
Nasal drainage	37 (93%)	35 (92%)
Nasal congestion	40 (100%)	37 (97%)
Sneezing	29 (73%)	31 (82%)
Headache	24 (60%)	24 (63%)
Muscle ache	22 (55%)	21 (55%)
Fever*	10 (25%)	14 (37%)

Data are shown as *n* (%) except where indicated. \*Oral temperature > 98.6 °F.

### Duration of cold symptoms

All 78 patients were contacted daily during the study and returned their symptoms scores charts at the completion of the study. Table 2 shows the time to cold resolution and the duration of individual symptoms in the zinc and placebo groups. The median time to cold resolution was significantly shorter in the zinc group (median [IQR] 4.3 days [2.5–5.5]) compared to the placebo group (6 days [5–8.5]) ( $p = 0.002$ ). Days to resolution of all but any

one common cold symptom were also significantly shorter in the zinc group ( $p = 0.006$ ). In the 18 patients positive for rhinovirus PCR, the median time to cold resolution was also shorter in the zinc group (3 days [2.5–3.5]) compared to the placebo group (6 days [4.5–7.5]) ( $p = 0.02$ ). Therefore, the absolute difference in the median duration of illness between the zinc and placebo groups for all 78 patients was 1.7 days, and for the 18 patients with positive rhinovirus PCR, it was 3 days. Duration of hoarseness, sore throat, nasal drainage and nasal

**Table 2** Time to cold resolution and duration of individual symptoms (in days)

	Zinc (n = 40)	Placebo (n = 38)	<i>p</i> *
Resolution of cold	4.3 (2.5–5.5)	6 (5–8.5)	0.002
Resolution of all but one symptom	4.0 (2.5–5.5)	5.3 (4–8)	0.006
Cough	1.8 (0–5.5)	3.3 (0.5–6)	0.14
Hoarseness	1 (0–3)	3 (0.5–5.5)	0.02
Scratchy throat	1.5 (0.25–3.75)	3.5 (1.5–4)	0.06
Sore throat	1.5 (0–2.5)	3.3 (1–4)	0.05
Nasal drainage	4 (2.25–5)	5 (4–7.5)	0.003
Nasal congestion	4 (2.25–5.5)	5.5 (3.5–7.5)	0.01
Sneezing	1.5 (0.5–3.5)	2.5 (1–5)	0.08
Headache	1 (0–2.25)	1.5 (0–4)	0.47
Muscle aches	0.25 (0–1.75)	0.3 (0–2.5)	0.81
Fever**	0 (0–1)	0 (0–1.5)	0.75

Results are shown as medians (IQR). \*Wilcoxon Rank Sum test (two-tailed). \*\*Oral temperature >98.6 °F.

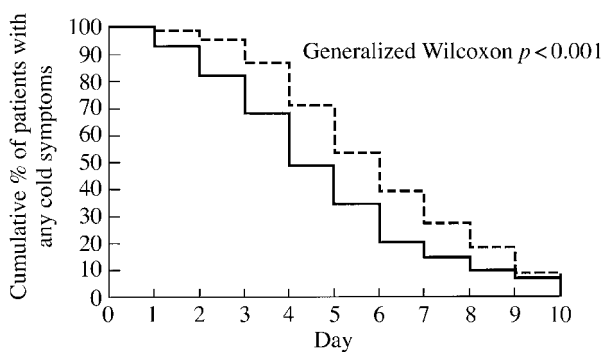
congestion were significantly shorter in the zinc group than in the placebo group (Table 2). Duration of scratchy throat and sneezing were shorter in the zinc group than in the placebo group, but not significantly so. Duration of cough, headache, muscle aches and fever were similar in both groups. A Kaplan-Meier curve depicts the cumulative significant difference in the percentage of patients in both groups who had any cold symptoms for the duration of the study ( $p < 0.001$ ) (Figure 2).

### Severity of cold symptoms

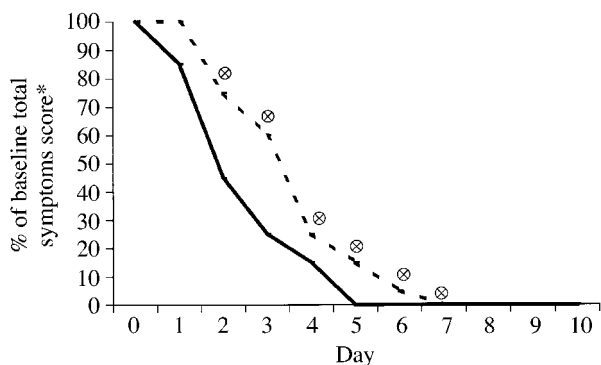
There was a statistically significant reduction in the percentage of baseline total symptoms scores (Figure 3) and of the absolute symptoms scores in the zinc group, compared with the placebo group, starting from the second day of the study through day 7. Symptom scores for throat symptoms were statistically significantly lower than baseline on days 2, 3, and 4 in the zinc group, compared with the placebo group (data not shown). Similarly, symptom scores for nasal symptoms were statistically significantly lower than baseline on days 3, 4, 5, 6, 7, and 8 in the zinc group, compared with the placebo group (data not shown).

### Compliance and adequacy of blinding

Compliance with the study drug was better in the zinc group compared to the placebo group (weight factor 1.5 [1–2] vs. 1.2 [1–1.3],  $p = 0.01$ ). However, a similar proportion of patients in both groups correctly identified their group assignment on the first day of taking the study drug; 48% in the zinc



**Figure 2.** Cumulative difference in the proportion of patients with any cold symptoms. Solid line, zinc group; dotted line, placebo group.



**Figure 3.** Percentage of baseline total symptom scores on each day of the study. Solid line, zinc group; dotted line, placebo group. \*Median. Time points at which there were statistically significant differences between the two groups (Wilcoxon Rank Sum test  $p$  value).

group and 58% in the placebo group ( $p = 0.66$ ). None of the patients reported taking any other cold medications, including acetaminophen, during the period of the study.

## Adverse effects

There were no statistically significant differences in the reported adverse effects between the zinc and placebo groups (Table 3). Nasal stinging or burning sensation was the most common adverse effect reported in both groups.

## Discussion

This study showed that zincum gluconicum applied in a nasal gel shortens the duration and reduces the severity of symptoms of the common cold starting from the second day of drug use. The absolute difference in the median duration of illness between the zinc and placebo groups was more obvious in patients who had positive rhinovirus PCR, than in the whole group. The most prominent symptoms of the common cold—nasal drainage, nasal congestion, and sore throat—were the symptoms that were affected the most. The number and type of reported adverse effects were similar in both groups.

The rate of rhinovirus identification by culture or PCR in this study was similar to that in previous studies.<sup>21,27</sup> Even though more patients had rhinovirus identified in the placebo group than in the zinc group, this difference was not statistically significant. With few exceptions, there are only minor differences in the severity and duration of symptoms of the common cold caused by different viruses.<sup>29</sup>

Hirt *et al.*<sup>14</sup> also found that nasal burning was the most common adverse effect, occurring in 42% of

the zinc recipients and in 37% of the placebo recipients in their study. This adverse effect is more likely to be related to the emulsification components of the nasal gel, rather than to the zinc component. Nausea and bad taste, which were common adverse effects seen in previous studies with zinc gluconate lozenges<sup>12</sup> were not observed in this study.

Neither viral serum antibody titres, nor daily nasal viral titres were measured. However, in two previous studies, one showing a beneficial effect of zinc gluconate,<sup>10</sup> the other not,<sup>15</sup> the degree of nasal viral shedding was not affected. Therefore, these measures may not be reliable to assess the effect of therapy. In addition, the effect of zinc on levels of pro-inflammatory cytokines, which have been found in nasal secretions of patients with colds in previous studies,<sup>30</sup> was not measured. One previous study showed that in zinc-deficient people, mononuclear cells produce large amounts of interleukin-1 beta, which can be normalized by zinc supplementation.<sup>31</sup> This suggests that zinc has an immunomodulatory effect on pro-inflammatory cytokines. However, the study by Prasad *et al.*<sup>13</sup> did not find a significant difference between zinc and placebo groups in the levels of plasma soluble interleukin-1 receptor antagonist, soluble tumour necrosis factor receptor, or neopterin. Similarly, the study by Turner and Cetnarowski<sup>21</sup> found no effect of treatment with zinc gluconate or acetate on IL-8 concentration in nasal lavage specimens. Although the plasma zinc levels were not measured, absorption from topical application of zinc on the nasal mucosa is expected

**Table 3** Side effects of study drug

	Zinc (n = 40)	Placebo (n = 38)	p*
Nasal stinging or burning	5 (12.5%)	2 (5%)	0.43
Faint headache	2 (5%)	1 (3%)	1.00
Runny nose	2 (5%)	0 (0%)	0.49
Increased congestion	2 (5%)	1 (3%)	1.00
A little achy	1 (2.5%)	0 (0%)	1.00
Post nasal drainage worse	1 (2.5%)	0 (0%)	1.00
Dry skin	1 (2.5%)	0 (0%)	1.00
Sneezing	0 (0%)	1 (3%)	0.49
Irritating smell	0 (0%)	1 (3%)	0.49
Burned throat	1 (2.5%)	0 (0%)	1.00
Nasal bleeding	1 (2.5%)	1 (3%)	1.00
Sleepy	0	1 (3%)	0.49
<i>Number of side-effects reported</i>			0.26**
0	28 (70%)	33 (87%)	
1	9 (23%)	3 (8%)	
2	2 (5%)	1 (3%)	
3	1 (3%)	1 (3%)	

\*Fisher's Exact test (two-tailed). \*\*Fisher's Exact test (two-tailed) for the 2×4 table. p for one or more side-effects (30% zinc vs. 13% placebo) is 0.10.



to be minimal. However, the long-term effects of cumulative doses of nasal zincum gluconicum are currently unknown.

Several limitations should be acknowledged. First, because only healthy subjects were included, the results may not be applicable to people with chronic illnesses or those with compromised immune systems. There were more women than men included in this study, and the study population was fairly young. Even though this was a highly selected population, reducing the duration and severity of the common cold only in healthy people would have significant social and economic benefits for the whole community. Second, viral isolation was not performed at the end of the study as a 'test of cure' due to financial constraints, but would have been unlikely to be useful, in view of the low frequency of virus identification at the beginning of the study. Third, assessment of response depended entirely on subjective measures, as was the case in most previous studies for treatment of the common cold. The chance of recall bias was reduced by making daily telephone calls to ensure that symptoms scores charts were being filled daily, and by asking subjects to return the completed charts within 24 h of their completion of the study. Fourth, patients were asked if they knew which drug they were taking only on the first day and not at the end of the study. Therefore, patients may have changed their opinion during the course of the study as a result of a response or a lack of one to the nasal gel. The placebo used has not been shown previously to have no perceived difference in taste or smell from Zicam. Problems with establishing the blind in placebo-controlled trials of zinc for the common cold have previously been discussed.<sup>32</sup> However, in the current study, the lack of difference in the correct identification of group assignment and in the reported side-effects, suggests adequacy of the blinding process. Finally, even though the enrolled patients were instructed not to use symptom relief medication with the exception of acetaminophen, covert use of other cold remedies still cannot be excluded.

On the other hand, several facts support the validity of the results. First, the same person recruited all patients, thus decreasing variability in evaluation. Second, studies for viral isolation were performed, and the results of the study in the whole group were similar to those in patients with positive rhinovirus PCR. Third, a strict definition for the common cold and its resolution was used. Patients who had symptoms for <24 h were not enrolled, in order to include only those with an established illness. Fourth, compliance was enhanced by daily telephone calls, and measured

objectively by weighing the pumps. Finally, multiple measures were implemented to ensure adequacy of the blinding procedure.

In summary, topical nasal zincum gluconicum appears to be effective in reducing the duration and symptom severity of the common cold in healthy adults, when started within 24–48 h of the onset of illness, and was generally well tolerated. Larger studies that include other patient populations are needed to confirm these findings.

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## References

1. Rice DP, Feldman JJ, White KL. *The Current Burden of Illness in the United States: Occasional Papers of the Institute of Medicine*. Washington DC, National Academy of Science, 1976:1.
2. Dingle JH, Badger GF, Jordan WS Jr. *Illness in the Home: Study of 25 000 Illnesses in a Group of Cleveland Families*. Cleveland, Press of Western Reserve University, 1964.
3. Novick SG, Godfrey JC, Godfrey NJ, Wilder HR. How does zinc modify the common cold? Clinical observations and implications regarding mechanisms of action. *Med Hypotheses* 1996; **46**:295–302.
4. Korant BD, Butterworth BE. Inhibition by zinc of rhinovirus protein cleavage: interaction of zinc with capsid polypeptides. *J Virol* 1976; **18**:298–306.
5. Pasternak CA. A novel form of host defense: membrane protection by  $\text{Ca}^{2+}$  and  $\text{Zn}^{2+}$ . *Biosci Rep* 1987; **7**:81–91.
6. Harisch G, Kretschmer M. Some aspects of a non-linear effect of zinc ions on the histamine release from rat peritoneal mast cells. *Res Commun Chem Pathol Pharmacol* 1987; **55**:39–46.
7. Berg K, Bolt G, Andersen H, Owen TC. Zinc potentiates the antiviral action of human IFN-alpha tenfold. *J Interferon Cytokine Res* 2001; **21**:471–4.
8. Kelly RW, Abel MH. Copper and zinc inhibit the metabolism of prostaglandin by the human uterus. *Biol Reprod* 1983; **28**:883–9.
9. Eby GA, Davis DR, Halcomb WW. Reduction in duration of common cold by zinc gluconate lozenges in a double-blind study. *Antimicrob Agents Chemother* 1984; **25**:20–4.

10. Al-Nakib W, Higgins PG, Barrow I, Batsone G, Tyrell DA. Prophylaxis and treatment of rhinovirus colds with zinc gluconate lozenges. *Antimicrob Agents Chemother* 1987; **20**:893–901.
11. Godfery JC, Conant Sloane B, Smith DS, Turco JH, Meercer N, Godfery NJ. Zinc gluconate and the common cold: a controlled clinical study. *J Internat Med Res* 1992; **20**:234–46.
12. Mossad SB, Macknin ML, Medendorp SV, Mason P. Zinc gluconate lozenges for treating the common cold; a randomized, double-blind, placebo-controlled study. *Ann Intern Med* 1996; **125**:81–8.
13. Prasad AS, Fitzgerald JT, Bao B, Beck FWJ, Chandrasekar PH. Duration of symptoms and plasma cytokine levels in patients with the common cold treated with zinc acetate: a randomized, double blind, placebo-controlled trial. *Ann Intern Med* 2000; **133**:245–52.
14. Hirt M, Nobel S, Ernesto B. Zinc nasal gel for the treatment of common cold symptoms: a double blind, placebo-controlled trial. *ENT J* 2000; **79**:778–82.
15. Farr BM, Conner EM, Betts RF, Oleske J, Minnefor A, Gwaltney JM Jr. Two randomized controlled trials of zinc gluconate lozenge therapy of experimentally induced rhinovirus colds. *Antimicrob Agents Chemother* 1987; **31**:1183–7.
16. Douglas RM, Miles HB, Moore BW, Ryan P, Pinnock CB. Failure of effervescent zinc acetate lozenges to alter the course of upper respiratory tract infection in Australian adults. *Antimicrob Agents Chemother* 1987; **31**:1263–5.
17. Weismann K, Jakobson JP, Weismann JE, Hammer UM, Nyholm SM, Hansen B, Lomholt KE, Schmidt K. Zinc gluconate lozenges for common cold: a double blind clinical trial. *Dan Med Bull* 1990; **37**:279–81.
18. Smith DS, Helzner EC, Nuttall CE, Collins M, Rofman BA, Ginsberg D, Goswick CB, Magner A. Failure of zinc gluconate in treatment of acute respiratory tract infections. *Antimicrob Agents Chemother* 1989; **33**:646–8.
19. Macknin ML, Piedmonte M, Calendine C, Janosky J, Wald E. Zinc gluconate lozenges for treating the common cold in children: a randomized controlled trial. *JAMA* 1998; **279**:1962–7.
20. Turner RB, Cetnarowski WE. Effect of treatment with zinc gluconate or zinc acetate on experimental and natural colds. *Clin Infect Dis* 2000; **31**:1202–8.
21. Belongia EA, Berg R, Liu K. A randomized trial of zinc nasal spray for the treatment of upper respiratory illness in adults. *Am J Med* 2001; **111**:103–8.
22. Turner RB. Ineffectiveness of intranasal zinc gluconate for prevention of experimental rhinovirus colds. *Clin Infect Dis* 2001; **33**:1865–70.
23. Jackson JL, Peterson C, Lesho E. A meta-analysis of zinc salts lozenges and the common cold. *Arch Intern Med* 1997; **157**:2373–6.
24. Eby GA. Zinc ion availability: the determinant of efficacy in zinc lozenge treatment of common colds. *J Antimicrob Chemother* 1997; **40**:483–93.
25. Gwaltney JM Jr. Rhinovirus infection of the normal human airway. *Amer J Respir Crit Care Med* 1995; **152**:S36–9.
26. Lewis FA, Kenneth ML. Comparison of rhinovirus-sensitive HeLa cells and human embryo fibroblasts for isolation of rhinoviruses from patients with respiratory disease. *J Clin Microbiol* 1976; **3**:528–32.
27. Steining C, Aberle SW, Popow-Kraupp T. Early detection of acute rhinovirus infections by rapid reverse transcription-PCR assay. *J Clin Microbiol* 2001; **39**:129–33.
28. Jackson G, Dowling H, Spresman I, Boand A. Transmission of the common cold to volunteers under controlled conditions. *Arch Intern Med* 1958; **101**:267–78.
29. Kirkpatrick GL. The common cold. *Prim Care* 1996; **23**:657–75.
30. Noah TL, Henderson FW, Wortman IA, Delvin RB, Handy J, Koren HS, Becker S. Nasal cytokine production in viral acute upper respiratory infections of childhood. *J Infect Dis* 1995; **171**:584–92.
31. Beck FW, Prasad AS, Kaplan J, Fitzgerald JT, Brewer GJ. Changes in cytokines production and T cell subpopulations in experimentally induced zinc-deficient humans. *Am J Physiol* 1997; **272**:E1002–7.
32. Desbiens NA. Lessons learned from attempts to establish the blind in placebo-controlled trials of zinc for the common cold. *Ann Intern Med* 2000; **133**:302–3.