

Is intranasal zinc effective and safe for the common cold?

A systematic review and meta-analysis

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ABSTRACT

OBJECTIVE: To systematically review the evidence for effectiveness of intranasal zinc used to treat a common cold, and pool the results in a meta-analysis.

DATA SOURCES: A literature search was undertaken in the Cochrane register of controlled trials, MEDLINE and EMBASE databases. Inclusion criteria were randomised placebo controlled trials in patients with a common cold.

RESULTS: Five studies were found. Three were relevant to the issue of treatment of common colds with intranasal zinc and the results were combined in meta-analysis. High doses of intranasal zinc preparation (2.1mg zinc/day) were reported in two studies to shorten the duration and reduce the symptom severity of common cold in healthy adults, when started within 24 to 48 hours of onset of illness. A lower dose study (0.044mg zinc/day) found no benefit in resolution, but did report a significant improvement in symptoms at day 1 and day 3. Combining the three studies, the relative risk for benefit at day 3 was 0.62 (95%CI 0.18 to 2.19) (random effects). There were no studies with children. There were no significant harms reported.

CONCLUSION: Results from individual trials suggest some benefit from zinc for symptoms of a common cold, at least in adults. Pooling the results for symptom relief at day 3, in a conservative meta-analysis, suggests a non-significant benefit. Unquantified concerns about permanent anosmia following the use of intranasal zinc may mean that the issues raised will never be scientifically resolved.

KEYWORDS: Administration, intranasal, zinc, common cold, meta-analysis, olfaction disorders, review

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Introduction

Viral upper respiratory illness is a common problem, with adults having two to three colds per year.^{1,2} Although antibiotics have no role in treating a common cold unless there are significant bacterial complications,³ many doctors prescribe them, at least in part because they feel pressure to do what they think patients expect.⁴ There is global concern about increasing resistance to antibiotics and a need to reduce their use, particularly in primary care.⁵

One approach to reducing antibiotic consumption is to identify and promote effective non-anti-

biotic symptom control.⁶ Antihistamine, nasal decongestants, echinacea, antitussives, mucolytics and vitamin C are widely used to control or prevent cold symptoms, but few, if any, of these agents have proven benefit.⁶ Zinc has been used in various forms to treat the common cold and a number of studies have evaluated its benefits. The mechanism of action is unknown, but it is thought that the zinc ion may compete for viral receptors in the nasal epithelium.⁷ Evidence of the effects of zinc lozenges for treating the common cold is inconclusive.⁷⁻⁹ One review stated that intranasal zinc can be effective, but did not

assess study quality, pool the data or explore heterogeneity.⁷

The objective of this review was firstly to pool all the available data investigating the efficacy of intranasal zinc in reducing severity and duration of common cold symptoms, and, secondly, to assess the quality of included studies and explore heterogeneity. Our primary outcome of interest was improvement in symptoms at day 3 of treatment. We assumed that if there was no benefit by day 3, then any patients who knew this would be unlikely to seek it for symptom control.

Methods

Search strategy

The literature search was performed using MEDLINE from 1966 to 2007, EMBASE from 1980 to 2007, and the Cochrane Controlled Trials Register of 1st quarter 2007. The search terms included 'common cold', 'viral upper respiratory tract infection', 'intranasal zinc' and 'randomised controlled trials'. The abstracts of all potentially relevant studies were viewed by authors HD and BA and agreement on inclusion was reached by discussion. Extraction of the data was done independently by all authors and agreement achieved by discussion. The authors of randomised controlled trials were contacted for missing data and knowledge of unpublished studies. There was no language restriction.

Inclusion and exclusion criteria

This review sought randomised controlled trials assessing effectiveness of intranasal zinc compared to placebo to treat symptoms of a common cold. Intranasal zinc used as prevention was excluded.

Data analysis

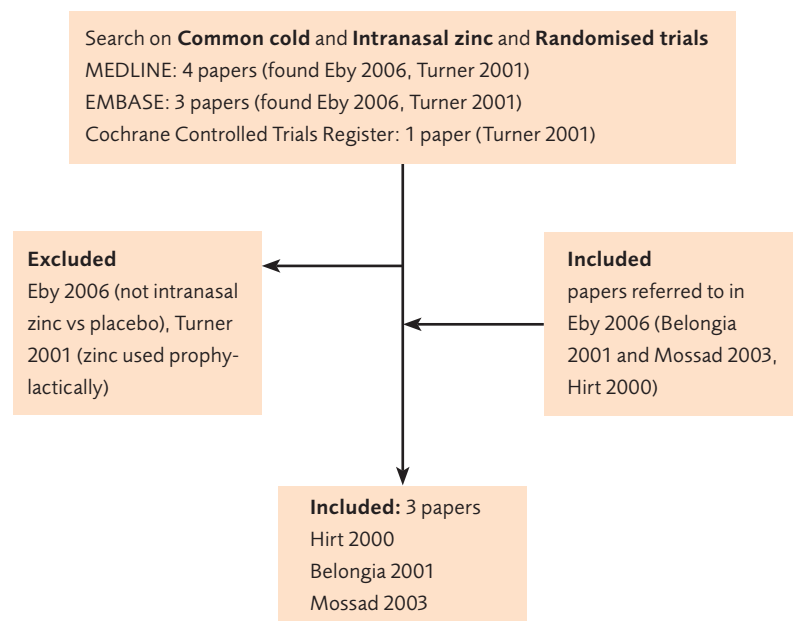
We sought data on three outcomes, namely resolution of symptoms, symptom score and days to resolution of symptoms. The included studies all used a similar treatment for a similar condition in similar patients, hence we thought it appropriate to pool the data. The pooled relative risks and 95% confidence intervals were assessed with Stata 9.2.

WHAT GAP THIS FILLS

What we already know: There is conflicting evidence about the effectiveness of intranasal zinc in treating symptoms of the common cold. A previous review did not consider study quality, did not pool results, and did not consider heterogeneity.

What this study adds: This review suggests that intranasal zinc may be effective in reducing the duration and severity of symptoms of the common cold. However, the possible risk of permanent anosmia (inability to perceive smells) limits its usefulness.

Figure 1. Search strategy



Results

Studies identified

Of the eight studies identified in the original search, five compared the effectiveness of intranasal zinc against placebo in patients with the common cold (Figure 1). Hirt,¹⁰ Belongia¹¹ and Mossad¹² met all inclusion criteria, and were in naturally occurring colds. Turner¹³ studied patients with an experimental cold, but intranasal zinc was used prophylactically and the data was therefore not pooled to measure treatment benefit but is included in consideration of adverse events.

Eby¹⁴ used a combination of oral and intranasal zinc so was excluded from the analysis.

Study quality

In each study the authors state that the packaging and formulation of the medication was identical apart from the absence of zinc in the placebo. Turner reported that, at day 3 (prior to viral inoculation), 21/41 in the zinc group and 20/51 in the placebo group believed they were on active treatment ($p=0.29$). Mossad assessed adequacy of blinding on day 1 so that confounding with improvement was not an issue. They reported that 48% of the zinc group correctly identified their medication compared with 58% in the placebo group ($p=0.66$).

The methodology and an evidence table of the participants, interventions and outcomes for the three included studies summarises our findings. All three studies included a statement that the medication and placebo were allocated randomly. Nevertheless, compared with the other studies, Hirt provided minimal details on randomisation and other important methodological criteria.

Efficacy for symptoms

None of the papers reported all three key outcomes we sought, namely resolution of symptoms, symptom score and days to resolution of

symptoms. Two of the studies (Hirt and Mossad) reported a statistically significant benefit in terms of resolution of symptoms at day 3. Belongia reported an improvement in total symptom score at day 1 ($p=0.002$), mostly due to an improvement in nasal symptoms ($p=0.02$). The pooled relative risk (RR) for all three studies, for any symptoms persisting at day 3 was 0.63 (95% CI 0.56 to 0.70) using a fixed effects analysis and 0.62 (95% CI 0.18 to 2.19) on a random effects analysis (Figure 2). The I-squared (which estimates the variation in RR attributable to heterogeneity) was 99.2%. A sub-analysis pooling the two high dose zinc studies (Mossad and Hirt), for any symptoms at day 3, gave a relative risk of 0.43 (95% CI 0.35 to 0.53) using a fixed effects model.

Adverse effects

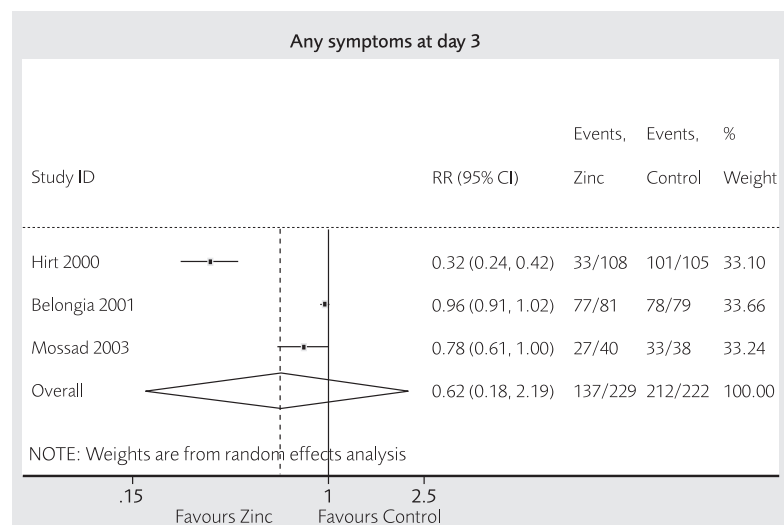
Adverse effects were more common in the study by Mossad in the zinc group; nine (23%) compared with three (8%) in the placebo group; the most common was nasal stinging and burning five (12.5%) and two (5%) $p>0.05$ respectively. There were no statistically significant differences in adverse effects in Belongia, Hirt and Turner.

Discussion

The pooled relative risk for having any ongoing symptoms at day 3 was 0.63 using a fixed effects analysis and 0.62 using a random effects model. However, the fixed effects model was statistically significant and the random effects model was not. We have chosen to present only the more conservative random effects model in Figure 2. The high I-squared suggests that the fixed effects model is not appropriate as the studies were too heterogeneous to meet the assumptions of the fixed effects model. In large part this heterogeneity is due to the extreme effect of the Hirt study, being markedly different from that of the other two studies. If we believe the Hirt study was well conducted and well reported, it would be reasonable to ignore the warning of the high I-squared and accept the fixed effects model. However, the Hirt result seems implausibly favourable to zinc, and this is the most poorly reported study.

The dose of zinc used by Belongia was so much lower than Mossad or Hirt that perhaps it was

Figure 2. Meta-analysis plot for any symptoms at day 3; random effects model



simply inadequate. This leaves Mossad as a plausible study, the only one reported as recommended by the CONSORT statement,¹⁵ with some positive results reported within the paper; in particular the mean duration of symptoms in the treatment group was median 43 days (inter-quartile range 2.5 to 5.5) versus control median six days (inter-quartile range 5 to 8.5), $p=0.002$.

All of the studies had inclusion criteria that reasonably selected cases of acute viral respiratory tract infection. Belongia and Hirt included patients with symptoms present less than 24 hours, while Mossad entered only patients with symptoms present 24–48 hours (which is relevant if an important mechanism of action of zinc is limiting replication of virus in the nasal mucosa). It is assumed that all studies included only adult cases, although no age group was mentioned in

ate and permanent anosmia after using a zinc gluconate nasal preparation, following what was presumably a single application, as all were associated with marked local pain.¹⁶ The studies included in this review report no cases of anosmia amongst the 277 patients treated with zinc in randomised trials.^{10–14} As a symptom in the general population, anosmia seems surprisingly common, according to a survey of all otorhinolaryngology services in hospitals in Germany, Switzerland and Austria.¹⁷ Nasal zinc was not a recognised cause—the ‘vast majority’ were attributed to sinonasal disease (and zinc was among the therapies that have been used in an attempt to treat it). However, intranasal zinc sulphate is widely used to produce experimental anosmia in animals including sheep,¹⁸ birds,¹⁹ rats (where it may not be effective),²⁰ mice (where the effect can last up to one month)²¹ and dogs (where the effect

Jafek reported a case series of 10 people with immediate and permanent anosmia after using a zinc gluconate nasal preparation, following what was presumably a single application, as all were associated with marked local pain

Hirt; however the invitation process and diary-keeping requirements of the study seem more applicable to adults than to children. Belongia excluded patients who smoked tobacco products in the past 12 months and Mossad excluded patients who were habitual smokers. This would suggest that these results are generalisable at least to non-smoking adults. There were no data about children.

A strength of this review is that the original authors were contacted; this did not result in finding additional studies. The weaknesses of the review reflect the limits on quantity and quality of the original studies.

There did not appear to be any significant difference in adverse effects in the three studies of naturally occurring symptoms. However, Jafek reported a case series of 10 people with immedi-

can last several months).²² On the other hand, Hulisz claims that zinc sulphate has sufficiently different properties to zinc gluconate that the effects of the sulphate on nasal mucosa cannot be presumed to apply to the gluconate.⁷ Given that the maker of one popular zinc preparation in the US has settled multiple legal claims for anosmia,²³ we may never see further studies.

Conclusion

Even though intranasal zinc may be effective and some might even think it a ‘natural’ alternative to antibiotics, one would need to establish the prevalence of permanent anosmia as a side effect before recommending widespread and routine use. On the other hand, practitioners might wish to recommend zinc, which may work, rather than antibiotics, which cannot work, especially as side effects can be far worse.

Table 1. Participants, interventions and outcomes for the three included studies

Study	Participants	Intervention	Restrictions	Numbers	Outcomes
Mossad 2003	Inclusion: Age 18–55 years, symptoms for 24–48 hours. Common cold symptoms 2 major and 1 minor, or 3 minor where major = nasal drainage, sore throat and minor = nasal congestion, sneeze, scratchy throat, hoarseness, cough, headache, muscle aches and fever. Exclusion: Known immune system disorder, diabetes mellitus, uncorrected deviated nasal septum, otitis, history of recurrent sinusitis or recurrent bronchitis.	Nasal spray 33mmol/L zincum gluconicum nostril, once each nostril 4 times a day, dose 2.1mg per day. Placebo identical without zinc. Used for 10 days or until all symptoms resolved.	No cold remedies including aspirin, decongestants, antihistamines, other zinc products. Paracetamol (acetaminophen) allowed.	Zinc 40, placebo 40.	Resolution of symptoms at day 3 was 27/40 in zinc group and 33/38 in placebo group. At 5 days it was 19/40 and 27/38. Mean days (sd) to resolution of symptoms was 4.3 (0.75) in the zinc group and 6 (0.88) in the placebo group. There was a significant reduction in days to resolution of the following symptoms in the zinc group: hoarseness, sore throat, nasal drainage, nasal congestion, but not in cough, sneezing, muscle aches or fever >98.6°F. There was no significant difference in the adverse effects which included nasal stinging or burning, faint headache, runny nose, congestion, a little achy, post nasal drainage, dry skin, sneezing, irritating smell, burned throat, nasal bleeding, sleepiness.
Belongia 2001	Inclusion: Symptoms < 24hrs, symptoms 2 or more of: cough, stuffy nose, runny nose, hoarseness, sore/itchy throat, headache, sneezing, or muscle ache. Exclusion: Pregnant, smoked tobacco products during past 12 months, any immunodeficiency, recent sinus infection, chronic lung disease, zinc allergy, allergic rhinitis, positive test for Group A Streptococcus. The age of participants was not stated.	Isotonic preparation 0.12% zinc (as zinc sulphate heptahydrate). Two sprays each nostril 4 times daily, total dose 0.044mg zinc per day. Placebo identical without the zinc. Used until symptoms resolved or max of 14 days.	No cough and cold medications, multivitamin containing zinc. Paracetamol (acetaminophen) allowed.	Zinc 81, placebo 79.	Total symptom score were significantly different on day 1; mean total symptom score (sd) 6.4 (3.0) in zinc group versus 7.9 (3.3) in placebo group. At day 3 this was 4.5 (4.1) and 5.4 (4) respectively. The median time to resolution of nasal symptoms was 6 days in each group and for throat symptoms 3 days in the zinc group and 4 days in the placebo group (p=0.16). The mean (SD) days to resolution was 7.51 (2.93) in the zinc group and 7.72 (2.52) in the placebo group. The resolution in the zinc group at day 3 was 77/81 and 78/79 and at day 5 was 56/81 and 62/79. Adverse effects included vomiting, nausea, abdominal pain, nasal irritation, bloody nose, mouth irritation, bad taste, headache, dizziness, dry mouth.
Hirt 2000	Inclusion: Symptoms up to 24 hours, at least 3 of: cough, headache, hoarseness, muscle ache, nasal drainage, nasal congestion, scratchy throat, sore throat, sneezing. Exclusion: Pregnant, immunocompromised, or 'the use of certain medications'.	Nasal spray 33mmol/L zinc gluconate. One dose each nostril 4 times per day, total dose zinc 2.1mg per day. Used for duration of symptoms.	None reported.	Zinc 108, placebo 105.	Resolution of symptoms at day 3 was 33/108 in zinc group and 101/105 in placebo group. At day 5 it was 1/108 and 98/105. Mean days (sd) to resolution of symptoms was 2.3 (0.9) in the zinc group and 9 (2.5) in the placebo group. Forty-five patients on zinc and 39 on placebo reported a slight tingling or burning; no patients reported other adverse effects.

Table 2. Methodology for the three included randomised controlled trials

Study	Method of randomisation	Concealment of allocation	Blinding	Follow-up	Outcome measures
Mossad 2003	An independent company prepared a computer-generated randomisation code in blocks of 10 (5 zinc and 5 placebo).	The examining physician and the clinic coordinator who assigned the pumps were blind to the allocation group.	Active and placebo appearance identical. 19/40 on zinc and 23/40 on placebo correctly guessed their group assignment at the start of the trial (p=0.37).	Details given of participant flow. Specific intention to treat analysis. Compliance monitored by study co-ordinator phoning 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 the day of completion.	Twice daily diary of severity of each of 8 symptoms on a scale from 0 (absent) to 3 (severe). Scores summed daily. Primary outcome was days to complete resolution.

Table 2 cont.

Study	Method of randomisation	Concealment of allocation	Blinding	Follow-up	Outcome measures
Belongia 2001	The active and placebo nasal spray bottles were randomly placed in blocks of 4 by the manufacturer, who held the randomisation key until data had been entered at the end of the study.	All study personnel were blinded to the group assignments.	Active and placebo appearance identical. 22/81 participants in the zinc group and 18/79 in the placebo group guessed that they received the zinc preparation ($p=0.59$).	Exclusions accounted for, but not included in analysis. Phone calls to participants on days 2 and 6 to encourage compliance, answer questions, and assess adverse reactions. Participants asked to return for an exit interview after symptoms had resolved for at least 24 hours or upon completion of 14 days of treatment.	Twice daily diary of severity of each of 8 symptoms on a scale from 0 (absent) to 3 (severe). Scores summed daily. Primary outcome was days to first day of resolution defined as 2 consecutive days with total score 0 or 1.
Hirt 2000	Study population 'randomly assigned'.	Zinc nasal gel and placebo 'dispensed in a double-blind fashion'.	Active and placebo appearance identical.	No details given about loss to follow-up. Subjects asked to return to their study site within 24 hours of symptom resolution for verification and follow-up.	Twice daily diary of severity of each of 9 symptoms on a scale from 0 (absent) to 3 (severe). Scores summed daily. The primary endpoint was complete resolution of symptoms.

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COMPETING INTERESTS

None declared.