Zinc for the treatment of the common cold: a systematic review and meta-analysis of randomized controlled trials

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CRD summary
The moderate quality of evidence suggested that orally administered zinc reduced the duration of symptoms of the common cold. However, the evidence of benefit was limited to adults, and even in this patient group uncertainty remained about its clinical benefit. This was a well-conducted review and the conclusions seem appropriate.

Authors’ objectives
To evaluate the efficacy and safety of zinc for the treatment of the common cold.

Searching
MEDLINE, EMBASE, the Cochrane Central Register of Controlled Trials (CENTRAL), CINAHL and AMED (Allied and Complementary Medicine Database) were searched for relevant studies to September 2011. Conference proceedings from 2005 to 2011 through the Web of Science and Open-SIGLE databases, and clinical trial registries (ClinicalTrials.gov, Current Controlled Trials and the US National Institutes of Health database) were searched. No restrictions were placed on language. Search terms were reported (supplementary data). Reference lists of key articles were reviewed for additional studies.

Study selection
Randomised controlled trials that involved patients of any age with the common cold and compared oral zinc treatment started within three days of symptoms with placebo or no intervention were eligible for inclusion. Studies in which zinc was administered intranasally or that used zinc in a combined formulation with other minerals or vitamins were excluded.

The primary outcome was the duration of cold symptoms. Secondary outcomes included the severity of cold symptoms, the presence of symptoms after three and seven days and adverse events.

Studies were conducted in UK, USA, Australia, Turkey and Denmark. Patients’ age ranged from one to 65 years (where reported). Three trials included children, 13 included adults, and 1 trial included both adults and children. Treatment regimens included zinc gluconate lozenges or tablets, zinc acetate lozenges and zinc sulphate syrup compared with placebo. Duration of symptoms before treatment ranged from less than 24 hours to less than 72 hours (where reported). The duration of treatment was different in all trials (range 3–14 days or until symptom resolution). The definition of symptom resolution included absence of all or most of the cold symptoms such as headache, fever, sneezing or muscle pain. Most studies were funded by pharmaceutical industry.

Two reviewers independently screened the titles and abstracts of identified studies. Any disagreements were resolved by consensus or by discussion with the third reviewer.

Assessment of study quality
Trial quality was assessed independently by two reviewers according to the Cochrane Risk of Bias tool, which covered random sequence generation, allocation concealment, blinding, incomplete outcome data, selective reporting and other bias. The level of evidence for each outcome was assessed using the GRADE approach (low, medium, high level of evidence). Any disagreements were resolved by consensus.

Data extraction
Outcomes were extracted from each study to calculate mean differences (MD), standardised mean differences (SMD) and risk ratios (RR) with their 95% confidence intervals (CI). When only the median and interquartile range (IQR) were reported, the reported median was used to reflect the mean, and the standard deviation calculated by dividing the interquartile range by 1.35 standard deviations. Study authors were contacted for further details.
Two reviewers were involved in data extraction. Any disagreements were resolved by discussion to reach consensus.

Methods of synthesis
Data were pooled using a random-effects model. For continuous outcomes, mean difference was used when the measurement scale was the same (duration of cold symptoms) and standardized mean differences were used when the scale varied (symptom severity). Risk ratios were used for dichotomous outcomes. Heterogeneity was evaluated using the I² statistic. I² of 40% or greater was considered substantial heterogeneity, in which case subgroup analyses were performed.

Subgroup analyses was performed to investigate the effects of age (under 18 versus 18 years or older), experimentally induced versus naturally acquired colds, zinc formulation, daily dose of ionized zinc (below 75mg versus 75mg or more), high versus low risk of bias, timing of treatment initiation (under 24 hours versus 24 hours or more) and funding source (industry versus non-industry). Subgroup credibility was assessed using the criteria described by Sun and colleagues.

Sensitivity analysis was performed by excluding trials with induced colds.

Results of the review
Seventeen trials (2,121 patients, range 12 to 281) were included in the review. All the trials were low or unclear risk of bias in randomisation, allocation concealment and blinding. Some trials were high risk in incomplete outcome assessment, selective reporting and other bias.

Duration of symptoms: The meta-analysis suggested that zinc reduced the duration of cold symptoms (MD −1.65 days, 95% CI −2.50 to −0.81; eight trials; I²=95%). Though, there was significant heterogeneity, the quality of the evidence for this finding was considered moderate. Subgroup analysis showed zinc shortened the duration of cold symptoms in adults (MD −2.63, 95% CI −3.69 to −1.58; five studies; I²=82%) but not in children (MD −0.26, 95% CI −0.78 to 0.25; three trials; I²=84%), greater reduction with high doses of ionic zinc (MD −2.75, 95% CI −3.89 to −1.60; three trials; I²=78%) than with lower doses (MD −0.84, 95% CI −1.50 to −0.18; five trials; I²=89%).

Severity of symptoms: There was no significant difference in severity of symptoms between the zinc group and the placebo group. The quality of evidence was low given the substantial heterogeneity (I²=55%) and imprecision in the summary estimate.

Presence of symptoms at three and seven days: There was no significant difference in the proportion of patients who were symptomatic after three days, but there was a significant difference in the proportion who were symptomatic after seven days, favouring the zinc group (RR 0.63, 95% CI 0.44 to 0.90; nine trials). There was a high level of heterogeneity and the quality of the evidence was considered low.

Adverse events: The occurrence of any adverse event (RR 1.24, 95% CI 1.05 to 1.46, nine trials; I²=37%), bad taste (RR 1.65, 95% CI 1.27 to 2.16; eight trials) and nausea (RR 1.64, 95% CI 1.19 to 2.27; nine trials) were more common in the zinc group than in the placebo group. There was no difference between groups in the occurrence of abdominal pain, constipation or diarrhoea.

Other subgroup and sensitivity analysis results were reported.

Authors' conclusions
The moderate quality of evidence suggested that orally administered zinc reduced the duration of symptoms of the common cold. However, the evidence of benefit was limited to adults, and even in this patient group, uncertainty remained about its clinical benefit.

CRD commentary
The review addressed a clear question and was supported by appropriate inclusion criteria. The search covered a wide range of relevant sources with no language restrictions which reduced the potential for publication bias and language bias. Study selection, data extraction and quality assessment were conducted in duplicate which reduced the potential for error and bias.
Study quality was assessed using appropriate criteria and the analysis was appropriate. There was significant heterogeneity which the authors tried to explore by using different subgroups and sensitivity analyses. Most included studies were funded by pharmaceutical companies.

This was a well-conducted review and the conclusions seem appropriate.

**Implications of the review for practice and research**

**Practice:** The authors stated that until further evidence becomes available, there was only a weak rationale for physicians to recommend zinc for the treatment of the common cold. The questionable benefits must be balanced against the potential adverse effects.

**Research:** The authors stated that large high quality trials that enrolled adults and children, and that report adverse effects were needed.

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This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on the reliability of the review and the conclusions drawn.