Zinc for the common cold:
The zinc for the common cold review by Singh and Das has a number of problems which should be considered when the review is next time updated

Harri Hemilä
Department of Public Health
University of Helsinki
Finland
http://www.mv.helsinki.fi/home/hemila/
harri.hemila@helsinki.fi

Feedback submitted by Harri Hemilä, 5 September 2011
This is Feedback to the following Cochrane review:

Singh M, Das RR:
Zinc for the common cold.
Cochrane Database Syst Rev. 2011 Feb 16;(2):CD001364.
http://www.ncbi.nlm.nih.gov/pubmed/21328251
http:dx.doi.org/10.1002/14651858.CD001364.pub3

This Feedback is published within the above Cochrane review.
The Feedback part of the Cochrane review is available at:
http://www.mv.helsinki.fi/home/hemila/H32P.pdf

This is an open access version of the Feedback.
This version has active links to all the references.

No replies to these comments were published by April 2013

This feedback was motivated by differences in the analysis and in the conclusions compared with the meta-analysis:

Hemilä H. **Zinc lozenges may shorten the duration of colds: a systematic review.**
Open Respir Med J 2011;5:51-8.
http://www.ncbi.nlm.nih.gov/pubmed/21769305
http://dx.doi.org/10.2174/1874306401105010051
http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3136969/
See references available for this paper as links at:
http://www.mv.helsinki.fi/home/hemila/Zn/TORMJ.htm

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Harri Hemilä
Department of Public Health
University of Helsinki
Finland

1) Search of the studies

Eby and Halcomb (2006) reported a randomized double-blind placebo-controlled trial on zinc for the common cold [1], which is missing from the review. The trial is included in MEDLINE (PMID: 16454145) and Singh and Das should have found it and listed among the trials requiring an assessment.

2) Extraction of data

Singh and Das describe that "*The lead review author (MS) entered data directly into Review Manager. An independent coder verified accuracy of data entry*". However, looking at their Analysis 1.1 led me to wonder how can they claim that the findings of the Petrus (1998) trial were non-significant (the 95%CI covering the "no effect"), given that Petrus (1998 p. 600) wrote that "*t-test showed that the mean duration of all symptoms was significantly lower in the zinc group (3.8±0.2 days) than in the placebo group (5.1±0.4 days)(P=0.008)*". In their Analysis 1.1, Singh and Das give the mean duration of colds in the zinc group as 4.4 days, and not as the 3.8 days reported by Petrus (above). The value of 4.4 days is given in the Petrus (1998) Table II as the overall mean duration of colds, i.e. the mean for all zinc and placebo participants combined, but Table II also gives the 3.8 days for the duration of colds in the zinc group.

In their paper, Petrus (1998) gives the accuracy of the mean as the SE (standard error), whereas the Review Manager needs the SD (standard deviation). The SE values reported by Petrus (1998) are highly inaccurate (above), yet Singh and Das calculated the corresponding SD estimates from them. To get the accurate Petrus (1998) trial results, I contacted the statistician of the group and got their results: 3.797 (SD 1.630) days in the zinc group and 5.106 (SD 2.955) in the placebo group (Ken Lawson, email 4 Mar 2009). The Petrus (1998) values in Analysis 1.1 should be replaced with these correct and accurate values.

3) The characteristics of included studies table

In the Characteristics of included studies table, Singh and Das write about the Al-Nakib (1987) trial that there was "*unclear risk*" for the item "*incomplete outcome data addressed*?". However, Singh and Das write that "*there were no drop-outs or withdrawals*". Lack of drop-outs does not justify

their judgment ("*unclear risk*"). Furthermore, Singh and Das state that in the Al-Nakib trial there is "*high risk*" for the item "*free of selective reporting?*". The statement that there is "*high risk*" calls for justification, whereas none is given. Furthermore, Singh and Das list six outcomes for the Al-Nakib (1987) trial, yet only one of them is relevant to the review: "*the severity of symptoms*". However, I cannot see this outcome in any of their Analysis tables. The outcome section of the included studies table should list only those outcomes that are used in the review. Furthermore, it would help the reader if the included studies table describes in which Analysis the values of the outcomes are presented.

Singh and Das state that in the Smith (1987) trial there is "*low risk*" for the item "*incomplete outcome data addressed?*". Smith started with 176 participants and reported the results for only 110 participants, which means that they reported data for only 62% of the initial participants. In their Methods section, Singh and Das write that "*we considered that incomplete outcome data had been adequately addressed if 85% or more of the participants were included in the analysis, or if less than 85% were included but adequate steps were taken to ensure or demonstrate that this did not bias the results.*" In their included studies table, Singh and Das do not describe why the analysis of 62% of initial participants is acceptable for the Smith (1987) trial although they give the limit of 85% in their Methods. Stating that the Smith (1987) trial has "*low risk*" with the 38% drop-out rate, and the Al-Nakib (1987) trial has "*unclear risk*" with no drop-outs (above) is puzzling.

Singh and Das use an inclusion criterion "*randomized controlled trials*". Weismann (1990) did not report the method of allocation in their trial report. Nevertheless, Singh and Das describe in their included studies table the Weismann (1990) trial: "*Methods: randomized trial*". Since their report did not describe the method of allocation, I contacted Kaare Weismann, who wrote to me "*It was a consequetive allocated study with the same number of patient in the two groups*" (email 2 Jul 2010). Thus, the Weismann (1990) trial was not randomized. Given their inclusion criteria, Singh and Das should exclude the Weismann trial or they should rewrite the inclusion criteria so that they also include pseudo-randomized trials which have used, for example, alternative allocation.

Furthermore, Singh and Das state that there is "*unclear risk*" for the item "*allocation concealment?*" in the Weismann (1990) trial, even though the trial was double blind. The term double-blind means that both the patients and researchers are unaware of the type of treatment until the trial is concluded. Consequently, neither of them can know to which group a patient had been allocated. Thus, double-blind means that there must have been allocation concealment. Otherwise the patients and researchers could not remain blind after randomization. This same error is seen in the description of the Al-Nakib (1987) and Petrus (1998) trials, which also were double-blind trials. As a consequence of this error, Figure 1 gives an impression that several studies were methodologically less satisfactory than they actually were.

More details of the trials should be given in the included studies table. For example, in their "*implications for practice*", Singh and Das state that "*We could not find any trials conducted in low-income countries, so our results cannot be applied to people living in low-income countries.*" However, three trials by Kurugol (2006a, 2006b, 2007) were carried out in Turkey, and one trial by Vakili (2009) was carried out in Iran. These are low-income countries. According to World Bank statistics, the GDP per capita in Turkey and Iran is 80% and 90% lower than in Germany, as an example. Thus, the above statement is false although there are countries which are much poorer than Turkey and Iran. To help the reader to understand the contexts of the trials, it would be useful to describe the country and the settings of the trials. Such information affects the generalization of the findings. Studies in Turkey and Iran cannot be directly extrapolated, for example, to the western countries.

4) The characteristics of excluded studies table

In the Characteristics of excluded studies table, Singh and Das comment on the Eby (1984) trial: "*Intention-to-treat analyses were not conducted; analyses were only conducted on a subset of those originally enrolled in the trial.*" However, this is also true for the Smith (1987) trial, which included only 62% of the initial participants in the analysis (above). Eby (1984 p. 20-21) described: "*Of 146 original volunteers, 120 subjects returned reports. Initially, to use as much of the data as possible, we analyzed the 80 complete reports from 108 subjects who had been ill for 10 days or less at the start of treatment. ... this report is restricted to those 65 subjects who reported being ill for 3 days or less before starting the experiment.*" Singh and Das use an inclusion criterion "*interventions commenced within three days of participants developing common cold symptoms*". Given such a criterion, Eby's post-randomization restriction to 65 subjects who were ill for 3 days or less before the treatment started is relevant data. In any case, Singh and Das should treat Eby (1984) and Smith (1987) trials consistently, so that both are included or excluded on the basis of the high rate of participants not included in the analysis.

Singh and Das further criticise the Eby (1984) trial: "*The trial relied on subjective assessment of symptoms by subjects.*" However, this applies to essentially all zinc and common cold studies. In evidence-based medicine, the subjective symptoms are most essential outcomes. Subjective symptoms determine whether a patient goes to work or school, stays at home, or visits a physician. Double-blinding prevents systematic bias in the subjective assessment of symptoms, and therefore "subjective" *per se* cannot cause bias in a double-blind trial. Furthermore, if Singh and Das consider that "*subjective assessment*" is a basis to exclude the Eby (1984) trial, they should apply the same criterion to the other trials.

Singh and Das also comment on the Eby (1984) trial: "*Inclusion criteria were not adequately addressed and therefore there may have been potential for selection bias to occur.*"

In randomized trials, the primary concern is the comparability of trial arms, so that there are no systematic differences that could lead to bias. All randomized trials use inclusion criteria of some kind, but that has nothing to do with the question whether the trial arms are comparable. Inclusion criteria are relevant when we consider the possibility to generalize the results, but not when considering the internal validity of a trial.

Finally, Singh and Das conclude their criticism of the Eby (1984) trial: "*In addition, no information was provided on how allocation to treatment groups was concealed, the power of the study was not stated and viral studies were not conducted*". First, in most other zinc and common cold studies there is no information about how allocation was concealed (i.e. how blinding was maintained). Second, statistical power is relevant when planning a trial, but not after the trial is concluded, since the confidence interval gives the same information. Third, given that the primary goal in evidence-based medicine is to find out whether a treatment has clinically important effects, viral studies are not relevant. All these issues are missing in most of the zinc and common cold studies. Thus, if Singh and Das consider that these arguments give a sound basis to exclude the Eby trial, they should apply the same criteria also to the other trials.

In the Characteristics of excluded studies table, Singh and Das comment on the Turner (2000) trial: "*Poor methodological quality. Not a randomised trial*". However, Turner writes "*Subjects who met the criteria for randomization to treatment were randomly assigned to 1 of the 4 treatments in accordance with the drug-randomization code*" (p. 1202), [for induced colds:] "*Subjects were randomized to receive study medication 24 h after challenge if they had a total daily symptom score ≥3*" (p. 1203), [for natural colds:] "*Subjects who presented to the study sites with a common-cold illness of ≤1 calendar day's duration (effectively 36 h), reported ≥2 different symptoms, and had a total symptom score of ≥2 were randomized to receive 1 of the 3 treatments*" (p. 1203). Thus, the statement by Singh and Das is false, unless they have information that disproves the text of the Turner (2000) report. In such a case, they should present their evidence. The Turner (2000) trial was reported as a randomized placebo-controlled double-blind study, and there is no basis to claim that it was of "*poor methodological quality*".

5) Different methods of administering zinc should be analyzed separately

The majority of the zinc trials examined zinc lozenges in the western countries. Three trials by Kurugol (2006a, 2006b, 2007) and one trial by Vakili (2009) administered zinc as syrup or tablets; however, all these trials were carried out in low-income countries, Turkey and Iran. Thus, it is possible that the benefit of zinc supplementation in these trials is caused by biological mechanisms that are different from the mechanisms of the zinc lozenges, which are intended to be dissolved slowly in the mouth. The daily dose of zinc in the Kurugol and Vakili studies varied from 10 to 30 mg per day, whereas the total daily dose of zinc in the zinc lozenge studies varied from

30 to 207 mg per day [2]. Thus, it is possible, or probable, that the benefits of the low dose zinc supplementation found by Kurugol and Vakili are explained by a sub-optimal dietary intake of zinc by children in Turkey and Iran. In contrast, it is possible that high dose zinc is needed in the lozenges to get benefit from them.

Although Singh and Das restrict their systematic review to tablets, syrup and lozenges, they should also take a look at the other zinc literature. A few studies have examined the use of nasal administration of zinc to treat colds and found significant benefit [3,4]. Still, patients should not be exposed to intranasal zinc, since there are cases of anosmia caused by such a therapy [5]. Nevertheless, the benefit of local application of zinc to the nose indicates that the effect of zinc lozenges may be caused by local effects in the mouth-throat region, instead of systemic effects such as those caused by the ingestion of tablets and syrup. Therefore it is inappropriate to pool the tablet and syrup trials with the lozenge trials. This is a good example of the apples and oranges problem.

6) The duration of the common cold should not be dichotomized

Singh and Das present three tables which show "*number of participants symptomatic after N days of treatment*", N being 3, 5 and 7. Dichotomization of continuous variables has been criticized [6]. Moreover, there is no need to dichotomize the duration of colds when analyzing the zinc lozenge trials. Although several trials did not report the mean and SD for the duration of colds in the trial arms, all of them reported data that makes it possible to calculate the mean and SD for cold duration [2]. The use of continuous outcome for common cold duration would also simplify the review as three redundant tables can be removed.

7) Duration of the common cold should be normalized so that placebo groups have length 100%

There is substantial variation in the duration of colds in the placebo groups of the zinc lozenge trials, from 5.1 days to 9.0 days and 10.8 days [2]. Although part of this variation is evidently caused by random variation, it is also caused by actual variations in the severity of disease in different patient groups and in differences in outcome definitions. Therefore, the relative effect of zinc on the common cold duration should be calculated in percentages, because the relative effect partly adjusts for the variations between patient groups and outcome definitions.

For example, if a 6-day cold is shortened by 1 day, it is not equivalent to a 1-day cold being shortened by the same amount although both differences are equal in absolute units. Consequently, it is much more reasonable to calculate the relative effect of zinc, so that a 6-day cold shortened by 2 days and a 1-day cold shortened by 0.33 days both correspond to an equivalent 33% reduction. Calculating the relative effect corresponds to the normalization of all control groups to an episode duration of one unit or 100%. Therefore, in our Cochrane review on vitamin C and the common cold we calculate the relative effect [7]. The use of relative effect in the analysis of common cold

duration corresponds to using the risk ratio in the analysis of binary data.

In their Analysis 1.1, Singh and Das pool the results by the SMD method, which means normalizing the duration by the SD (i.e. 1 unit in the scale corresponds to the SD of each study). However, using such a scale (SD units) is very difficult for an ordinary reader to understand. In their abstract, Singh and Das write: "*Intake of zinc is associated with a significant reduction in the duration (standardised mean difference (SMD) -0.97)*". However, reporting should always give the unit of the measurement. In the SMD method, the unit is the SD unit. Thus, the above sentence should be re-written more accurately: "*zinc shortened the duration of colds by 0.97 SD units*". Such accurate reporting would reveal the main problem of the SMD procedure: what does the SD-unit mean?

I pooled the results of three large-dose zinc acetate lozenge trials and I found that "*zinc shortened the duration of colds by 42%*" [2], which is easy to understand. Most people can form an opinion whether 42% is small or large, but few people can form an opinion whether 0.97 SD units is small or large, or whether it is more or less than 42%. Thus, a relative scale would make the analysis of zinc trials easier to understand for the ordinary readers compared with the SD scale. The Cochrane Handbook comments (9.2.3.2): "*The standardized mean difference [SMD] is used as a summary statistic in meta-analysis when the studies all assess the same outcome but measure it in a variety of ways (for example, all studies measure depression but they use different psychometric scales)*." Thus, the SMD can be useful, for example, in psychiatry. In the case of common cold duration, the relative effect in percentages is much easier for readers.

8) Subgroup analysis should be carried out

Singh and Das write in the Background section that a "*significant correlation between total daily dosages of positively charged zinc species and a reduction in the mean duration of common colds*" has been reported. Therefore, the daily dose of zinc should be considered in the statistical analysis. However, in their Result section Singh and Das claim that "*subgroup analysis was not possible as there were not enough studies for each variable.*" This is not correct.

As noted above, there is a 6-fold variation in the total zinc dose (30 to 207 mg per day [2]) in the zinc lozenge studies. Given that the results of the zinc lozenge trials diverge so that some found no effect whereas some others found highly significant benefit, the relation between the dose and effect should be analyzed. Dose-response relation is a basic concept in pharmacology.
I analyzed 13 zinc lozenge trials and divided them into three subgroups on the basis of the total daily dose of zinc and the type of lozenge [2]. None of five trials with the lowest doses of zinc found benefit of the lozenge, suggesting that they may have been using too low a dose. In the high-dose trials, greater benefit was seen in three trials with zinc acetate, and smaller benefit in five non-acetate trials [2]. Further research should focus, in particular, on high doses of zinc acetate

(providing 80-90 mg/day of zinc) [2]. Thus, subgroup analysis is possible and it indicates a path to research that is needed. The syrup and tablet studies with children in the low-income countries should be presented as a separate group, on a separate Analysis table.

9) Pooling the adverse effects of all zinc trials is unsound

Eby has pointed out that the adverse effects of zinc lozenges, such as bad taste, can be explained largely by the differences in the composition of the lozenges [8-10]. In their Discussion, Singh and Das acknowledge this possibility: "*the increased incidence of bad taste and nausea ... may have been related to the use of different ligands (gluconate, acetate) rather than to zinc itself*." In addition, it is obvious that dissolving a high zinc dose lozenge slowly in the mouth causes different adverse effects compared with ingesting a low zinc dose tablet or syrup straight to the stomach. Nevertheless, Singh and Das combine the adverse effects of the tablet and the zinc lozenge trials together as if they could estimate a "*universal adverse effect of zinc*" in the dose range of 15 to 192 mg per day. Nevertheless, the lack of "*mouth irritation*" by zinc syrup in the Kurugol studies (Analysis 2.19) is fully uninformative for a reader who is interested in the possible adverse effects of zinc lozenges.

Thus, it would be much more informative to summarize the adverse effects as text, instead of pooling the results of such different trials. In the most recent zinc acetate lozenge trial, there were no significant differences between the zinc and placebo groups in the occurrence of adverse effects although the daily dose was 92 mg (Prasad 2008). Thus, it seems possible to formulate zinc lozenges that have minimal adverse effects. Furthermore, a patient suffering from acute adverse effects such as bad taste can simply stop taking the lozenges, whereas those who don't suffer from such adverse effects could benefit from the lozenges.

Although Singh and Das restrict their systematic review to treating the common cold, they should also take a look at other zinc literature for information about zinc safety. For certain patients, zinc has been administered at high doses, 150 mg/day, for therapeutic purposes for months [2,11-12]. On the basis of such long-term studies with high zinc doses, there does not seem to be any basis for assuming that treating the common cold for a week with high doses of zinc (80-90 mg/day) in the form of lozenges might cause unanticipated harm.

10) Credit should be given to earlier work on the same topic

In their Introduction, Singh and Das write "*The last review of all available RCTs of zinc for the common cold was published in 1999*", which is erroneous. Although it is not reasonable to discuss in detail all the earlier literature on the topic, the main reviews should be cited and briefly commented. Jackson's [13] and Caruso's [14] systematic reviews on zinc and the common cold were published after 1999. In the Discussion section, RevMan proposes a subtitle "*Agreements and*

disagreements with other studies or reviews". Evidently, the same issue can be discussed under some other title. In any case, it would be important for Singh and Das to describe to what extent their review agrees and disagrees with the earlier reviews, such as [13,14]. If the conclusions do not differ from earlier reviews, then a new review does not increase our understanding about the topic. If the conclusions are different, then the reasons for the differences should be briefly discussed.

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There are many more reports than refs. 11 and 12 about therapeutic usage of high doses of zinc at a dose of 150 mg/day of zinc for months and in some cases for a few years, and case reports of people taking up to 2000 mg/day zinc for years:

http://www.ncbi.nlm.nih.gov/pubmed/359844
http://www.ncbi.nlm.nih.gov/pubmed/3335323
http://www.ncbi.nlm.nih.gov/pubmed/3407636
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http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1991851/
http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1991648/

Many of these studies found that high dose long term zinc decreased copper levels and led to haematological changes. However, the changes were reversible with cessation of zinc intake. Thus, given that months or years of ≥150 mg/day zinc does not cause permanent harms, it is obvious that 1-2 week use of 80-100 mg/day of zinc as lozenges cannot cause irreversible adverse effects.
These kinds of reports should be taken into consideration when considering the safety of zinc, whereas Singh and Das ignore them.

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See main problems of the Caruso review:
http://www.mv.helsinki.fi/home/hemila/H33.pdf

Submitter agrees with default conflict of interest statement:
I certify that I have no affiliations with or involvement in any organization or entity with a financial interest in the subject matter of my feedback.

Contributors

Harri Hemilä