
A meta-analysis of the effects of oral zinc in the treatment of acute and persistent diarrhea

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CRD summary

This review assessed the effect of supplementary oral zinc in children with acute and persistent diarrhea. The authors concluded that the duration and severity was reduced through zinc supplementation. The reliability of this conclusion was unclear given uncertainty over clinical significance of some outcomes and between-study variability.

Authors' objectives

To assess the efficacy and safety of supplementary oral zinc compared with placebo in children with acute and persistent diarrhea, including dysentery.

Searching

MEDLINE (1966-2006), the Cochrane Central Register of Controlled Trials (2006), EMBASE (1974-2006), LILACS (1982-2006), CINAHL (1982-2006), Current Controlled Trials (2006) and abstracts in Pediatric Research (1991-2006) were searched. Proceedings of the first (2000) and second (2004) World Congress of Pediatric Gastroenterology, Hepatology and Nutrition were also searched. Search terms were not reported. Reference lists and bibliographies of identified trials were also searched. Both published and unpublished studies were included.

Study selection

Randomised controlled trials (RCTs) comparing the efficacy and safety of supplementary oral zinc with placebo in children with acute (up to 14 days) and persistent (>14 days) diarrhea, including dysentery, were eligible for inclusion. Random allocation to treatment groups and concealment of allocation had to be met to ensure inclusion. Study groups receiving zinc supplements and oral rehydration solution or zinc supplements with vitamin A were excluded. The included studies assessed zinc salt of any formulation (including sulphate, sulphate/copper sulphate, gluconate or acetate) at doses of 5 mg/day or over for any duration. Included studies were in children aged 0 to 60 months. Most studies were conducted in developing countries. Primary outcomes included average duration of diarrhea and presence of diarrhea episodes at days one, three and five. Secondary outcomes included vomiting frequency, vomiting frequency by therapy type, stool frequency reduction and probability of diarrhea continuation. The definition of diarrhea and duration of diarrhea varied across studies.

The authors did not state how the papers were selected for the review, or how reviewers performed the selection.

Assessment of study quality

Three authors assessed the studies for integrity of randomisation and allocation concealment and resolved any disagreements through consensus.

Data extraction

Data were independently extracted by three reviewers onto a data extraction sheet, with disagreements resolved through consensus. Authors were contacted for additional information or verification, where necessary.

Methods of synthesis

The studies were combined in a fixed-effects meta-analysis. Pooled relative risks (RRs) were calculated for dichotomous outcomes using the Mantel-Haenszel method, while weighted mean differences (WMDs) were calculated for continuous outcomes with 95% confidence intervals (CIs) reported around the weighted effect size. Statistical heterogeneity was investigated using X^2 and I^2 statistics. Publication bias was not assessed. Gravity values were calculated to assess which, if any, studies were unusually influential.

Results of the review

Sixteen RCTs (n=15,231) for acute diarrhea and six (n=3,104) for persistent diarrhea were included. Five studies were not double-blinded.

Acute diarrhea trials

Children who received zinc compared with placebo had lower duration of diarrhea (WMD 0.24 days, 95% CI: 0.21, 0.27, $p < 0.001$), but there was significant heterogeneity ($I^2 = 84.3\%$; $p < 0.001$). The proportion of participants (11 trials, $n = 4,438$) who vomited after the initial dose was significantly greater for zinc than placebo (RR 1.55, 95% CI: 1.30, 1.84, $p < 0.001$) and again there was significant heterogeneity ($p = 0.004$). No significant differences were reported for other outcome measures.

Persistent diarrhea trials

Children who received zinc compared with placebo (five trials, $n = 489$) had lower duration of diarrhea (WMD 0.30 days, 95% CI: 0.12, 0.48, $p < 0.001$), without significant heterogeneity. In two trials of persistent diarrhea a significantly lower occurrence of diarrhea was observed at day three for those taking zinc compared with placebo (RR 0.70, 95% CI: 0.51, 0.94, $p = 0.02$). A higher proportion (four trials, $n = 2,969$) vomited on zinc than placebo (RR 3.64, 95% CI: 1.02, 13.02, $p = 0.047$).

Results for other outcomes were reported.

Authors' conclusions

The duration and severity of acute and persistent diarrhea was reduced through zinc supplementation.

CRD commentary

The review addressed a clear question and was supported by clear inclusion criteria. The search strategy was extensive, but search terms were not reported. The authors searched for unpublished material to reduce the possibility of publication bias, but they did not formally test for its presence. It was unclear whether there were any language restrictions in place, thus there was the possibility of language bias. The authors did not state how the papers were selected for review or how many reviewers performed the selection, which may mean that the selection process was subject to bias. It was unclear whether the outcomes were pre-specified. Mortality was reported in very few trials, but was initially specified as a primary outcome, therefore, it was uncertain whether the primary outcomes were those that were originally listed or those that were most frequently reported. WMD were reported in days and in these results might be statistically significant due to the large numbers of patients, but they might not have represented findings that were clinically significant. A fixed-effects meta-analysis was used, but given the presence of significant heterogeneity between studies this seemed questionable. The influence of one large study with a short duration of diarrhoea was apparent through the standardised gravity results. In light of the methodological shortcomings and the significant heterogeneity between studies, the authors' conclusions should be interpreted with caution.

Implications of the review for practice and research

The authors did not state any implications for practice or further research.

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