Meta-analysis: zinc supplementation for acute gastroenteritis in children
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CRD summary
The authors concluded that available data confirm zinc supplementation can be useful for treating acute gastroenteritis in children, particularly those from developing countries. A large number of trials with large sample samples were included in the review. This was generally a well-conducted review. The authors’ conclusions appear reliable.

Authors’ objectives
To assess the effectiveness of zinc in treating acute gastroenteritis in children, particularly in developed countries.

Searching
PubMed, EMBASE and Cochrane Central Register of Controlled Trials (CENTRAL) were searched (up to November 2007). Search terms were reported. Reference lists of relevant studies and review articles were handsearched.

Study selection
Randomised controlled trials (RCTs) that compared the effects of zinc (any dose and form) to placebo/no intervention in treatment of acute gastroenteritis as an adjunct to treatment of diarrhoea were eligible for inclusion. Studies needed to be in children aged five years or younger. Studies of chronic diarrhoea, prevention of diarrhoea or combined therapy were excluded. Primary outcome measures were duration of diarrhoea (number of days) and stool output. Secondary outcome measures were stool frequency, diarrhoea that lasted longer than seven days and vomiting.

Most studies were from developing countries. A number of studies excluded severely malnourished children and some were primarily of malnourished children or of children with stunting or wasting. Acute diarrhoea was defined in most of the studies as passage of at least three watery stools in the previous 24 hours or at least one loose stool that contained blood. Participants’ nutritional status, aetiology of diarrhoea and dose and form (syrup, tablets), types (sulphate, gluconate, acetate) and duration of zinc therapy were varied. Participants’ ages ranged from one to 60 months. Doses of zinc ranged from 5mg to 45mg. Duration of zinc supplementation ranged from five to 15 days.

Two reviewers independently assessed studies for inclusion; disagreements were resolved by discussion.

Assessment of study quality
Study quality was assessed according to methods described in Cochrane Handbook for Systematic Reviews of Interventions. Key criteria assessed included the adequacy of allocation concealment, blinding (investigators, participants, outcome assessors and data analysts), intention-to-treat (ITT) analysis and completeness of follow-up.

The reviewers independently assessed study quality; the authors did not report how any disagreements were resolved.

Data extraction
Data on the number of events in experimental and control groups were extracted to calculate relative risks (RRs) and their corresponding 95% confidence intervals (CIs) for dichotomous outcomes. Means and their standard deviations (SDs) were extracted to calculate weighted mean differences (WMDs) or standardised mean differences (SMDs), with 95% CIs for continuous outcomes. Missing standard deviations were calculated from standard errors.

Two reviewers independently performed data extraction; disagreements were resolved by discussion.

Methods of synthesis
Pooled relative risks, WMDs or SMDs (with their 95% CIs) were calculated using random-effects where evidence for significant heterogeneity was present; otherwise, the fixed-effects model was used. Statistical heterogeneity was assessed using $X^2$ and $I^2$ tests. Publication bias was assessed using a funnel plot. Post-hoc subgroup analysis was
conducted according to nutritional status of participants. Data were reported as a narrative synthesis where results were not pooled.

Results of the review
Eighteen RCTs were included (n=11,180 reported in the text, but n=10,683 reported in table one, sample size ranged from 50 to 2,002). Allocation sequence concealment, randomisation, blinding and rates of follow-up were adequate in most studies. ITT analysis was used in only four studies.

Compared to placebo, use of zinc was associated with a significant reduction in diarrhoea duration (days) (WMD -0.69, 95% CI -0.97 to -0.40, I²=78%; n=5,643 infants, 13 RCTs; no evidence of publication bias) and risk for diarrhoea lasting longer than seven days (RR 0.71, 95% CI 0.53 to 0.96; n=5,769 infants, eight RCTs).

Compared to placebo, use of zinc was not associated with a significant reduction in stool volume (three RCTs) and stool frequency (stools/per day) (three RCTs).

Compared to control agent, use of zinc was associated with a significant increase in risk of vomiting (RR 1.22, 95% CI 1.05 to 1.43; n=3,156, five RCTs).

Subgroup analysis: Zinc supplementation had a greater effect on the duration of diarrhoea in malnourished patients (mean difference, MD -1.23, 95% CI -1.45 to -1.01, I²=60%; n=373, three RCTs) than in groups without severe malnutrition (MD -0.70, 95% CI -0.90 to -0.49, I²=19%; n=2,665, eight RCTs) or with no malnutrition at all (MD -0.65, 95% CI -1.29 to -0.01; n=280, one RCT).

Authors’ conclusions
Available data confirm that zinc supplementation can be useful for treating acute gastroenteritis in children, particularly those from developing countries. Although zinc supplementation appeared to be a promising option for treatment of diarrhoea in children, there was not enough evidence to support its routine use in children from developed countries.

CRD commentary
The review question was clearly stated. Three relevant databases were searched. Limited efforts were made to search for unpublished studies, but the large number of trials identified made publication bias unlikely. Steps were taken to minimise reviewer error and bias in the conduct of review processes. Study quality was assessed using appropriate criteria and quality was reported to be high. The methods used to combine study results and account for statistical heterogeneity were appropriate and justified. A large number of trials were included in the review. There was a discrepancy in the reported sample sizes.

This was generally a well-conducted review. The authors’ conclusions appear reliable.

Implications of the review for practice and research
Practice: The authors stated that although zinc supplementation appeared to be a promising option for treatment of diarrhoea in children, there is not enough evidence to support its routine use in children from developed countries.

Research: The authors stated that further RCTs were needed to investigate the role of zinc supplements in treating children with acute gastroenteritis in developed countries. Studies were needed to identify the mechanism of action of zinc and to determine its optimal delivery to the neediest populations. Further studies were needed to determine whether zinc supplementation was beneficial to all children (including children without malnutrition).

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