Zinc for the treatment of diarrhoea: effect on diarrhoea morbidity, mortality and incidence of future episodes
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CRD summary
This review concluded that zinc for treatment of diarrhoea was an important child-survival intervention and in combination with oral rehydration solutions was key for a reduction in overall child mortality. These conclusions should be interpreted with some caution, given that results were based on estimates using a small number of studies.

Authors’ objectives
To assess the effect of zinc supplementation for treatment of diarrhoea and prevention of death due to diarrhoea.

Searching
The authors searched PubMed, The Cochrane Library and all World Health Organization (WHO) regional databases for publications in any language. Searches covered the period 1990 to 31 January 2009 and were updated on 15 October 2009. Search terms were reported. Unpublished material was sought.

Study selection
Eligible studies needed to be of zinc supplementation for treatment of acute and persistent diarrhoea in children younger than five years of age. Studies needed to be conducted in low- and middle-income countries (LMICs). Zinc was given as a diarrhoea treatment for seven days or more to infants and children aged between one and 59 months. Zinc could be given alone or in combination with vitamins. Zinc dose was between 10 and 40mg/day in line with WHO recommendations. Both syrups and tablets were eligible. Studies of zinc-fortified oral rehydration solutions were excluded due to dosage that did not meet WHO guidelines. Studies that provided iron were excluded, as were studies solely in specific populations such as those with cholera. Studies were randomised controlled trials (RCTs) with a placebo or suitable control group. They were required to present one of the following outcomes: all-cause mortality, diarrhoea mortality, diarrhoea hospitalisations, pneumonia hospitalisations, prolonged diarrhoea (episode lasting >7 days), diarrhoea and pneumonia incidence in the period up to three months following treatment.

Some trials included children who received less than the recommended WHO dosage. Most trials administered zinc for 14 days. Control groups received oral rehydration solutions alone or with placebo or multivitamins.

The authors did not state how many reviewers were involved in the selection of studies for the review; they stated that Child Health Epidemiology Reference Group (CHERG) guidelines were followed.

Assessment of study quality
Studies were assessed according to the CHERG adaptation of the GRADE technique. Any study with a very low grade (based on study design, intention-to-treat analysis and statistically significant strong effects) was excluded.

The authors did not state how many reviewers were involved in the validity assessment; they stated CHERG guidelines were followed.

Data extraction
Studies were double data extracted into a standardised form for each outcome of interest.

Methods of synthesis
Studies were pooled in a series of meta-analyses using random-effect models in cases of unexplained heterogeneity. Pooled relative risks (RR) with 95% confidence intervals (CI) were generated. CHERG Rules for Evidence Review were applied to the collective diarrhoea morbidity and mortality outcomes to generate a final estimate for reduction in diarrhoea mortality and pneumonia mortality.
Results of the review
Twelve studies were included in the review. The total number of participants was unstated. Ten studies were individually randomised trials and two were cluster-randomised trials. All studies had adequate allocation concealment and all used intention-to-treat analysis. There was between 0.9% and 7.3% loss to follow-up.

Four trials, when pooled, showed a benefit of zinc for all-cause mortality (RR 46%, 95% CI 12% to 68%). Two trials, when pooled, showed a benefit of zinc for diarrhoea hospitalisations (RR 23%, 95% CI 15% to 31%). Other outcomes were not statistically significant.

After application of CHERG rules and using diarrhoea hospitalisations as the closest and most conservative possible proxy for diarrhoea mortality, zinc treatment for diarrhoea was estimated to decrease diarrhoea mortality by 23% (two studies).

Authors’ conclusions
Zinc for the treatment of diarrhoea was an important child-survival intervention and in combination with oral rehydration solutions was key for a reduction in overall child mortality.

CRD commentary
This review was underpinned by inclusion criteria for participants, interventions, outcomes and study designs. Searching encompassed a range of sources. Attempts were made to locate unpublished research and research in languages other than English. Study quality was assessed and studies of very low quality were excluded from the review. Processes to guard against reviewer error and bias in study screening and quality assessment were not stated explicitly. The authors did not state the processes for study screening and quality assessment, but they stated that CHERG guidelines were followed and these aimed to minimise reviewer error and bias. Methods for synthesis appeared to be appropriate, although it appeared that the statistical heterogeneity resulting from several of these analyses was not investigated further. As acknowledged by the authors, final conclusions of the effect of zinc on diarrhoea mortality were based on estimates using CHERG rules (using a small number of studies) and there were difficulties in separating the effects of zinc from that of oral rehydration fluids. The authors’ conclusions should, therefore, be interpreted with some caution.

Implications of the review for practice and research
Practice: The authors stated that zinc in combination with oral rehydration solutions was key for a reduction in overall child mortality.

Research: The authors did not state any implications for practice.

Funding
Supported in part by a grant to the US fund for UNICEF from the Bill and Melinda Gates Foundation (grant 43386) to "Promote evidence-based decision making in designing maternal, neonatal and child health interventions in low- and middle-income countries".

Bibliographic details

PubMedID
20348128

DOI
10.1093/ije/dyq023

Original Paper URL
http://ije.oxfordjournals.org/content/39/suppl_1/i63.abstract
Indexing Status
Subject indexing assigned by NLM

MeSH
Child, Preschool; Diarrhea /drug therapy /epidemiology /mortality /pathology; Dietary Supplements; Female; Humans; Incidence; Infant; Male; Severity of Illness Index; Trace Elements /therapeutic use; Treatment Outcome; Zinc /deficiency /therapeutic use

AccessionNumber
12010003305

Date bibliographic record published
28/07/2010

Date abstract record published
03/11/2010

Record Status
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.