Zinc supplementation for treating diarrhea in children: a systematic review and meta-analysis

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Objective. To update the available evidence about zinc use for treating diarrhea in children and to assess its effect on the malnourished population, a subgroup that has not been fully explored in previous analyses.

Methods. A systematic review was performed of randomized clinical trials that assessed children up to 5 years old with acute diarrhea who received zinc supplementation. Controls received a placebo or oral rehydration therapy. After searching the main databases, without language restrictions, two independent reviewers selected eligible studies, extracted the data, and assessed the risk of bias of included studies. Meta-analyses were calculated using Mantel–Haenszel or inverse variance random effects.

Results. Eighteen of 1,041 studies retrieved were included in the review (n = 7,314 children). Zinc was beneficial for reducing the duration of diarrhea in hours (mean difference [MD] = –20.12, 95% confidence interval [CI] = –29.15 to –11.09, I² = 91%). The effect was greater in malnourished children (MD = –33.17, 95% CI = –33.55 to –27.79, I² = 0%). Diarrhea prevalence on days 3, 5, and 7 was lower in the zinc group. The incidence of vomiting was significantly greater in the group that received zinc than in the control group. Included randomized controlled trials were of low risk of bias in most domains assessed.

Conclusions. Oral zinc supplementation significantly decreases diarrhea duration and has a greater effect on malnourished children. Zinc supplementation seems to be an appropriate public health strategy, mainly in areas of endemic deficiencies.

Key words zinc; diarrhea; child; malnutrition; review.

Diarrhea is responsible for 15% of all deaths in children under 5 years of age and accounts for about 1.4 million annual infant deaths worldwide (1, 2). Data from the World Health Organization (WHO) and the United Nations Children’s Fund (UNICEF) have shown a substantial decrease in deaths in adults over the age of 30, and the mortality rate for children under age 5 from acute diarrhea has fallen from 4.5 million deaths annually in 1979 to 1.6 million deaths in 2002. Despite these improvements, mortality due to diarrhea in developing countries remains too high (3). Severe diarrhea can quickly cause life-threatening dehydration. One major advance in reducing mortality from diarrhea was the introduction of WHO oral rehydration solution (ORS). However, WHO ORS is unable to reduce the volume, frequency, and duration of diarrhea; consequently, other approaches to improve or supplement ORS have been researched (3). Among the available treatments, WHO currently recommends early oral rehydration therapy and zinc.
supplementation to treat diarrhea in children between 6 and 60 months of age (1, 4–6). This recommendation is based on systematic reviews (7–11) that have demonstrated the beneficial effect of zinc treatment in reducing the duration and severity of diarrhea episodes in children less than 5 years old (4, 6, 12). However, the effect of zinc in malnourished children is less known. The aim of this systematic review is to update the available evidence on zinc efficacy for treating acute diarrhea in children and to investigate the effect of zinc supplementation on malnourished children.

MATERIALS AND METHODS

Study eligibility criteria

Randomized controlled trials (RCTs) that met the following criteria were considered to be eligible for the systematic review: hospital or community based, included children up to 5 years old with acute diarrhea, used zinc sulfate or gluconate associated or not with oral rehydration therapy in any dose for up to 14 days, and used placebo or oral rehydration therapy controls.

Study outcomes included diarrhea duration, stool frequency, and adverse events. Acute diarrhea was defined as three or more episodes of liquid stool within a 24-hour period (7).

The exclusion criteria were as follows: studies that included children with persistent diarrhea, studies that assessed zinc without a defined dose, and studies that assessed zinc as supplementation for prevention of diarrhea and other diseases.

A malnourished child was defined as having a low weight-for-height Z score (< –2) (13–15) or with zinc depletion (below 14 μmol/L). Other comorbid conditions were not considered, as the study population was heterogeneous and could have various conditions causing low weight.

Data sources and search strategy

A search was conducted regardless of language or publication status on Medline, Embase, Central, mCRT, LILACS, and SciELO databases. The most recent literature search was performed in January 2013.

The search strategy in Medline (via PubMed) was:

1. “infant”[mesh] or “infants” [tiab] or “child, preschool”[mesh] or “preschool child”[tiab] or “child”[mesh] or “child”[tiab]
2. “diarrhea”[mesh] or “diarrhea”[tiab] or “diarrheal”[tiab]
3. “zinc”[mesh] or “zinc”[tiab]
4. (therapy/broad[filter])
5. (1 and 2 and 3 and 4).

RESULTS

A total of 1,041 studies were retrieved (Figure 1) (17–46). After the titles and abstracts were assessed for eligibility, 18 RCTs were included in the review (n = 7,314 children).

Included studies were considered to be of acceptable quality with a low risk of bias. Potential biases detected did not appear to compromise the results obtained. All studies were classified as “unclear” for the possibility of the occurrence of selective reporting of the outcomes, as the reviewers were unable to access the study protocols. Almost 50% of the studies were classified as unclear for allocation concealment, as they did not inform whether patient allocation remained inaccessible to the teams that were directly involved in the studies (Figure 2).

Funnel plot inspection (data not presented) showed asymmetry of the findings, indicating a possible risk of publication bias as it is possible that small studies that found unfavorable results were not published (47).

Study characteristics are shown in Table 1 (29–46). Only three studies had a population of fewer than 100 patients, and all studies were conducted in countries considered to be “emerging and developing economies” (48).

Of the studies also presented similar outcomes, although the units of measure or form of analysis often differed, thus precluding inclusion of the complete data in the review. This phenomenon occurred particularly in stool frequency data.

In placebo-controlled studies, oral rehydration therapy was used to replace lost fluid in dehydrated children, whether before or during the zinc treatment.

Diarrhea duration comparing zinc with placebo is presented in Figure 3 (29, 31–34, 36–38, 40, 41, 43, 45, 46). Despite significant heterogeneity among included studies, zinc reduced the duration of diarrhea in children. Diarrhea prevalence on days 3, 5, and 7 of the study was also lower in the zinc-treated group (Table 2) (30, 32–35, 37, 38, 42, 43); on day 7, the difference was statistically significant. According to these results, it is necessary to treat 22 children with zinc to prevent 1 case of diarrhea on day 7 (number needed to treat = 22; 95% CI = 14–55).

As one study (26) excluded a significant number of children in both study...
groups, a sensitivity analysis was performed to verify the impact of this exclusion on the outcome reported in the study with regard to the prevalence of diarrhea on day 7. No statistically significant difference was found in the results, even considering that all 16 children excluded from the zinc group and all 24 children excluded from the control group still had diarrhea on day 7 (relative risk = 0.64; 95% CI = 0.49–0.84).

Four studies evaluated the stool frequency in the mean number of episodes/day (29, 34, 36), with an average reduction of 2.4 episodes of defecation (95% CI = 3.79–1.04).

The only relevant adverse reaction reported was vomiting, which had the highest incidence in the zinc-treated group (Figure 4) (29, 30, 35, 37, 39).

Malnourished population analysis

Five studies evaluated only malnourished children or included an evaluation of this subgroup (31, 35, 38, 41, 49). Three of these studies (29, 36, 37) included children with zinc deficiency, who are labeled as malnourished children in this review. Other studies that also included malnourished children were not included in this assessment because a subgroup analysis was not reported in the original papers, thus rendering it impossible to obtain segregated data for this assessment.

The meta-analysis presented in Figure 5 shows zinc as being more effective for this population, as it reduced diarrhea duration by 33.17 hours (95% CI = –38.55 to –27.79) (29, 31, 33, 36, 37).

Heterogeneity

Significant heterogeneity was observed between studies for the outcomes of diarrhea duration and the prevalence of diarrhea on days 3, 5, and 7. The sensitivity analysis showed that the nutritional status of the children might explain the heterogeneity across studies for diarrhea duration. When only malnourished population data were assessed, no heterogeneity was found (Figure 5). As most RCTs did not report separate results for well-nourished and malnourished children, the body of evidence could not be stratified to provide homogeneous results. No other causes of heterogeneity were identified.

The sensitivity analysis also showed that one study (43) contributed considerably toward the heterogeneity detected in the outcomes of diarrhea on days 3, 5, and 7. This outcome might be due to low adherence to the treatment in the study, which may have contributed to a smaller effect of the use of zinc in the population assessed.

DISCUSSION

This review updates and confirms existing evidence about the efficacy of zinc supplementation in children for reducing diarrhea, with more striking results in malnourished children, which is a population that has not been thoroughly assessed in previous reviews. A significant reduction in diarrhea duration occurred, thus endorsing the findings of previous systematic reviews (7–11).

Zinc is one of the most important micronutrients in the human diet; it is crucial for many cell functions, such as protein synthesis and cell growth and differentiation (49). Zinc’s mechanism of action for the treatment of diarrhea caused by different pathogens is not fully understood, but studies conducted in this field reveal that zinc plays different roles in the intestine, such as regulation of intestinal fluid transport and mucosal integrity and modulation of expression of genes encoding important zinc-dependent enzymes like cytokines, which play important roles in the immune system and in modulation of oxidative stress (49, 50). These different roles might explain the positive effect of zinc intake during acute diarrhea in children. Zinc supplementation seems
<table>
<thead>
<tr>
<th>Study</th>
<th>Blinding</th>
<th>Allocation concealment</th>
<th>N°</th>
<th>Interventions</th>
<th>Population</th>
<th>Setting</th>
<th>Country</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sachdev et al. 1988</td>
<td>Unclear</td>
<td>Unclear</td>
<td>50</td>
<td>Elemental zinc, 40 mg + ORT&lt;sup&gt;b&lt;/sup&gt;; placebo + ORT&lt;sup&gt;b&lt;/sup&gt;</td>
<td>6–18 months, malnourished and nourished children with acute diarrhea</td>
<td>Hospital</td>
<td>India</td>
<td>Diarrhea duration, stool frequency, duration of hospitalization, diarrhea on day 7</td>
</tr>
<tr>
<td>Roy et al. 1997</td>
<td>Yes</td>
<td>Yes</td>
<td>111</td>
<td>Elemental zinc, 20 mg + MTV&lt;sup&gt;c&lt;/sup&gt;; placebo + MTV&lt;sup&gt;c&lt;/sup&gt;</td>
<td>2–24 months, with acute diarrhea</td>
<td>Hospital</td>
<td>Bangladesh</td>
<td>Diarrhea duration, total stool output</td>
</tr>
<tr>
<td>Patro et al. 2010</td>
<td>Yes</td>
<td>Yes</td>
<td>141</td>
<td>Elemental zinc, 10 mg (3–5 months) or 20 mg (6–48 months) per day; placebo</td>
<td>3–48 months, with acute diarrhea</td>
<td>Hospital</td>
<td>Poland</td>
<td>Diarrhea duration; stool frequency on days 1, 2, and 3; vomiting frequency, side effects</td>
</tr>
</tbody>
</table>

Continues
even more necessary for malnourished children, as they already have a zinc deficiency, which predisposes them to diarrhea and worsens it (50). WHO recommends zinc supplementation for children in developing countries who have acute or persistent diarrhea at a dose of 10 mg in infants less than 6 months old and 20 mg in older infants daily for 10–14 days (51, 52).

Obtaining homogeneous results in the entire population was not possible. The

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**TABLE 1. Continued**

<table>
<thead>
<tr>
<th>Study</th>
<th>Age &gt; 6 months</th>
<th>Zinc</th>
<th>Control</th>
<th>Relative risk</th>
<th>95% CI</th>
<th>95% CI Year</th>
<th>Total effect</th>
<th>Mean Difference IV, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sachdev 1988</td>
<td>82</td>
<td>42.0</td>
<td>25</td>
<td>90.5</td>
<td>40</td>
<td>25</td>
<td>5.5%</td>
<td>-8.50 [−31.49, 14.49]</td>
</tr>
<tr>
<td>Faruque 1999</td>
<td>147.8</td>
<td>22.2</td>
<td>341</td>
<td>189.5</td>
<td>122.4</td>
<td>340</td>
<td>7.2%</td>
<td>-21.90 [−39.12, −6.68]</td>
</tr>
<tr>
<td>Bahl 2002</td>
<td>33.6</td>
<td>37.6</td>
<td>404</td>
<td>40.8</td>
<td>69</td>
<td>401</td>
<td>7.9%</td>
<td>-7.22 [−15.33, 0.93]</td>
</tr>
<tr>
<td>Al-Sobaili 2003</td>
<td>28.8</td>
<td>19.2</td>
<td>37</td>
<td>69</td>
<td>43.2</td>
<td>37</td>
<td>6.8%</td>
<td>-31.20 [−46.43, −15.97]</td>
</tr>
<tr>
<td>Boren 2006</td>
<td>72.48</td>
<td>46</td>
<td>150</td>
<td>80.08</td>
<td>76.8</td>
<td>130</td>
<td>6.8%</td>
<td>-15.60 [−39.87, −30.33]</td>
</tr>
<tr>
<td>Patel 2009</td>
<td>35.8</td>
<td>20.6</td>
<td>264</td>
<td>35.03</td>
<td>26.5</td>
<td>271</td>
<td>8.4%</td>
<td>0.77 [−2.71, 4.25]</td>
</tr>
<tr>
<td>Dutta 2011</td>
<td>49.1</td>
<td>21.7</td>
<td>41</td>
<td>88.2</td>
<td>23</td>
<td>43</td>
<td>7.7%</td>
<td>-24.10 [−33.66, −14.54]</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>1262</td>
<td>1247</td>
<td>50.3%</td>
<td>-14.89 [−25.29, −4.48]</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**FIGURE 3.** Diarrhea duration (hours) comparing zinc and control

**TABLE 2. Meta-analysis of effect of zinc on prevalence of diarrhea on days 3, 5, and 7**

<table>
<thead>
<tr>
<th>Study</th>
<th>Day</th>
<th>Zinc n</th>
<th>Zinc N</th>
<th>Control n</th>
<th>Control N</th>
<th>Relative risk</th>
<th>95% CI</th>
<th>Total effect</th>
<th>Heterogeneity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bahl et al. 2002 (34), Strand et al. 2002 (35), Patel et al. 2009 (43)</td>
<td>3</td>
<td>317</td>
<td>1202</td>
<td>403</td>
<td>1211</td>
<td>0.74</td>
<td>0.60–0.92</td>
<td>2.69</td>
<td>0.007</td>
</tr>
<tr>
<td>Dutta et al. 2000 (33), Bahl et al. 2002 (34), Bhatnagar et al. 2004 (38), Patel et al. 2009 (43)</td>
<td>5</td>
<td>70</td>
<td>844</td>
<td>94</td>
<td>842</td>
<td>0.65</td>
<td>0.37–1.12</td>
<td>0.98</td>
<td>0.33</td>
</tr>
<tr>
<td>Sazawal et al. 1995 (30), Faruque et al. 1999 (32), Bahl et al. 2002 (34), Strand et al. 2002 (35), Polat et al. 2003 (37), Bhatnagar et al. 2004 (38), Patel et al. 2009 (43), Roy et al. 2008 (42)</td>
<td>7</td>
<td>194</td>
<td>2228</td>
<td>297</td>
<td>2266</td>
<td>0.62</td>
<td>0.47–0.83</td>
<td>3.25</td>
<td>0.001</td>
</tr>
</tbody>
</table>

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**TABLE 2.** Meta-analysis of effect of zinc on prevalence of diarrhea on days 3, 5, and 7
heterogeneity observed in the included studies was most likely caused by non-stratification of the population by nutritional status, as the analysis showed that the effect of zinc was more pronounced and consistent among stratified studies and studies that included only malnourished children. The heterogeneity observed raises concerns about the external validity of the data (16, 53); however, this phenomenon has been an issue in previous systematic reviews, which could not find other plausible explanations for the differences across study results.

No new evidence was found related to children less than 6 months old, thus leaving intact the conclusions drawn in the Cochrane review (7) about the lack of benefit of zinc administration at that age.

Although an evaluation of the mortality rate was not the objective of this study, it can be hypothesized that the use of zinc in conjunction with oral rehydration therapy would contribute to decrease child mortality by reducing the duration of diarrhea, especially in children less than 5 years old. Nevertheless, further studies to evaluate the mortality rate reduction due to the use of zinc in children with diarrhea are required to confirm this hypothesis.

The results summarize the most recent body of literature in the field and support the WHO recommendation to include zinc with oral rehydration therapy for children with diarrhea under the age of 5 years (1, 5). This recommendation is supported by cost studies that show zinc is a cost-effective strategy for treating childhood diarrhea (41, 54, 55). Opposing results were found in a recent evaluation of zinc and copper use in children with diarrhea, but the authors did not consider the entire body of evidence for assessing the effectiveness of zinc (56).

**Conclusion**

Oral zinc supplementation significantly decreases the duration of diarrhea and has a greater effect on malnourished children.
children. As a public health measure, zinc administration is a good strategy for preventing diarrhea in addition to the use of oral rehydration therapy and is particularly important in countries where zinc deficiency is prevalent. Further research should consider presenting the results according to the nutritional status of the children to provide evidence with greater applicability.

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REFERENCES


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Galvao et al. • Zinc supplementation for treating diarrhea in children

RESUMEN

Administración de suplementos de zinc para tratar la diarrea infantil: revisión sistemática y metaanálisis

Objetivo. Actualizar los datos probatorios disponibles acerca del uso del zinc en el tratamiento de la diarrea infantil y evaluar su efecto en la población malnutrida, un subgrupo no plenamente estudiado en análisis anteriores.

Métodos. Se llevó a cabo una revisión sistemática de ensayos clínicos aleatorizados que evaluaban a niños de hasta 5 años de edad con diarrea aguda y a los que se les había administrado suplementos de zinc. A los controles se les había administrado un placebo o terapia de rehidratación oral. Después de efectuar búsquedas en las principales bases de datos, sin restricciones en cuanto a idiomas, dos revisores independientes seleccionaron los estudios idóneos, extrajeron los datos y evaluaron el riesgo de sesgo de los estudios incluidos. El metaanálisis se efectuó mediante el modelo de efectos aleatorios de Mantel–Haenszel o de la varianza inversa.

Resultados. En la revisión se incluyeron 18 estudios de los 1 041 recuperados (n = 7 314 niños). El zinc tuvo un efecto beneficioso en la reducción de la duración de la diarrea en horas (diferencia media [DM] = –20.12, intervalo de confianza del 95% [IC] de –29.15 a –11.09, I² = 91%). Este efecto fue más intenso en niños malnutridos (DM = –33.17, IC del 95% de –33.55 a –27.79, I² = 0%). La prevalencia de diarrea en los días 3, 5 y 7 fue inferior en el grupo tratado con zinc. La incidencia de vómitos fue significativamente mayor en el grupo tratado con zinc que en el grupo de referencia. Los ensayos aleatorizados controlados que fueron incluidos mostraron un bajo riesgo de sesgo en la mayoría de los dominios evaluados.

Conclusiones. La administración oral de suplementos de zinc reduce significativamente la duración de la diarrea y tiene un efecto aún mayor en niños malnutridos. La administración de suplementos de zinc parece ser una estrategia de salud pública apropiada, principalmente en las zonas afectadas por carencias endémicas.