Two Weeks of Zinc Administration to Nepalese Children with Pneumonia Does Not Reduce the Incidence of Pneumonia or Diarrhea during the Next Six Months\textsuperscript{1–3}

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Abstract

Diarrhea and pneumonia are the 2 main causes of death in children under 5 y of age. Short courses of zinc administration are now recommended for treatment of childhood diarrhea and some studies have also shown its beneficial effect on treatment of pneumonia. The objective of our study was to assess the efficacy of zinc administration (10 mg/d for children 2–11 mo and 20 mg/d for ≥12 mo of age) for 14 d on preventing diarrheal and respiratory illnesses for 6 mo of follow-up. This was a randomized, double-blind, placebo-controlled trial in children 2–35 mo of age with community-acquired pneumonia. The number of illness episodes and time until the first episode of various illnesses were compared between the 2 study groups. After 14 d of zinc supplementation, plasma zinc was significantly higher in the group receiving zinc. However, this difference was not detectable at 1 and 2.5 mo after the end of zinc administration. Of 2628 enrolled cases, a total of 2599 (99.1%) were available for assessment after the completion of zinc supplementation. The number of hospital visits and the median number of days until the first episode of pneumonia, diarrhea, and dysentery was similar in the 2 groups. The hazard ratios (95% CI) were 1.02 (0.92, 1.14) for nonsevere pneumonia, 1.11 (0.72, 1.73) for severe pneumonia, 1.07 (0.91, 1.26) for diarrhea, and 0.96 (0.69, 1.34) for dysentery. A short course of zinc supplementation given during an episode of pneumonia did not prevent diarrheal or respiratory illness over the next 6 mo. J. Nutr. 140: 1677–1682, 2010.

Introduction

Zinc deficiency is a common public health problem in Nepal (1–3) and other developing countries (4,5) with presumably serious consequences for growing children (6). The magnitude of zinc deficiency in some settings is greater than deficiencies of other nutrients, including those of iron and vitamin A (7–9). The available zinc in the body may further decrease during infections as a result of the acute phase response, possibly due to redistribution (10,11). Adequate zinc status is a prerequisite for the proper physical and mental development of children and for maintaining normal immunity. In children under the age of 5 y, respiratory infections are among the main causes of consultations in health centers and of hospital admissions (12,13) and pneumonia is one of the leading causes of death (14).

Preventive daily zinc supplementation reduces the burden of diarrhea and pneumonia by reducing its duration or severity (15–17). Weekly zinc supplementation for 12 mo has also been reported to prevent these diseases and to reduce mortality (18). Correction of zinc deficiency in a setting where it is common has been estimated to have potential to reduce under 5 mortality by 6% (19). A pooled analysis of recently published clinical trials on preventive daily supplementation from Southern Nepal and Zanzibar on mortality (20) showed no overall effect in 1- to 48-mo-old children but a reduction of mortality (relative risk = 0.82, 95% CI = 0.70, 0.96) in children older than 12 mo of age (21). The strategy to replenish zinc through daily or high-dose weekly supplementation for a longer period poses programmatic challenges. The current study was conducted to assess the efficacy of zinc administration during an episode of pneumonia on preventing diarrheal or respiratory illness over the next 6 mo.
and compliance challenges. To overcome these problems, short courses of zinc supplementation, which seems feasible to implement, could be an alternative. Short courses of zinc of 10- to 14-d duration is now recommended by WHO and UNICEF for the treatment of childhood diarrhea as a safe and inexpensive strategy in developing countries (22). Nepal is one of the first countries that endorsed this recommendation; several campaigns with partnerships with the private sector were launched, and zinc tablets were made freely available at primary government health facilities since May 2007 (23,24).

Although some studies have shown that short courses of zinc supplementation can reduce the burden of infections by decreasing the number of new episodes beyond the period of administration, the available data are still inconclusive (25–27) and often based on small trials and restricted to children with severe malnutrition (28,29), which limit their generalizability. We conducted a large randomized clinical trial on the efficacy of zinc supplementation in community-acquired pneumonia (CAP)9 from January 2004 to June 2007. One of the hypotheses that was tested in this trial was whether a short course of zinc supplementation given during CAP in children 2–35 mo of age would reduce subsequent morbidity by decreasing duration and severity of pneumonia and diarrheal episodes for up to 6 mo.

**Participants and Methods**

**Study site and population.** The children participating in this study were residents of the Bhaktapur municipality and its outskirts, which constitute a mixed rural-urban population. Bhaktapur is located 15 km east of the capital Kathmandu. The study area is densely populated (1895 people/km²) and most of the inhabitants belong to the Newar ethnic group (30). Within and around the municipality, there are ~50 carpet factories where immigrant workers from different ethnic backgrounds (mostly Tamang and Lama) work. These workers are relatively marginalized compared with the local residents of Bhaktapur, because they usually do not have their own land and therefore are highly dependent on their daily wage earnings.

Most of the families (97%) in the study area have access to piped drinking water and toilets with central drainage (88%). The vaccine coverage is >90% for all vaccines included in the national extended program on immunization schedule (31). The sociodemographic characteristics of the population of Bhaktapur and RNA-virus etiology of pneumonia among the children enrolled in this study have been described elsewhere (9,32).

**Enrollment, intervention, cointervention and follow-up procedures.** The study children were participants of a randomized, double-blind, clinical trial evaluating the efficacy of zinc supplementation as an adjuvant therapy for CAP (33). The outcomes of this main study were risk of treatment failure and time until recovery and have been published elsewhere (33). Children 2–35 mo of age with cough/difficulty breathing who fulfilled the WHO criteria for severe and nonsevere pneumonia (34) and who attended our study clinic at Siddhi Memorial Children Hospital were screened for enrollment. The exclusion criteria were: already enrolled in the study hospital for examination whenever deemed necessary. At this hospital, we provided 24-h free service for all enrolled children. We scheduled 2 follow-up visits at 3 and 6 mo after enrollment to interview the caretakers about the health of their child during the last 3 mo. During these visits, the physician recorded details of illness that had prompted a visit to any health facility or a hospital admission. We started to count new episodes of illness after the last day of zinc administration or after recovery from the enrollment episode, whichever came last.

**Blood sampling.** We collected a blood sample from the cubital vein in micronutrient-free heparinized polypropylene syringes (Sarstedt) for zinc analysis. We randomly selected 28 blocks for blood sampling on the day of enrollment. From all other children, a capillary blood specimen was collected for Hb and CRP measurements. From all other children, a capillary blood specimen was collected for Hb and CRP measurements. We also collected a second venous blood sample on d 14 (n = 185), 45 (n = 84), or 90 (n = 81) after enrollment. This way we had a pre- and postsample from 350 children and a maximum of 2 blood samples was obtained from each child. The heparinized blood was centrifuged at 760 × g for 10 min at room temperature and separated and the plasma was transferred to micronutrient-free polypropylene vials (Eppendorf). These vials were initially
frozen at \(-20^\circ\text{C}\) at the field laboratory and on the same day transported on ice to the laboratory at the Institute of Medicine, Kathmandu and stored at \(-80^\circ\text{C}\). These samples were transferred out of Nepal on dry ice stored at \(-75^\circ\text{C}\) for 3–5 y until analysis.

Plasma zinc concentration was determined by an inductively coupled plasma mass spectrometer (PlasmaQuad 3, VG Elemental) at the University of Colorado Health Sciences Center, Denver, CO. Rhodium was used as an internal standard and \(^{66}\text{Zn}\) was diluted 350 times using 6 parts/billion rhodium solution in 2% (by volume) HNO\(_3\) (OPTIMA, Fisher Scientific). A set of zinc standards was inserted every 12th specimen for external drift correction. A cutoff value of plasma zinc of 9.9 \(\mu\text{mol/L}\) was used to define zinc deficiency (5).

**Data management and statistical analysis.** All questionnaires were double entered using Microsoft Visual FoxPro version 6.0 with logic, range, and consistency checks. If there was a visit for the same diagnosis within 2 wk, only the first episode was counted. We used 6 mo as the follow-up period in the morbidity analysis for the children who were available for 6 mo of follow-up visits. If the 3- or 6-mo forms were missing, we obtained information from the time under observation based on the last available spontaneous hospital visit. For the 22 children in whom the initial pneumonia episode lasted for >14 d, we started follow-up after they had recovered from this episode. The anthropometric measures at baseline were calculated using the WHO child growth standards (33) and underweight, stunting, and wasting were defined as weight-for-age \(Z\)-score < -2, height-for-age \(Z\)-score < -2, and weight-for-height \(Z\)-score < -2, respectively.

The number of disease episodes, based on physician’s diagnoses over follow-up time, was calculated for pneumonia (severe and nonevolved), diarrhea, and dysentery. The incidence of pneumonia and diarrheal diseases were calculated dividing the total number of illness episodes by the follow-up days contributed by each child in the study and multiplied by 30.42 to obtain a monthly rate. The difference in time until the first episode of these illnesses after the end of zinc/placebo supplementation was modeled by Cox proportional hazards regression. HR of 1 indicated a shorter time until a new episode in the zinc recipients compared with the placebo group. A total of 419 children were enrolled in the study more than once; thus, we adjusted for the repeated enrollments in the regression analyses by using the cluster option in Stata. We compared the mean zinc concentrations between the study groups using the Student’s \(t\) test. A \(P\)-value < 0.05 was considered significant. Logistic regression analysis was used for dichotomous outcomes. The analyses were undertaken using Stata version 9.2 (STATA). Values in the text are mean \(\pm\) SD unless otherwise indicated.

**Results**

**Baseline features.** A total of 2628 cases with CAP were enrolled and among them 148 (6%) had severe pneumonia. A child could be reenrolled if at least 6 mo had lapsed since the last enrollment. A total of 2201 episodes were first-time enrollments, 396 second-time, and 31 third-time enrollments. None of the associations in the current analyses were modified by severity or age, so stratum-specific estimates are not shown. The field workers directly administered the supplements to the children on most of the days of the week except Saturday, when the caretakers administered the supplements. Only on 22 d (10 in the placebo vs. 12 in the zinc group) was it reported that the child did not receive supplementation. Fifty-two percent (1357) of children were infants and 85% (2225) were still breast-feeding with a frequency of 12.6 \(\pm 3.6\) times/24 h. Their Hb concentration was 111 \(\pm 12\) g/L and 729 of the children (40%) who were aged above 6 mo were anemic (Hb < 110 g/L) and distributed evenly in zinc and placebo groups. A total of 10% children in both groups required iron supplementation, which was given to children above 6 mo of age with Hb < 100 g/L. The median intraquartile range (IQR) plasma CRP concentrations were 15.5 (8–29) and 14.5 (8–27) mg/L in the zinc-supplemented group and in the placebo group with concentrations > 40 mg/L in 16% of the zinc group and 14% of the placebo group. The oxygen saturation at enrollment was <90% in 59 children (2%) and <93% in 991 (38%) children. The baseline characteristics were well balanced in the 2 study groups, except birth weight, which was 53 g (95% CI = 9–96 g) less in the placebo group (Table 1). Wheezing was heard on auscultation in 33% and crepitations in 26% of the children diagnosed with pneumonia during the 6-mo follow-up visit. A total of 457 (17%) of the enrolled children, evenly distributed between the zinc and the placebo groups, were censored or did not complete the 6 mo of follow-up. Most of the censoring was due to migration. For the morbidity analysis, children in the zinc and placebo group contributed 7354 and 7339 child-months of follow-up, respectively.

**Plasma zinc concentration.** At baseline, the plasma zinc concentration did not differ between the zinc (8.9 \(\pm 2.9\) \(\mu\text{mol/L}\)) and placebo (8.8 \(\pm\) 2.3 \(\mu\text{mol/L}\)) groups. Overall, 70% of children were zinc deficient at baseline. The plasma zinc concentration was 0.76 (95% CI: 0.03, 1.49) and 0.89 (0.32, 1.46) \(\mu\text{mol/L}\) lower in children with a plasma CRP concentration > 40 mg/L (\(P = 0.04\)) or if the axillary temperature of the child was higher than 38°C (\(P = 0.002\)), respectively. After 14 d of zinc or placebo administration, plasma zinc concentrations were substantially higher in children who received zinc (14.6 \(\pm\) 7.3 \(\mu\text{mol/L}\)) compared with those in the placebo group (9.2 \(\pm\) 2.5 \(\mu\text{mol/L}\); \(P < 0.0001\)). However, the plasma zinc concentrations in the 2 study groups did not differ in blood samples taken on 45 or 90 d after enrollment (Fig. 1).

**Morbidity during 6 mo of follow-up.** During the 6 mo of follow-up after end of supplementation, a total of 7380 spontaneous visits for different illnesses were recorded by study physicians. Most of these visits were for cough or cold (42%) followed by pneumonia (34%) and diarrheal illness (12%).

**TABLE 1** General baseline characteristics of the 2628 children aged 2–35 mo included in a study evaluating the effect of zinc supplementation on pneumonia and subsequent morbidity in Bhaktapur, Nepal

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Zinc</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>1314</td>
<td>1314</td>
</tr>
<tr>
<td>Age, mo</td>
<td>13.5 ± 8.4</td>
<td>13.6 ± 8.4</td>
</tr>
<tr>
<td>Infants, n (%)</td>
<td>678 (52)</td>
<td>679 (52)</td>
</tr>
<tr>
<td>Hb, g/L</td>
<td>110 ± 12</td>
<td>111 ± 12</td>
</tr>
<tr>
<td>Hb &lt; 110 g/L, n (%)</td>
<td>365 (40)</td>
<td>384 (40)</td>
</tr>
<tr>
<td>Iron supplementation, n (%)</td>
<td>120 (10)</td>
<td>116 (10)</td>
</tr>
<tr>
<td>Stunted, (height-for-age Z-score &lt; -2), n (%)</td>
<td>278 (21)</td>
<td>290 (22)</td>
</tr>
<tr>
<td>Underweight, (weight-for-age Z-score &lt; -2), n (%)</td>
<td>158 (12)</td>
<td>159 (12)</td>
</tr>
<tr>
<td>Wasted, (weight-for-height Z-score &lt; -2), n (%)</td>
<td>53 (4)</td>
<td>54 (4)</td>
</tr>
<tr>
<td>Illiterate or primary educated mother, n (%)</td>
<td>857 (65)</td>
<td>892 (65)</td>
</tr>
<tr>
<td>Breast-feeding, n/24 h</td>
<td>12.7 ± 3.7</td>
<td>12.5 ± 3.6</td>
</tr>
<tr>
<td>Birth weight, g</td>
<td>2.881 ± 457</td>
<td>2.838 ± 481</td>
</tr>
</tbody>
</table>

1 Values are mean ± SD or n (%).
2 Infants more than 6 mo of age.
3 Iron supplementation was given to children above 6 mo of age with a Hb < 100 g/L.
4 Among 2225 breast-fed infants.
5 Among 1818 children where birth weight were recorded documented or recalled.
Based on caretaker-defined illness during the regular follow-up visit at 3 mo after enrollment, 64% reported that they had taken their child to a health facility for at least 1 episode of respiratory problems and 23% for at least 1 episode of diarrhea. Similar numbers were also reported during the 6-mo follow-up visit, where we collected morbidity information for the last 3 mo of follow-up. The frequencies of these morbidities recorded by a physician or caretaker were similar between children who received zinc and those in the placebo group (Table 2).

**TABLE 2** Number of visits for respiratory and diarrheal illness during 3 and 6 mo of follow-up after zinc or placebo supplementation for 2 wk based on caretaker’s report among young Nepalese children with pneumonia

<table>
<thead>
<tr>
<th>Morbidity</th>
<th>3 mo follow-up</th>
<th>6 mo follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Zinc</td>
<td>Placebo</td>
</tr>
<tr>
<td>n</td>
<td>1150</td>
<td>1150</td>
</tr>
<tr>
<td>Respiratory illness</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥1 episode, n (%)</td>
<td>735 (63.9)</td>
<td>759 (66.0)</td>
</tr>
<tr>
<td>≥2 episodes, n (%)</td>
<td>451 (39.2)</td>
<td>460 (40.0)</td>
</tr>
<tr>
<td>Total episodes, n</td>
<td>1785</td>
<td>1786</td>
</tr>
<tr>
<td>Hospitalization, n (%)</td>
<td>33 (2.7)</td>
<td>33 (2.8)</td>
</tr>
<tr>
<td>Diarrheal illness</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥1 episode, n (%)</td>
<td>273 (23.7)</td>
<td>257 (22.3)</td>
</tr>
<tr>
<td>≥2 episodes, n (%)</td>
<td>82 (7.1)</td>
<td>70 (6.1)</td>
</tr>
<tr>
<td>Total episodes, n</td>
<td>404</td>
<td>358</td>
</tr>
</tbody>
</table>

1 Only respiratory and diarrheal illnesses that required visit to a health facility were recorded.

2 p-values were obtained by logistic regression analysis.

Severe pneumonia and hospital admission. The caretakers of 33 children (2.5%) from both groups reported that their children required hospital admission for pneumonia within 3 mo after the end of zinc supplementation. These figures were comparable during the next 3 mo of follow-up (1.8% in the zinc group and 2.1% in the placebo group). Based on physicians’ records, 43 children (3.4%) in the zinc group and 39 children (3.1%) in the placebo group required hospitalization at the study hospital for severe pneumonia. There were no pneumonia- or diarrhea-related deaths among the enrolled children during the 6-mo follow-up period. However, 2 children in the zinc group died of injuries due to accidents.

**Discussion**

Maintaining proper zinc status in children in developing countries is considered as a potentially important intervention to reduce morbidity and mortality (36). This could be achieved by continuous preventive, intermittent, or short-course zinc supplementation. Most of the studies carried out during the last 2 decades on the effect of preventive or intermittent zinc supplementations have shown a reduction in the incidence of common childhood illnesses when given for 3–12 mo (15,18,37). However, long-term zinc supplementation does not seem feasible, because it is time consuming and requires considerable resources as well as high compliance. Thus, an alternative strategy of giving a short course of oral zinc during visits for acute illnesses could be a feasible option for improving zinc status.

A short course of zinc therapy was beneficial for the prevention of subsequent morbidities in some studies (25,38).
but not in others (26,28). The beneficial effects were mainly observed in selected children who were malnourished or recovering from acute or persistent diarrhea (15,29). Moreover, short-course zinc supplementation has been found to be more efficacious in preventing diarrheal than respiratory infections (25). The effect on respiratory illnesses has ranged from beneficial (38) through no effect (29) to increased occurrence (25).

Our study, which is the largest so far that has assessed the delayed effect of short-course zinc given during pneumonia, did not show any beneficial effect in terms of preventing diarrhea and pneumonia. The total number of episodes of these illnesses did not differ between the treatment groups. We also calculated the incidence rate ratios for diarrheal and respiratory illnesses using negative binomial regression analyses. All of the incidence rate ratios were also very close to 1 (data not shown). This lack of effect is underscored by the fact that our effect measures are highly precise as evidenced by our narrow CI. This is in concordance with our previous report where we gave zinc during an episode of acute diarrhea (2) and followed the children for another month. In a recent study in young infants, zinc was given for 14 d during acute diarrhea and the children were followed for another 3 mo. This study also failed to detect any beneficial effect; in fact, the prevalence of diarrheal illness was significantly higher among the zinc recipients (27). Zinc is not stored in the body and regular intake is therefore recommended to maintain proper zinc nutriture (39,40). This fact is also supported by our finding that the plasma zinc concentration was higher in the zinc recipients only until the end of supplementation and not after that.

Misclassification or lack of specificity of the outcomes can cause bias toward a null effect (41), which could also be the case for our study. We used WHO/Integrated Management of Childhood Illness guidelines for the definition of pneumonia, which has low specificity, especially for nonsevere pneumonia (17). However, we think that our approach of passive rather than active surveillance increased the specificity of our outcomes, because fewer milder cases were probably taken to the clinic. Furthermore, we were not able to see an effect on any of our outcomes, even for illnesses with high specificity such as pneumonia, based on the judgments of a physician, dysentery, hospitalizations, or lower chest indrawing, etc. By using this passive surveillance design, we faced the risk of underreporting, because some of the caretakers could possibly take their children to other health providers. We therefore also assessed outcomes on the basis of the caretaker’s recall during scheduled visits at 3 and 6 mo after enrollment. The number of spontaneous visits to our study hospital was 2.87 ± 2.3/child during the 6 mo of follow-up, which corresponds well with that reported by the caretakers. If there were spontaneous visits for the same diagnosis within 2 wk, we did not count it as a separate episode. However, at the 3- and 6-mo follow-up visits, we recorded all the illness that prompted caretakers to seek consultation at health facilities. During these visits, we asked mothers or caretakers for the total numbers of respiratory or diarrheal illnesses that prompted them to seek consultation at health facilities. We did not differentiate whether it was just cough and cold or pneumonia and diarrhea or dysentery. So we expect some overestimation of illnesses in these 3- and 6-mo follow-up visits. The study hospital is located within walking distance for most of the children and we provided treatment free of cost. Thus, we do not think that we have missed many major illness episodes because of our passive surveillance approach. In previous studies on continuous supplementation, some subgroups benefited more from zinc supplementation than others, i.e. being a male child (42), anemic (43), older than 1 y (21), and having low baseline plasma zinc concentration (44). However, we did not see any effect of zinc even in these subgroups (data not shown). It should be noted that the study was not designed to assess effect modifications, and the power to assess the effect of zinc in the above-mentioned subgroups, particularly among those that were anemic and required iron supplementation, was low.

In theory, any delayed effect of short-course zinc supplementation could be mediated by a less severe inclusion episode. However, we did not demonstrate any beneficial effect on the enrollment episode in terms of reduction in duration or severity (33).

In conclusion, short-course zinc supplementation did not reduce the incidence and prevalence of respiratory or diarrheal illness during 6 mo of follow-up among young Nepalese children diagnosed with pneumonia at enrollment. Short-course zinc administration during pneumonia may not be effective in preventing childhood infections.

Acknowledgments

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Literature Cited


