Zinc supplementation as adjunct therapy in children with measles accompanied by pneumonia: a double-blind, randomized controlled trial

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ABSTRACT

Background: Zinc deficiency, common in developing countries, is associated with decreased immunocompetence. Zinc supplementation benefits children with acute and persistent diarrhea and prevents pneumonia. Most deaths from vaccine-preventable diseases are from measles and whooping cough; pneumonia is the most common complication of measles and often the proximate cause of related deaths.

Objective: We evaluated the effect of zinc supplementation on episodes of illness in children with measles accompanied by pneumonia.

Design: In a double-blind, randomized controlled trial, children aged 9 mo–15 y who were admitted to the Infectious Diseases Hospital in Calcutta with clinically severe measles accompanied by pneumonia and who had been ill for ≤ 7 d were randomly assigned to receive zinc (20 mg, in elemental form as acetate, twice daily for 6 d) or a placebo. All patients received standard treatment with antibiotics and an initial 100 000-IU dose of vitamin A (as palmitate) by mouth.

Results: Time-to-event analysis using the Cox proportional hazards model (42 in the zinc group and 43 in the placebo group) showed that the time needed for the resolution of fever and tachypnea, the return of appetite, and the achievement of a “much improved” or “cured” status was not different between the 2 groups. A high proportion of children had low serum retinol and zinc concentrations. Improvement in serum zinc and retinol concentrations after 6 d of treatment was not different between the 2 groups.

Conclusion: Children with severe measles accompanied by pneumonia treated with antibiotics and vitamin A did not show any additional benefit from also receiving a zinc supplement.

SUBJECTS AND METHODS

Subjects

Children aged 9 mo–15 y with measles accompanied by pneumonia who were admitted to the Infectious Diseases Hospital in Calcutta were randomly allocated to 1 of 2 treatment groups: a group that received a zinc supplement and a group that received a placebo supplement. The effect of zinc therapy on the clinical course of illness was evaluated. The subjects were children admitted to the hospital with an illness that was compatible with measles (generalized maculopapular rash with fever and at least...
one of the following: cough, coryza, or conjunctivitis) and a clinical
diagnosis of acute lower respiratory tract infection (tachypnea,
lower chest indrawing and auscultatory signs, or both). The
treatment effect was evaluated by comparing the 2 groups for the
time needed for the resolution of fever, tachypnea (an indicator
of acute lower respiratory tract infection), or “significant illness”
[as judged by a clinician (AC) who was blinded to the treatment
group assignment] during the 6 d of treatment with zinc under
observation.

Children aged 9 mo–15 y who had been ill for ≤7 d and who
had no congenital anomalies, chronic diseases, or severe malnu-
trition (ie, clinically obvious marasmus or edema) were enrolled
in the study after written, informed consent was obtained from a
parent or guardian. A master randomization schedule was
decided by the use of permuted blocks of random numbers. Serially num-
bered bottles were randomly allocated to contain either a zinc acetate mixture or a placebo mixture; the mixtures were identical in
color, consistency, and taste. The serial numbers on the bottles
corresponded to the patients’ serial numbers. The medicine bott-
les were prepared by a pharmaceutical manufacturer under the
supervision of an independent pharmaceutical chemist acting on
our behalf. Random samples of the bottled mixture were tested by
atomic absorption spectrophotometry for zinc concentration.

A zinc acetate mixture containing 20 mg elemental Zn or a
placebo mixture was given twice daily for each day of stay. Placebo
consisted of the syrup base used for the zinc mixture to which
permitted an astringent material was added to give an astringent taste sim-
lar to that of the zinc mixture. A taste test was performed with adult
volunteers who were unaware of the nature of the mixture. All
patients were treated for pneumonia and associated problems
according to a standard treatment schedule based on the existing
practice at the study hospital. The antibiotics usually used were
either ampicillin and gentamicin or cefotaxime alone, all given by
injection, as was the prevailing practice at this hospital. All patients
received 100,000 U vitamin A (as palmitate) by mouth on the day of
admission, because large-dose vitamin A supplementation in hospi-
talized children with measles markedly reduces measles-associated
mortality (5). Giving a large dose of vitamin A to patients admitted
with measles was not routine at this hospital. However, physicians
agreed to this dose of vitamin A after discussion with the investig-
at. A complete blood count was performed and a chest X-ray was
taken on admission, as is routine at this hospital. Blood samples
were also obtained on the day of admission and on day 6 for meas-
urement of serum zinc and serum retinol concentrations. The study
protocol was approved by the Ethics Committee of the hospital.

Methods

Sample size

The consensus among clinicians treating such patients at the Infect-
ious Diseases Hospital was that 50% of the patients would have no
significant illness after 5 d of treatment. With zinc as adjunct therapy,
they expected that 80% would be free of significant illness. The number
calculated for each group (with 80% power and a 5% significance level)
would be 41, including a dropout rate of 10%. With the use of similar
assumptions for the proportion of patients having fever or tachypnea
after 5 d of treatment, the calculated sample size would be the same.

Analysis

Data were recorded on standard forms, entered into a micro-
computer, and edited by the use of EPI INFO software, version 6.03
(Centers for Disease Control and Prevention, Atlanta, and WHO,
Geneva). Baseline comparisons were made between the 2 treat-
ment groups. Categorical outcome variables were compared by
use of the chi-square test or Fisher’s exact test. Survival analysis
(Cox proportional hazards model) was used to compare the dura-
tion of events (eg, significant illness, fever, and tachypnea) to
allow adjustment for censored information with STATA software,
version 7.0 (Stata, College Station, TX). To compare the incre-
ments in the serum zinc or serum retinol concentration in the zinc
and placebo groups from admission to discharge, multiple linear
regression models were used to adjust for prognostic factors such
as age, sex, and admission values.

RESULTS

A total of 85 children aged 9 mo–15 y were admitted into the
study, 42 in the zinc group and 43 in the placebo group (Table 1).
In the group aged 10–15 y, there were slightly more than twice as
many children recruited in the placebo group than in the zinc
group. In addition, more girls were admitted in the placebo group.
Most children were admitted after 2–4 d of rash. These patients
generally were very ill. About 88% had difficulty in eating or feed-
ing, and 57 children were in a state of altered consciousness on
admission. Forty-eight children received some antibiotics before
admission. A history of measles immunization was available for
only 12% of the children. Most of the children came from poor
homes. Most (80 of 85) were clinically diagnosed as having pneu-
monia; the rest had tachypnea and fever with a history of cough
and fulfilled the WHO criteria for a diagnosis of pneumonia. In
the placebo group, 2 patients had associated bloody diarrhea
(i.e., dysentery) and 3 had measles and encephalopathy accompa-
nied by pneumonia, as judged by the clinician.

The parents of 5 children in the placebo group and of 3 chil-
dren in the zinc group withdrew their children at various points
before the study had lasted 6 d. One child in the zinc group was
dropped from the study because the assigned medicine bottle was

TABLE 1
Characteristics of subjects on admission and serum zinc and retinol
concentrations on admission and at discharge

<table>
<thead>
<tr>
<th>Age</th>
<th>Zinc group (n = 42)</th>
<th>Placebo group (n = 43)</th>
</tr>
</thead>
<tbody>
<tr>
<td>9 mo–5 y</td>
<td>29</td>
<td>23</td>
</tr>
<tr>
<td>&gt;5 y–10 y</td>
<td>8</td>
<td>9</td>
</tr>
<tr>
<td>&gt;10 y–15 y</td>
<td>5</td>
<td>11</td>
</tr>
<tr>
<td>Male participants (%)</td>
<td>43 [18]</td>
<td>58 [25]</td>
</tr>
<tr>
<td>Duration of measles rash (d)</td>
<td>3.17 ± 1.06²</td>
<td>3.07 ± 0.91²</td>
</tr>
<tr>
<td>Weight-for-age (z score)</td>
<td>−1.85 ± 1.17</td>
<td>−2.00 ± 1.08</td>
</tr>
<tr>
<td>Height-for-age (z score)</td>
<td>−1.08 ± 1.64</td>
<td>−1.28 ± 1.99</td>
</tr>
<tr>
<td>Looking very ill (%)</td>
<td>93 [39]</td>
<td>95 [41]</td>
</tr>
<tr>
<td>Difficulty in eating or feeding (%)</td>
<td>88 [37]</td>
<td>88 [38]</td>
</tr>
<tr>
<td>At discharge 12.977 ± 5.582 [38]</td>
<td>11.672 ± 2.903 [36]</td>
<td></td>
</tr>
<tr>
<td>Serum retinol (μmol/L)</td>
<td>On admission 0.383 ± 0.279 [40]</td>
<td>0.387 ± 0.223 [38]</td>
</tr>
<tr>
<td>At discharge 1.178 ± 0.576 [38]</td>
<td>1.352 ± 0.520 [36]</td>
<td></td>
</tr>
</tbody>
</table>

1 n values in brackets. No significant differences between groups.
2 ± SD.
was not significantly different between the 2 groups (dropped to 21% and 31%, respectively, at discharge. Improvement in zinc group and 68% in the placebo group; these proportions in the zinc and placebo groups is reported in the median (quartiles) time (h) required for resolution of fever and tachypnea, return of appetite, and achievement of a much-improved or cured status, as evaluated by a physician, in the zinc and placebo groups is reported in Table 2. There was no significant difference in any of these clinical features between the 2 groups (Cox proportional hazards model adjusted for age and sex and including censored data).

In 36 patients in each group, serum zinc concentrations were estimated by atomic absorption spectrophotometry (6) both on admission and at discharge (6). A high proportion of patients had very low serum zinc concentrations (< 9.95 μmol/L): 50% in the zinc group and 68% in the placebo group; these proportions dropped to 21% and 31%, respectively, at discharge. Improvement in the serum zinc concentration (analysis of variance adjusted for age, sex, and serum zinc and retinol concentrations on admission) was not significantly different between the 2 groups (Table 2).

Similarly, serum retinol concentrations were estimated on admission and discharge by the use of HPLC in 36 patients from each group (7). The serum retinol concentrations were very low (<0.349 μmol/L) on admission in 63% and 53% of patients in the zinc and placebo groups, respectively. All patients received a single oral dose (100 000 IU) of vitamin A on admission. A marked improvement was noted in the serum retinol concentrations in both groups by day 6 (Tables 1 and 3).

**DISCUSSION**

The study did not show a clinically worthwhile benefit from the administration of zinc as an adjunct therapy in children with measles and pneumonia. These children routinely received a large dose of vitamin A, which is known to reduce the morbidity and mortality associated with measles (5).

Serum retinol concentrations were very low in these children on admission, which may have represented both a state of deficiency and a consequence of severe infection. It has also been shown that, apart from an acute phase response after infection, retinol may be lost in the urine, particularly in the context of a febrile illness (8). The retinol concentrations improved markedly in these very ill children: 3.3% on admission and 83.3% at discharge had serum retinol concentrations >0.698 μmol/L. This improvement may have been due to a combination of factors such as recovery from a severe acute illness and the administration of vitamin A on admission.

Serum zinc concentrations were low on admission in most of these children, which could have been a consequence of a state of deficiency, an infection, or both. The serum zinc concentration does not consistently reflect zinc status. Very low serum zinc concentrations may be attained in conditions such as an acute phase response, in which the element is redistributed to other tissues. However, after 5 d of zinc administration (40 mg/d as oral acetate) to the study group and of a placebo to the control group, serum zinc status improved in both groups. The hospital diet did not contain items known to have a high zinc content. This suggests that the low zinc concentrations on admission were more likely to be due to redistribution after infection, as discussed above. Serum zinc concentrations are homeostatically controlled and, in states of marginal zinc deficiency, may be maintained within the normal range.

Zinc is essential for human metabolism, growth, and immune function (9). Many aspects of the immune system can malfunction, and epithelial barriers are compromised during infection (10). The oral administration of zinc as adjunct therapy for acute diarrhea in children in developing counties has shown consistent benefits in reducing the duration and the severity of that illness (2).

### Table 2

<table>
<thead>
<tr>
<th>Duration of clinical indicators of disease: results of time-to-event (survival) analysis adjusted for age and sex</th>
<th>Zinc group (n = 40)</th>
<th>Placebo group (n = 38)</th>
<th>Hazards ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time to return of appetite</td>
<td>110 (92, 135)</td>
<td>104 (73, 104)</td>
<td>0.82 (0.47, 1.44)</td>
</tr>
<tr>
<td>Time to absence of fever</td>
<td>96 (72, 116)</td>
<td>96 (74, 116)</td>
<td>1.08 (0.67, 1.74)</td>
</tr>
<tr>
<td>Time to absence of tachypnea</td>
<td>72 (47, 92)</td>
<td>68.5 (47, 82.5)</td>
<td>1.26 (0.78, 2.05)</td>
</tr>
<tr>
<td>Time to much improved or cured status</td>
<td>132 (117, 139)</td>
<td>122 (106.5, 140.5)</td>
<td>1.07 (0.64, 1.78)</td>
</tr>
</tbody>
</table>

1 Cox proportional hazards model. Each model was adjusted for age and sex. There were no significant differences between the groups for any variable.
2 Medians; quartiles in parentheses.
3 As judged by the caretaker.
4 Skin temperature ≤ 36.7 °C.
5 Respiratory rate of < 40 breaths/min.
6 As judged by a clinician who was unaware of the assigned treatment group.

### Table 3

<table>
<thead>
<tr>
<th>Increases in the serum concentrations of zinc and retinol from admission to discharge</th>
<th>Zinc group (n = 36)</th>
<th>Placebo group (n = 36)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zinc increment (μmol/L)</td>
<td>2.384 (4.81)</td>
<td>2.47 (3.06)</td>
</tr>
<tr>
<td>Retinol increment (μmol/L)</td>
<td>0.805 (0.553)</td>
<td>0.969 (0.516)</td>
</tr>
</tbody>
</table>

7 Adjusted P values from multiple linear regression analysis. In 2 regression models, the increments in serum zinc and serum retinol concentrations were adjusted for age, sex, and admission values of serum zinc and serum retinol. In the regression model, zinc concentration on admission was an independent predictor (inversely related) of zinc increment (P = 0.001). No significant differences between groups.
Several studies have also shown that routine zinc supplementation in children in developing countries prevents acute lower respiratory tract infection and pneumonia (3). However, therapeutic trials of zinc as adjunct therapy for pneumonia alone or in association with measles have not been reported. We can only speculate as to why zinc supplementation in children with measles accompanied by pneumonia did not lead to any measurable clinical improvement. The therapeutic effect of zinc in acute diarrhea can be explained by its direct effect on the mucosa and a gut-associated immune response, which may be different from an immune response in the respiratory system. Whereas a favorable immune response to zinc supplementation may explain why pneumonia is prevented in children, in an acute illness such as measles-associated pneumonia, there probably is insufficient time for mounting an immune response to favorably modify an acute illness. Thus, the administration of zinc to severely ill children with measles and pneumonia treated with vitamin A and supportive therapy showed no additional benefit.

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REFERENCES


