Effect of zinc supplementation on infants with severe pneumonia

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Original article

Background: **Pneumonia is a common respiratory infectious disease in infancy. Previous work shows controversial results on the benefit of zinc supplementation in patients with pneumonia. We conducted this study to investigate serum zinc status amongst infants with severe pneumonia and the clinical impact that zinc supplementation has on those patients with low serum zinc levels.**

Methods: **This study design was a non-blinded prospective randomized controlled trial. The study is approved by the Ethics Committees of Beijing Children's Hospital. A total of 96 infants diagnosed with severe pneumonia and hospitalized in the pediatric intensive care unit between November 2011 and January 2012 were enrolled. Enrolled patients were divided into low serum zinc and normal serum zinc group. The low serum zinc group was randomized into treatment and control groups. Only the treatment group received zinc supplementation within 48-72 hours after hospitalization.**

Results: **The prevalence of zinc deficiency on admission was 76.0%. The low zinc level was most apparent in infants between 1 and 3 months of age. The serum zinc level increased in the zinc treatment group and returned to a normal level (median, 53.20 μmol/L) on day 12±2. There was no statistical difference in the pediatric critic illness score, lung injury score, length of hospital stay, and duration of mechanical ventilation between the zinc treatment group and control group.**

Conclusions: **Zinc deficiency is common in infants with severe pneumonia. Normalization of zinc levels with zinc supplementation did not improve clinical outcomes of infants with pneumonia.**

World J Pediatr 2016;12(2):166-169

Key words: **infant; pneumonia; supplementation; zinc**

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doi: 10.1007/s12519-015-0072-9
Online First December 2015

Introduction

Pneumonia is a major cause of death in children <5 years of age. Researchers have focused on the relationship between zinc, an important trace element, and infectious diseases, such as diarrhea and respiratory infections. Studies have shown that in children with pneumonia, the serum zinc level is significantly lower than healthy controls.[1] Prophylactic zinc supplementation can reduce the incidence of pneumonia.[2,3] However, the effect of zinc supplementation on pneumonia is controversial. It has been reported that zinc supplementation can shorten the duration of pneumonia.[4] Mathew et al[5] found no obvious benefit of zinc supplementation in patients with community-acquired pneumonia (CAP). Data regarding changes in serum zinc levels during zinc supplementation are limited.

The aim of this study was to determine the serum zinc levels among children <1 year of age with severe community acquired pneumonia and to observe the changes in serum zinc levels after zinc supplementation and whether these changes influence the clinical outcomes of critically ill infants with community acquired pneumonia.

Methods

Trial design and participants

This prospective study was conducted in the Pediatric Intensive Care Unit (PICU) in Beijing Children's Hospital between November 2011 and January 2012. Infants between 1 and 12 months of age who were diagnosed with severe pneumonia and hospitalized in the PICU were enrolled.[6]

The exclusion criteria included the following: 1) length of hospital stay <24 hours; 2) premature with corrected gestational age <38 weeks; 3) history of chronic gastrointestinal disease or inability to tolerate food by mouth and 4) history of abdominal surgery 6 months before admission.

Clinical management was carried out according to standard practices in the intensive care unit.

Interventions

Peripheral blood (20 μL) was obtained from each infant within 24 hours of admission, to determine the initial serum zinc levels (with elemental analyzer for blood and serum, BH5100T atomic absorption spectrometer, Beijing Bohui Innovation Technology Company Limited). Infants were then divided into low serum zinc and normal serum zinc group (normal reference range of serum zinc: 58.00-100.00 μmol/L). Infants in the low serum zinc group were then randomized into treatment and control groups.

The treatment group was given licorice zinc particles orally in addition to other treatment for pneumonia. The licorice zinc dosage was based on the guidelines of the World Health Organization for the clinical treatment of acute diarrhea with zinc supplementation in 2004 (10 mg per day for infants <6 months of age and 20 mg per day for infants >6 months of age).[7] The trial was approved and monitored by the Ethics Committees of Beijing Children's Hospital. Informed consent was recieved from patients' parents before laboratory tests and interventions were carried out.

Clinical outcomes

The pediatric critical illness score (PCIS)[8] and lung injury score (LIS)[9] were assessed within 24 hours of admission. The serum zinc level was retested on days 7 and 12±2 of admission. Data, such as length of hospital stay and duration of mechanical ventilation, were collected after discharge from PICU.

Sample size

Formula $n_1=n_2=2[\frac{(t_{\alpha/2}+t_{\beta})S}{\delta}]^2$ was used for sample size estimation in this study (n_1 is sample size in group 1; n_2 is sample size in group 2; $t_{\alpha/2}$ is t value at level of α=0.05; t_{β} is t value at level of β=0.2; S is standard deviation; δ means difference between group 1 and group 2). The result showed 95 patients were needed in this trial.

Randomization

Children in the low serum zinc group were divided into treatment and control groups using the randomized digital table.

Statistical analysis

SPSS18.0 statistical software was applied to the clinical and experimental data for statistical processing. All of the data were entered twice to ensure that the raw data were accurate and correct. The Kolmogorov-Smirnov method was applied to determine whether or not the data had a normal distribution for a large sample size, and the Shapiro-Wilk method was used when the sample size was <50. Measurement data conforming to a normal distribution is described as the mean±standard deviation, while measurement data not conforming to a normal distribution is described as the "median (interquartile spacing)". Measurement data, such as the level of serum zinc, PCIS, duration of mechanical ventilation and length of hospital stay, if fitted normally distributed, were compared using a t test (correction t test if heterogeneity of variance) between the two groups and variance analysis between three groups (rank sum test if heterogeneity of variance). The rank sum test was used when the data did not conform to a normal distribution. The rate of low serum zinc level was compared by Chi-square test. P values <0.05 were statistically significant.

Results

Basic clinical data

A total of 96 infants were enrolled [65 boys (67.7%) and 31 girls (32.3%), with male-to-female ratio=2.1:1] and median age of 2 months. The distribution of age is shown in Table 1, and patient's characteristics are shown in Table 2.

Serum zinc level during admission

76.0% (73/96) of infants had serum zinc level lower than the normal reference range. Patients between 1-3 months had lower serum zinc levels than those between

Table 1. The serum zinc levels in different months of age

Groups	Zinc level (μmol/L)	Low zinc rate
1-3 mon (n=70)	40.75±17.02	85.7%
4-12 mon (n=26)	58.00±19.22	50.0%
U value	-3.904	4.483
P value	0.000	0.001

Table 2. Basic clinic information of normal serum zinc group and low serum zinc group

Variables	Low serum group		Normal serum group		P value
	n	Value	n	Value	
Age (mon), mean±SD	73	2.0±2.0	23	4.0±3.0	0.309
Gender					
Male, %	49	67.1	16	69.6	0.827
Female, %	24	32.9	7	30.4	
Breastfeeding only, %	49	51.0	12	12.5	0.194
Hemoglobin (g/L), mean±SD	73	108.0±26.5	23	107.0±29.0	0.811
Serum albumin (g/L), mean±SD	73	36.4±4.9	23	35.6±5.9	0.945
Etiology					
Bacteria, %	31	42.5	7	30.4	
Virus, %	5	6.8	2	8.7	
Others, %	8	11.0	1	4.3	
Unknown, %	29	39.7	13	56.5	

SD: standard deviation.

Table 3. Change of serum zinc levels during hospitalization (μmol/L)

Groups	Within 24 h (*n*=93)	D7 of admission (*n*=74)	D12±2 of admission (*n*=26)	X^2	F	*P* value
Normal serum zinc group, mean±SD	63.80±21.00	59.23±14.25	59.20±12.70	5.109		0.078
Treatment group, mean±SD	40.77±8.54	50.18±11.30	53.20±10.75	21.212		0.000
Control group, mean±SD	42.55±9.34	46.84±10.74	43.76±4.66		1.514	0.228
X^2/F	51.786	4.483	17.543			
P value	0.000	0.015	0.000			

SD: standard deviation; D: day.

4-12 months (Table 1).

The respective PICS and LIS were 78.4±6.2 and 0.59±0.37 in the normal serum zinc group, and 77.6±6.2 and 0.67±0.84 in the low serum zinc group. The respective length of hospital stay and duration of mechanical ventilation was 9.0±6.0 days and 6.0±3.8 days in the normal serum zinc group, and 8.0±6.0 days and 5.0±5.0 days in the low serum zinc group. There were no statistical difference in the PCIS, LIS, length of hospital stay, and duration of mechanical ventilation between the low serum zinc and normal serum zinc groups (7 patients in both groups who discharged against medical advice were excluded when comparing the duration of mechanical ventilation; 27 patients who discharged against medical advice or underwent surgery were excluded when comparing the length of hospital stay).

Effect of zinc supplementation

Changes in serum zinc levels

The serum levels of zinc within 24 hours, on day 7, and day 12±2 of admission in the normal serum zinc, treatment, and control groups are shown in Table 3. Within 24 hours, the level of serum zinc in the treatment and control groups were not significantly different, while the serum level of zinc in the normal serum zinc group was higher than the treatment and control groups ($P<0.01$). On day 7 of admission, the serum zinc level in the normal serum zinc group was higher than the control group ($P<0.05$), but was not significantly different from the treatment group ($P>0.05$). On day 12±2 of admission, the serum zinc levels in the normal serum zinc and treatment groups were higher than the control group ($P<0.01$); there was no statistically significant difference between these two groups ($P>0.05$).

There was no apparent change in the serum zinc levels in the normal serum zinc and control groups during hospitalization ($P>0.05$), while the serum zinc level increased with the increase in hospital length of stay in the treatment group under zinc supplementation ($P<0.01$).

Effect of zinc on the course of the disease

The time needed for mechanical ventilation in the control group appeared slightly shorter than the normal serum zinc and treatment groups ($P=0.05$). There were no significant differences in the duration of mechanical ventilation and length of hospital stay among the three groups (Table 4).

Table 4. Hospital stay and duration of mechanical ventilation in three groups

Groups	Length of hospital stay (d)	Duration of mechanical ventilation (d)
Normal serum zinc group (*n*=23), mean±SD	9.0±6.0	6.0±3.8
Treatment group (*n*=39), mean±SD	9.0±6.0	6.0±5.0
Control group (*n*=3), mean±SD	7.0±4.0	3.5±3.0
X^2	4.136	4.064
P value	0.126	0.131

SD: standard deviation.

Discussion

Zinc is involved in maintaining the integrity of the epithelial cells and the proliferation and development of immune cells, such as lymphocytes. In addition, zinc has antioxidant properties and may reduce inflammatory damage to the cytomembrane.

Studies have revealed that the serum zinc levels are decreased in patients with infectious diseases.[1,2] This has been regarded as a defensive reaction to infection.[10] In our study, the zinc level in peripheral blood is reduced in 76% of critically ill infants with severe pneumonia. This is consistent with findings in the literature.[1] The decrease of the serum zinc concentration was most evident in the 1-3 month group. These children were fed only with breast milk and/or cow's milk; their dietary intake of zinc might be lower than that of the other age groups who consumed a wider variety of food before hospitalization. The PCIS, duration of mechanical ventilation and length of hospital stay were similar in the low serum zinc and normal serum zinc groups, which suggests that the serum zinc concentration does not influence the severity of the pneumonia in infants.

A few reports described the duration and recovery of the low zinc status during infection.[11] A number of papers addressed the effect of zinc supplementation in children with infectious diseases, such as pneumonia and diarrhea.[2-4] Data on the change in zinc status during clinical treatment is lacking. The current study included a short-term observation on serum zinc changes in infants during hospitalization and the influence

of zinc supplementation on their serum zinc concentration. There was no obvious change of serum zinc concentration of the infants in normal serum zinc group and control group during their hospital stay. Treatment group showed an increase in serum zinc group on day 7, and reached normal reference ranges by day 12±2, which is higher than that of the control group. Serum zinc levels did not change in patients who did not receive zinc supplementation. Zinc supplementation, 10-20 mg per day, is effective treatment for low serum zinc levels.

The effect of zinc supplementation in children with pneumonia is controversial in the literature. A randomized controlled study of children with severe pneumonia in Bangladesh indicated that zinc supplementation improved anoxia, shortened the course of the disease, and decreased the hospital length of stay.[4] A meta-analysis suggested there was no benefit to adding zinc to the standard treatment of childhood CAP.[6] A study in Nepal showed no benefit of zinc supplementation in patients with severe pneumonia.[12] It has been speculated that the value of zinc supplementation in children with severe pneumonia may depend upon the prevalence of zinc deficiency in the community.[13] Recent studies on zinc supplementation in the treatment of lower respiratory infection in China have small sample sizes. This study showed no difference in the length of hospital stay and duration of mechanical ventilation between the treatment and control groups. Factors, however, as the short-term intervention and the mixed infections in the PICU may obscure the effect of zinc supplementation.

In conclusion, zinc deficiency is common in infants with severe pneumonia, which is most apparent in infants between 1 and 3 months of age. Serum zinc level remained the same in infants with severe pneumonia without zinc supplementation. Zinc supplementation can increase the serum zinc level to normal in infant with zinc deficiency. No benefit in clinical outcomes was seen with patients given zinc supplementation. Further studies with expanded sample, specific pathogenic infection and standardized treatment scheme are needed to explore further evidences.

Acknowledgements

Here we would like to thank Dr. Heng-Miao Gao, Dr. Jian-Sheng Zeng and Dr. Quan Wang from PICU and Emergency Department in Beijing Children's Hospital for their revises and comments for this manuscript.

Funding: This study was supported by a grant from the Capital Health Research and Development of Special (No. 2011-2009-01).

Ethical approval: The trial was approved and monitored by the Ethics Committees of Beijing Children's Hospital.

Competing interest: None declared.

Contributors: Qian SY gave the general guidance of the study. Yuan X made the detailed design, collected data and did the analysis and completed the writing. Li Z did as an instructor during clinical work and data collection. Zhang ZZ did the preliminary experiment and helped with data analysis.

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Received March 11, 2015
Accepted after revision October 19, 2015