Original Article

Single dose oral zinc as adjuvant therapy in children admitted with severe pneumonia: A randomized, placebo-controlled study

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Received – 03 December 2015 Initial Review – 23 January 2016 Published Online – 20 February 2016

ABSTRACT

Background: Childhood pneumonia is one of the major causes of under-five mortality in developing countries. Any interventions which can reduce the mortality and morbidity of pneumonia are of great importance. Adjuvant zinc therapy is one such intervention studied in various parts of the world with inconclusive results. **Objective:** We aim to study the impact of a single dose of zinc therapy on the outcome of childhood severe pneumonia. **Material and Methods:** Randomized, placebo-controlled study of young children between 2 and 24 months was conducted to study the impact of single dose zinc administration on time to resolution of severe pneumonia. The subjects were assigned two groups, zinc group and non-zinc group, by stratified randomization. The zinc group received unlabeled oral zinc syrup 20 mg of elemental zinc as single dose for children >6 months of age and 10 mg of elemental zinc as single dose for children <6 months. The non-zinc group children were administered unlabeled non-zinc containing placebo as single dose. **Results:** From April 2011 to December 2011, 1284 children screened for pneumonia as per Integrated Management of Neonatal and Childhood Illnesses guidelines and 126 children were included in the study. Of these 126 children, 63 were randomized to receive zinc and 63 to receive placebo. The mean duration of respiratory distress before hospitalization was 1.4±0.5 days in zinc group as compared to 1.1±0.5 days in non-zinc group (p=0.001). The mean duration of resolution of distress was 52.47±33.99 h in zinc group as compared to 74.17±37.76 h in the non-zinc group (p=0.05). Similarly, the mean duration for resolution of symptoms was 65.52±36.03 h in zinc group as compared to 88.00±37.97 in non-zinc group (p=0.05). The 23% of the children in non-zinc group had treatment failure (p=0.03). **Conclusion:** Single dose of adjuvant oral zinc therapy in severe pneumonia, reduces the duration of respiratory distress, resolves the symptoms early and decreases the incidence of treatment failure. However, the total duration of hospitalization was not affected by zinc therapy.

Key words: *Adjuvant zinc therapy, Childhood, Outcome, Pneumonia*

The estimated number of deaths globally in children aged <5 years was 6.6 million in 2012. 22% of these under 5 deaths occur in India. The leading causes of death among children under 5 years of age include pneumonia (17%), pre-term birth complications (15%), intrapartum complications (10%), diarrhea (9%), and malaria (7%) [1]. Interventions which can prevent or reduce the morbidity of pneumonia are of great importance to improve the childhood survival.

Zinc deficiency is common among children in low-income countries due to a variety of factors such as low food intake, particularly from animal sources; limited zinc bioavailability from local diets; and loss of zinc during recurrent diarrheal illnesses. Zinc deficiency is associated with immunodeficiency and increased rates of serious infectious diseases. The deficiency is widely recognized as contributing to the limited growth of children in both low-income and high-income countries [2].

It is estimated that zinc deficiency in association with diarrhea, pneumonia, and malaria contributes to 4.4% of deaths and 3.8% of lost disability-adjusted life years among children aged 6-59 months in Africa, Latin America, and Asia [3]. In a meta-analysis of clinical trials evaluating, the preventive role of zinc as a daily supplementation led to 14% and 8% reductions in the risk of diarrhea and pneumonia, respectively [4]. The World Health Organization now recommends zinc for the treatment of children with diarrhea [5] because there is sufficient evidence demonstrating that supplementation reduces the severity and duration of the episode [6]. The benefit of zinc in the treatment of pneumonia is, however, unclear. Although zinc as adjuvant therapy for hospitalized children with pneumonia was found to be beneficial in one clinical trial in Bangladesh [7], but other trials in India [8] and Australia [9,10] found no effect. Whether zinc administration has a beneficial effect when given to children hospitalized with severe pneumonia needs to be clarified. As the outcome has to be measured even before completion of this adjuvant therapy, the utility of longer duration of therapy is debatable. To address these two issues, we studied the impact of single dose oral zinc therapy on the outcome of children hospitalized with severe pneumonia.

MATERIAL AND METHODS

This was a randomized, placebo-controlled trial in young children between 2 and 24 months designed to measure the impact of single dose zinc administration on time to resolution of severe pneumonia. An important secondary outcome was the risk of treatment failure. Clearances were obtained from the Ethical Board of the Indira Gandhi Institute of Child Health (IGICH), Bengaluru, India.

Children aged 2-24 months presenting to the IGICH with complaints of a cough lasting <14 days and/or difficult breathing of <72 h duration with lower chest indrawing (LCI) were screened and classified as per the Integrated Management of Neonatal and Childhood Illnesses (IMNCI) algorithm [11]. Children with severe pneumonia were included in the study. Children with other co-morbid conditions which predisposes to recurrent and or severe pneumonia-like neuromuscular disorders, recurrent aspiration syndromes, congenital heart disease, children with multisystem diseases, congenital lung malformations, nosocomial infections, primary or secondary immunodeficiency were excluded. Children with recurrent wheezing (defined as three episodes over the past 6 months and on treatment with bronchodilators), disappearance of LCI after nebulized salbutamol, severe wasting, severe anemia (hemoglobin 7 g/dL), documented tuberculosis, children who has received antibiotics for the same illness before hospitalization or concomitant diarrhea with dehydration were also excluded. We also excluded children who were receiving medication containing zinc.

Eligible children were initially assessed for hypoxia using pulse oximeter and presence of wheezing. Oxygen saturation (SpO_2) was recorded twice after stabilization of the reading for 1 min. The higher of the two readings was used. For children with SpO_2 of <90%, oxygen was provided before further evaluation. Children with wheezing were given up to three doses of nebulized salbutamol 20 min apart, reassessed, and excluded if LCI disappeared. A history of the child's illness was taken, and physical examination carried out by a standardized form. Children were weighed using an electronic scale (sensitivity ±5 g). The recumbent length of the children was measured by an infantometer. Stunting (defined as length-for-age <2 Z score) and wasting (weight-for-length <2 Z score) were calculated using 2009 WHO Child Growth Standards [12].

Complete hemogram, acute phase reactants (serum C - reactive protein, quantitative), and blood culture were obtained at the baseline. A chest radiograph taken in all children was interpreted by a radiologist to rule out complications. Informed consent was obtained for eligible children from their parents or guardian after explaining the study protocol.

These eligible children were given the first dose of intravenous antibiotics. They were divided into two group by stratified randomization into zinc group and non-zinc group. The zinc group was administered unlabeled oral zinc syrup 20 mg of elemental zinc as single dose for children above 6 months of age and 10 mg of elemental zinc as single dose for children <6 months. The non-zinc group children were administered unlabeled non-zinc containing placebo as single dose. These were administered by the person who was not involved in the study. These syrups were administered through naso-gastric tube for those children who were not able to take orally. These children were observed for 20 min after the administration of these syrups for vomiting. For children who vomited within 20 min of administration of syrups, the dose was repeated with close monitoring.

Enrolled children were admitted to the hospital and monitored by pediatricians involved in the study at 8 hourly intervals until discharge. Amoxicillin-clavulanic acid (75 mg/kg/day intravenously in two divided doses) were given until clinical improvement, defined as the absence of danger signs, no episode of hypoxia for 24 consecutive h and no evidence LCI for a 48-h period. Patients were then discharged with advice to continue oral amoxicillin-clavulanic acid to complete treatment of a total duration of 10 days.

Antibiotics were changed to ceftriaxone in children who failed to improve, defined as persistence of LCI or of any danger signs despite 48 h of treatment or appearance of new danger signs or hypoxia with the deterioration of patient's clinical status any time after initiation of treatment. A decision to change antibiotics was made only after consultation with senior pediatricians involved in the study. For children unable to eat/drink or breastfeed, intravenous fluids based on daily requirements were initiated. Humidified oxygen was given to children with documented hypoxia.

During each physician visit, SpO_2 was documented after a washout period of 5-min and oxygen discontinued when they were no longer hypoxic. The absence of hypoxia was confirmed after a second reading taken 30 min later. Every 8 hourly, axillary temperature, respiratory rate, LCI, and wheezing and crepitations on auscultation were recorded by two independent pediatricians separately. Their findings were matched against those of an experienced pediatrician until the desired agreement was reached.

Outcome measurements

The primary outcome, time to resolution of severe pneumonia, was defined as the period starting from enrollment to the beginning of a 24-h consecutive period of absence of LCI, hypoxia, and any danger signs as per IMNCI [11]. The secondary outcome, treatment failure, was defined as a requirement for a change in antibiotics, development of complications, such as empyema or pneumothorax requiring surgical intervention, or requirement of ventilatory or inotropic support.

Statistical analysis

Student's *t*-test (two-tailed, independent) has been used to find the significance of study parameters on a continuous scale between two groups. Chi-square/Fisher exact test has been used to find the significance of study parameters on a categorical scale between two or more groups.

RESULTS

From April 2011 to December 2011, we screened 1284 children meeting inclusion criteria. Of these, 1158 (90%) children were not eligible for inclusion due to various reasons as shown in Fig. 1. After enrollment of the remaining 126 children, 63 were randomized to receive zinc and 63 to receive placebo (Fig. 1).

In the non-zinc group, 66.7% of the children were aged between 2 and 12 months. This was statistically significant (p=0.03). Other baseline demographic parameters were comparable in both groups (Table 1). Mean duration of respiratory distress before hospitalization was 1.4±0.5 days in zinc group as compared to 1.1±0.5 days in non-zinc group which was statistically significant (p=0.001). Severe respiratory distress (respiratory rate >60/min) was found in 70% of infants in the zinc group as against 35.7% of infants in the non-zinc group (p=0.004). Auscultatory crepitations were seen in 90.4% of the children in non-zinc group as compared 30.1% of the children in non-zinc group (<0.001) (Table 2).

Table 1: Baseline demographic parameters

Characteristics	Zinc group		Non-zinc group		p value
	n	Value (%)	n	Value (%)	
Age (months)					
2-12	30	47.6	42	66.7	0.03
13-24	33	52.4	21	33.3	
Mean age (in months)	63	15.33±5.98	63	13.57±7.05	0.13
Male	42	66.7	42	66.7	1.00
Female	21	33.3	21	33.3	
Rural	15	23.8	18	28.5	0.54
Urban	48	76.1	45	71.4	

Analyzes were done by intention to treat. The mean duration of resolution of distress was 52.47±33.99 h in zinc group as compared to 74.17±37.76 h in non-zinc group which was statistically significant (p=0.0493). Similarly, mean duration for resolution of symptoms was 65.52±36.03 h in zinc group as compared to 88.00±37.97 in non-zinc group (0.0491). However, there was no statistically significant difference in other outcome indicators such as mean duration for the disappearance of danger signs, to reach SpO_2 of >90% in room air and of hospital stay among both groups. 23% of the children in the non-zinc group as against 9.5% of the children in zinc group had treatment failure (Table 3).

DISCUSSION

This study was conducted to determine the impact of the single dose oral zinc therapy as adjunct therapy on the outcome of severe pneumonia in children. In the literature available so far, varying duration of oral zinc as adjuvant therapy in childhood severe pneumonia has been used to study its impact on the outcome of pneumonia. However, the outcome has to be measured even before completion of this adjuvant therapy, and the utility of longer duration of therapy is debatable. Hence, we studied the impact of single dose oral zinc therapy as compared to varying longer duration of therapy used in various other studies.

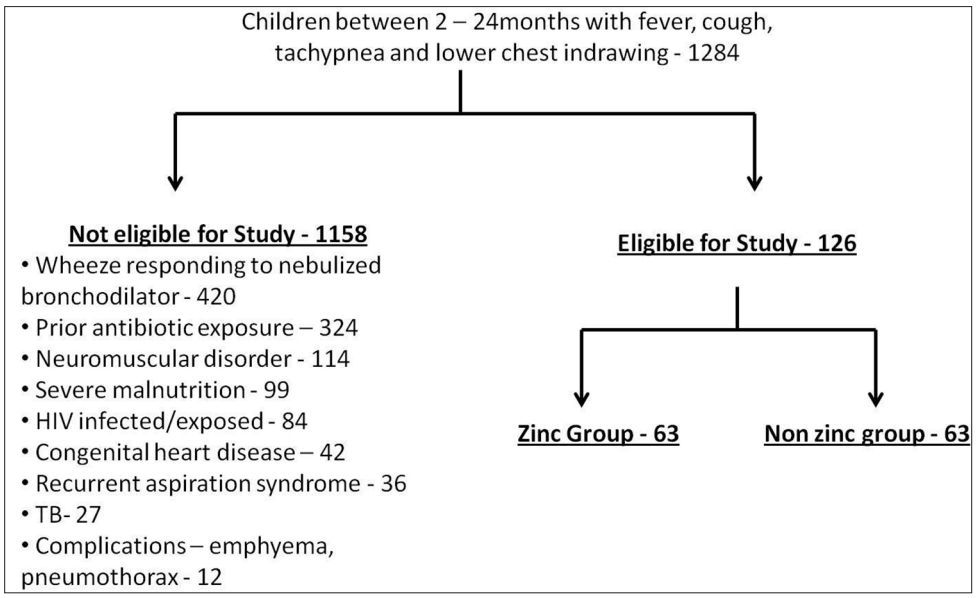

Figure 1: Trial profile of a randomized, placebo-controlled study of single dose oral zinc as adjunct therapy for severe pneumonia in children aged 2-24 months of age

Table 2: Baseline clinical parameters

Characteristics	Zinc group		Non-zinc group		p value
	n	Value	n	Value	
Mean duration of cough (in days)	63	3.8±2.0	63	3.6±2.1	0.58
Mean duration of fever (in days)	63	3.1±1.8	63	3.4±1.6	0.32
Mean duration of tachypnea (in days)	63	1.4±0.5	63	1.1±0.5	0.001
Respiratory rate (breaths per minute)					
2-12 months					
50-60	9	30.0	27	64.3	0.004
>60	21	70.0	15	35.7	
12-24 months					
40-50	24	72.7	12	57.1	0.24
>50	9	27.3	9	42.9	
SpO_2 at room air (%)					
<90	30	47.6	39	62.0	0.11
>90	33	52.3	24	38.0	
Danger signs					
Lethargy	18	28.5	15	23.8	0.54
Inability to drink	36	57.1	39	61.9	0.59
Convulsions	0	0.0	3	4.7	0.24
Stridor in calm child	6	9.5	6	9.5	1.00
Signs of severe pneumonia					
Lower chest retraction	63	100	63	100	1.00
Nasal flaring	3	4.7	6	9.5	0.30
Grunting	3	4.7	3	4.7	1.00
Cyanosis	36	57.1	30	47.6	0.28
Auscultatory findings					
Creptitations	19	30.1	57	90.4	<0.01
Wheeze	11	52.3	21	33.3	0.06
Bronchial breath sounds	6	9.5	9	14.2	0.58

SpO_2: Oxygen saturation

Table 3: Comparison of outcome among zinc group subjects with non-zinc group subjects

Variables	Zinc group	Non-zinc group	p value
Mean duration for the disappearance of danger signs (in h)	43.3±41.54	62.8±44.21	0.246
Mean duration to reach SpO_2>90 in room air (in h)	23.9±38.36	45.8±53.42	0.130
Mean duration for resolution of distress (in h)	52.47±33.99	74.17±37.76	0.0491*
Mean duration of hospital stay (in days)	6.14±3.55	7.14±3.57	0.37
Mean duration for the resolution of symptoms (in h)	65.52±36.03	88.00±37.97	0.0490*
No of children with treatment failure	6 (9.5%)	15 (23%)	0.03*

SpO_2: Oxygen saturation, *Statistically significant

This study shows a significant impact of single dose of adjuvant oral zinc therapy in reducing the duration of respiratory distress, resolution of symptoms, and incidence of treatment failure. This impact of single dose oral zinc therapy on the early resolution of respiratory distress and reduction in the incidence of treatment failure is even more significant considering the fact that zinc group included the children who had significantly longer duration of pre-hospitalization illness and significantly higher number of infants with severe pneumonia at the time of admission. However, the non-zinc group included significantly higher number of infants who are expected to have prolonged and severe disease which can be a confounding factor.

Furthermore, the children who received zinc therapy had modest, but not significant, decrease in duration for resolution of danger signs and shorter duration of oxygen dependency and hospital stay when compared to the children who had not received adjuvant zinc therapy.

In a study undertaken in Nepal, children who received single daily dose of zinc for 14 days recovered faster, and fewer had treatment failure [10]. A study of 120 Iranian children hospitalized with severe pneumonia randomized into two groups with oral zinc administered for 7 days, and a placebo showed a significant decrease in the hospital stay as well as the resolution of symptoms in zinc receiving children [13]. This is comparable to our study where children receiving zinc recovered faster and had fewer treatment failures.

In a large multicentric study from New Delhi, India showed no overall benefit of the addition of zinc to antibiotics in reducing the time to recovery from pneumonia but showed a possible benefit of zinc supplementation in a subgroup of children with very severe pneumonia [14]. The subgroup of children with very severe pneumonia in this study is comparable to our study which includes only children with severe pneumonia. However, a similar study conducted in Vellore, south India, showed no overall effect on the duration of hospitalization or of clinical signs associated with severe infection in young children hospitalized for severe pneumonia [8]. In this study, the dosage of zinc supplemented was 10 mg/day as compared to 20 mg/day in our study. Furthermore, significantly higher number of children had wheeze in both groups as compared to our study.

A Ugandan study, which compared daily zinc therapy for 7 days with placebo, showed no significant difference in time to normalization of the respiratory rate, temperature, and SpO_2

between the two arms, but showed a significant decrease in the case fatality rate [15]. In our study also, oral zinc therapy has no significant impact on reducing the duration of the oxygen dependency. However, our study showed significant impact by reducing the respiratory distress early. This contrast could be due to older study population and the inclusion of HIV-infected children in the Ugandan study.

Another study from Nepal compared 64 children who received zinc (loading dose of 20 mg/day on 1st day followed by maintenance dose of 10 mg/day for 7 days) with 53 children receiving placebo. The study did not show a significant reduction in the duration of severe pneumonia or reduction in hospital stay for children given daily zinc supplementation [16]. In contrast to our study, the outcome measured (duration of severe pneumonia) was not well defined in this study.

However, the homogenization of treatment is a challenge in this study as well as similar studies elsewhere because an individual child with pneumonia requires different therapeutic approach with respect to the choice of antibiotics and duration of therapy depending on the host and agent factors.

CONCLUSION

Single dose oral zinc as an adjuvant therapy in the children hospitalized with severe pneumonia was found to significantly reduce the duration of severe pneumonia in spite of these children had a longer duration of pre-hospitalization illness and severe disease at the time of admission. However, the total duration of hospitalization was affected significantly.

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Funding: None; Conflict of Interest: None Stated.

How to cite this article: Basavraj GV, Nijaguna N, Gembeeran R, Sanjeeva GN. Single dose oral zinc as adjuvant therapy in children admitted with severe pneumonia: A randomized, placebo-controlled study. Indian J Child Health. 2016;3(1):18-22.