Role of zinc as an adjuvant therapy in severe pneumonia – A double blind placebo controlled randomized clinical trial

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Abstract:

Diarrhea and pneumonia are the leading causes of illness & death in children upto 5 years of age. Zinc supplementation is effective for treatment of acute diarrhea and can prevent pneumonia. The study was carried out to compare duration of hospitalization among zinc supplemented and placebo group, in children aged 3 months to 5 years admitted with severe pneumonia: A double blind placebo controlled randomised clinical trial and to see whether the use of oral zinc therapy when compared to placebo, as an adjuvant to antibiotics, when compared to placebo reduce the duration of hospitalization by one day in children aged 3 months to 5 years with severe pneumonia. This randomized controlled trial was conducted in the Department of Pediatrics at Goldfield Hospital and Research centre, Village Chhainsa, Faridabad from 1st April 2013 to 30th April 2014. 83 Eligible Children aged 3 months to 5 years with a clinical diagnosis of severe pneumonia were taken and given Zinc supplementation for 14 days (10 mg in < 6 months age and 20 mg in 6 months or more in age) and compared against placebo groups for duration of hospitalization and other secondary variables. Results of our study showed that clinical resolution in both the groups (zinc versus placebo) was comparable in terms of median duration of hospitalization (137.23 hours versus 132.98 hours), duration of resolution of severe pneumonia (54.1 hours versus 53.83 hours), resolution of lower chest indrawing (54.1 hours versus 53.83 hours), resolution of fast breathing (69.65 hours versus 73.73 hours), time to start oral feeds (29.3 hours versus 26 hours), duration of intravenous fluid therapy (60.08 hours versus 57.43 hours) and duration of oxygen therapy (22.63 hours versus 19.80 hours). Thus there was no difference in the primary or secondary outcome variables between the zinc and placebo groups. In this randomized controlled trial, conducted to study the efficacy of zinc supplementation, as an adjunct to antibiotics, in the treatment of severe pneumonia, we conclude that short term supplementation with zinc, given during the course of illness does not shorten the duration of resolution of severe pneumonia in children between the age group of 3 months to 5 years. Zinc supplementation also does not shorten the duration of resolution of lower chest indrawing, fast breathing and inability to feed. Zinc supplementation also does not shorten the duration of intravenous fluid therapy, oxygen therapy and duration of hospitalization.

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Introduction:

Acute respiratory tract infection (ARTI) is a leading cause of mortality and morbidity in children below 5 years of age (1). The incidence of clinical pneumonia in children aged less than 5 years in developing countries worldwide is close to 0.29 episodes per child-year. This equates to 150.7 million new cases every year, 10 to 20 million (7–13%) of which are severe enough to require hospitalization (2). World Health Organization (WHO) estimates that 19% of under five deaths are caused by pneumonia and 75% of these occur in the age group of less than 1 year (3-4). More than 1.5 million children die from pneumonia every year in which an estimated 98% children live in developing countries, with India contributing to maximum number of deaths (5). For every 1 child that dies of pneumonia in a developed country, more than 2000 children die of pneumonia in developing countries (6).

WHO has recommended certain clinical criteria for diagnosis of pneumonia in children at primary health care level for control of lower respiratory tract infection deaths in developing countries. The clinical criteria for diagnosis of pneumonia include rapid respiration with or without difficulty in respiration. Rapid respiration is defined as respiratory rate of more than 60, 50 or 40 breaths/minute in children less than or equal to 2 months of age, 2 months to less than or equal to 1 year and 1 to 5 years of age respectively. Difficulty in respiration is defined as presence of lower chest indrawing (7).

Childhood pneumonia is caused by a combination of exposure to risk factors related to the host, the environment and infection. The definite risk factors include malnutrition (weight for age z-score < –2), low birth weight (≤ 2500 g), non-exclusive breast-feeding (during the first 4 months of life), lack of measles immunization (within the first 12 months of life) , indoor air pollution and crowding (8). Likely risk factors include parental smoking, zinc deficiency, mother's experience as a caregiver and concomitant diseases (diarrhea, heart disease, asthma). Possible risk factors include low level of mother's education, day-care attendance, rainfall (humidity), high altitude (cold air), Vitamin A deficiency, birth order and outdoor air pollution. Most of the environmental risk factors require multi-sectoral coordination for modification. In contrast, some of the childhood risk factors can be modified by simple interventions like exclusive breast feeding for six months and Vitamin A or zinc supplementation.

Zinc affects multiple aspects of the immune system. Zinc is crucial for normal development and function of cells mediating innate immunity, neutrophills, and natural killer cells. Macrophages are also affected by zinc deficiency. Phagocytosis, intracellular killing, and cytokine production all are affected by zinc deficiency. Zinc deficiency adversely affects the growth and function of T and B cells. The ability of zinc to function as an anti-oxidant and stabilize membranes suggests that it has a role in the prevention of free radical induced injury during inflammatory processes (9).

The therapeutic benefit of oral zinc in diarrhea has been well documented in a Cochrane review of 18 trials which showed that it shortened the recovery time in children with acute or persistent diarrhea in the age group of 6 months to 5 years (10). Further, it has also been shown that routine zinc supplementation lowers the risk of acute respiratory infections and clinical pneumonia in children (11). However, no consensus has evolved for the therapeutic role of zinc in pneumonia in children. Evidence on zinc supplementation as adjuvant therapy in children with severe pneumonia is conflicting with studies from Iran (12), Kolkata (13) and Bangladesh (14) showing a beneficial effect while similar studies from Nepal (15-16), Chandigarh (17), Kolkata (18) and Vellore (19) not showing any beneficial effect. In addition, there is paucity of evidence on role of zinc supplementation in case management of severe pneumonia from North India. Keeping these considerations, the present study was carried to find out the efficacy of zinc as an inexpensive therapeutic adjuvant when given to children hospitalized and treated with antibiotics for severe pneumonia and compare duration of hospitalization, time to resolution among zinc supplemented and placebo group and also risk of recurrent of pneumonia in both the groups.

Materials and Methods:

Study Setting

This randomized double blind placebo controlled clinical trial was conducted in the Department of Pediatrics at Goldfield Hospital and Research centre, Village Chhainsa, Faridabad from 1st April 2013 to 30th April 2014. This hospital is an approximately 400 bedded with 50 bedded pediatric ward which caters to economically underprivileged population ballabgarh, Faridabad

Study Design

A prospective randomized double blind placebo controlled clinical trial.

Outcome Measures

Primary outcome variables: The primary outcome variable of interest was

1. Duration of hospitalization

Secondary outcome variables:

1. Time to resolution of severe pneumonia
2. Time to resolution of lower chest indrawing, fast breathing and inability to feed
3. Duration of oxygen therapy
4. Duration of intravenous fluids
5. Recurrence of pneumonia within 3 months of discharge.

Sample Size

Based on a previous study in which the mean duration of hospitalization in children with severe pneumonia was 5 days (17), a sample size of 30 patients was calculated in each treatment arm to detect a 20% change (1 day) in the duration of hospitalization assuming 30% coefficient of variation with alpha error of 0.05 and 80% power. Sample size was calculated using the formula:

Sample size = $(8\ (CV)^2/(PC)^2\ )\ (1+(1-PC)^2)$. Where PC was the proportionate change in means and CV was the coefficient of variation. Assuming one third of the patients were lost to follow up, the final sample size in each arm was rounded off to 40.

Study Population

Inclusion Criteria

- Children aged 3 months to 5 years with a clinical diagnosis of severe pneumonia (20)

A child was said to have severe pneumonia if he/she fulfilled the following clinical criteria:

- History of fever of less than 14 days
- Cough < 14 days
- Tachypnea
- Lower chest in drawing
- And/or any one of the danger signs: poor feeding, lethargy, altered sensorium, irritability, and cyanosis.

Exclusion Criteria

- Children who received any form of micronutrient supplementation in preceding 4 weeks prior to onset of present illness
- Clinical evidence of underlying cardiac or chronic pulmonary disease
- Co-morbid condition (diarrhea, meningitis) present at the time of admission
- Those who required mechanical ventilation
- Those who had severe malnutrition as per WHO criteria (weight for height <-3 standard deviations of WHO standard) [21]
- History of recurrent wheezing (>3 episodes over past 6 months) and/or treatment with bronchodilators
- History of associated allergic disorders, asthma, chronic cough (cough >14 days)
- Early responders (detailed below under definitions)
- Documented patients having Tuberculosis
- Patients with severe anemia (Hemoglobin <7 g/dL)
- Documented use of antibiotics in past 48 hours prior to admission for current illness
- Illness requiring hospitalization in the previous 21 days
- Presence of pneumothorax, or pleural empyema.

Definitions

- Fever was defined as an axillary temperature >38°˚C.
- Tachypnea was defined as a respiratory rate of ≥50 per minute for infants between 3 months to 1 year and ≥40 per minute in children between 1 year to 5 year.
- Hypoxia was defined as oxygen saturation (measured using a pulse oximeter) <92% on room air.
- Early responder was defined as a child with wheezing, whose lower chest indrawing disappeared after nebulization with 3 doses of salbutamol, 15 minutes apart.
- Time to resolution of severe pneumonia was defined as the period starting from enrollment to the beginning of a 24 hour consecutive period of absence of lower chest indrawing, hypoxia and any danger signs (poor feeding, lethargy, altered sensorium, irritability, and cyanosis).
- The duration of hospitalization was defined as the time (in hours) between study enrollment and discharge.
- Recurrence of pneumonia was defined as any new episode of pneumonia requiring hospital admission within 3 months of discharge.

Randomization, Blinding and Treatment Allocation

1) Sequence generation:

a) Children enrolled in the study were randomly assigned to receive adjunctive zinc therapy or placebo. A randomization list from 1 to 80 was prepared by biostatistician through computer generated random number sequence using permuted blocks of 20, which was then sent to the hospital pharmacist.

b) A syrup formulation of zinc was used. Each 5 ml of the syrup contained 20 mg of elemental zinc. Both study syrups were identical in appearance and taste.

c) The manufacturer of zinc and placebo supplements labeled all bottles with a regimen code and kept the treatment identification codes until completion of follow-up for all participants.

d) The pharmacist stored the randomization list in a locked file cabinet and concealed allocation by covering the numeric regimen code on each bottle with a sticker.

Allocation concealment:

- Allocation concealment was done through SNOSE (Serially Numbered Opaque Sealed Envelopes). This was concealed from the principal investigator enrolling and assessing participants. Thus all study participants and research personnel (including the principal investigator, physicians and nurses) were unaware of treatment groups. The codes were broken only at the end of the study.

Intervention

Children less than 6 months were given 10 mg of zinc or the placebo while those aged 6 months or more were given 20 mg of zinc or placebo once daily for 14 days. For those children who were not able to take the syrup orally, a nasogastric/orogastric tube was inserted and the required dose was given through it. In case the child vomited within half hour, the zinc dose was repeated.

Data collection and monitoring during hospital stay

A detailed history, physical and systemic examination was carried out and recorded in a predesigned performa at the time of enrollment. Physical examination included vital signs such as temperature, heart rate, respiratory rate and blood pressure; assessment of breathing effort, cyanosis, mental status, chest auscultation for crepitations or wheezing, or both, and anthropometrical measurements (weight, length/height, head circumference).

Management Protocol

1) Antibiotics:

- All enrolled children were treated according to the standard protocol for treatment of infants and children with pneumonia. Patients received intravenous antibiotics as per standard protocol of the hospital.
- Intravenous ampicillin and gentamycin were used as first line antibiotics.
- Antibiotics were changed to second line in children with failure to improve, defined as persistence of lower chest indrawing or of any danger signs present at enrollment despite 48 hours of treatment or appearance of new danger signs or hypoxia with deterioration of patient's clinical status anytime after initiation of treatment.
- Intravenous ceftriaxone was used as second line antibiotic.
- Staphylococcal infection was recognized on basis of clinical and radiological features (skin boils, abscesses, rapid progression / deterioration, pneumatocele and empyema). Children with pneumothorax or empyema were however excluded.
- Intravenous cloxacillin was used as first line antistaphylococcal antibiotic. If the child did not improved within next 48 hours with cloxacillin, then it was replaced by vancomycin.
- A decision to change antibiotics was made only after consultation with senior pediatricians involved in the study.
- Oral antibiotics were started when the child was able to feed well and when oxygen saturation and respiratory rate got stabilized. Once the patient was on oral antibiotic, he or she remained under observation in the ward for a further 24 hours before discharge.

2) Oxygen:

- Humidified oxygen was initiated in presence of central cyanosis, severe lower chest indrawing, respiratory rate of ≥ 70, grunting, head nodding or oxygen saturation (SpO2) less than 92% on room air.
- Oxygen was discontinued when oxygen saturation (SpO2) was ≥92% while breathing room air for 30 minutes, respiratory rate was < 70 breaths/minute and there was absence of severe lower chest indrawing, grunting and cyanosis.

3) Feeds:

- For children unable to eat/drink or breastfeed, intravenous fluids based on daily requirements was initiated.
- Enteral feeds were started once the child's respiratory distress improved and oxygen saturation was ≥92%, and the baby was able to tolerate small sips of feeds. Feeds were started as early as possible to optimally balance fluid and caloric intake.

Discharge Criteria

- The patient was considered fit for discharge when he/she was afebrile, tachypnea and lower chest indrawing subsided, oxygen saturation (SpO2) was ≥92% on room air and oral feeding was resumed for a minimum continuous period of 24 hrs and the attending pediatrician decided that the patient's clinical condition had resolved and he/she did not require further hospital stay.
- Administration following discharge was not supervised by the investigators but parents were carefully counseled and the volume of unused syrup remaining in the bottle was checked on follow up.
- Children were also followed up on day 15, 1 month, 2 month and 3 months of illness to know whether there was any recurrence of pneumonia or any other reason of hospitalization.

Data Analysis

Statistical analysis was performed by the SPSS program for Windows, version 17.0. Continuous variables were presented as mean (SD) and categorical variables were presented as absolute numbers and percentage. The data was checked for normality using Shaipro Wilk test. Normally

distributed continuous variables were compared using the unpaired student's t test, whereas the Man-Whitney U test was used for those variables that were not normally distributed. Categorical variables were analyzed using either Chi square test or Fisher's Exact test. For all statistical tests, $P < 0.05$ was taken to indicate a significant difference.

Ethical Approval -

Approval from institutional ethical committee was sought and obtained before instituting the study

Observations and Results:

Study subjects were enrolled from the pediatric emergency over a period of 13 months from 1st April 2013 to 31st April 2014. Of the total admissions, 133 children with severe pneumonia were assessed for eligibility. Of these 50 children were ineligible because they did not fulfill study's prefixed inclusion or exclusion criteria. The most common reason for ineligibility was the age criteria, as 25 children were less than 3 months of age. Thus 83 children were eligible. Of these, 3 children were excluded because parents refused to give consent for the study. Finally 80 children were included in the study following the written informed consent. 40 children received oral zinc and 40 children received oral placebo(Table 1-8).

Table 1: Age wise distribution of Children in Zinc and Placebo Group

Age in Months	Zinc (%)	Placebo (%)
3-6	28	30
>6-12	38	33
>12-24	15	18
>24-36	5	10
>36-60	15	10

Table 2: Sex distribution (%) of children in Zinc and Placebo group

	Zinc group	Placebo group
Male	55 %	38 %
Female	45 %	63 %

Table 3: Baseline personal profile of the study participants

Parameters	N	Mean (SD)	Median (IQR)	Range
Age of child (months)	80	15.4 (14.5)	9 (6,16.5)	3-56
Present weight (Kg)	80	8.29 (2.65)	7.5 (6.5,8.8)	4.8-15
Present height (cm)	80	73.37 (12.14)	68.8 (65,78)	56.1-103
Head circumference (cm)	80	43.88 (2.84)	43.9 (41.9,45.4)	37-50
Weight for age Z score	80	-1.49 (0.71)	-1.39 (-1.85,-1.11)	(-) 3.4-0.6
Height for age Z score	80	-1.15 (0.91)	-1.19 (-1.72,-0.66)	(-)3.4-1.24
Weight for height Z score	80	-1.11 (0.95)	-1.13 (-1.69,-0.62)	(-)3.21-1.83

Table 4: Baseline personal profile in zinc versus placebo group

Parameters	Zinc Mean (SD)	Placebo Mean (SD)	*P* value
Age of child (months)	15.7 (14.7)	15 (14.5)	0.75
Present weight (Kg)	8.34 (2.53)	8.26 (2.79)	0.89
Present height (cm)	73.55 (11.94)	73.21 (12.48)	0.90
Head circumference (cm)	43.78 (2.68)	43.97 (3.04)	0.77
Weight for age Z score	-1.50 (0.78)	-1.48 (0.64)	0.89
Height for age Z score	-1.21 (0.98)	-1.10 (0.85)	0.59
Weight for height Z score	-1.11 (0.95)	-1.12 (0.96)	0.95

Table 5: Baseline gestation, immunization status and feeding profile of the study participants

Parameters	Total	Zinc		Placebo		*P* value
		Frequency	%	Frequency	%	
Gestation						
Term	74	36	90%	38	95%	
Preterm	6	4	10%	2	5%	0.68
Immunization status						
Fully immunized	47	22	55%	25	63%	
Partial immunized	19	10	25%	9	23%	
Unimmunized	14	8	20%	6	15%	0.77
Exclusive breast feed	29	18	45%	11	28%	0.10
Initiation of complementary feeding at 6 month (in children > 6 months)						
Yes	29	15	45.5%	14	45.2%	
No	35	18	54.5%	17	54.8%	0.98

Table 6: Baseline parameters on enrollment in zinc and placebo group

Parameters	Total Mean (SD)	Zinc Mean (SD)	Placebo Mean (SD)	*P* value
Duration of symptoms (days)	4.26 (1.46)	4.1 (1.33)	4.4 (1.58)	0.34
Respiratory rate (breaths per minute)	61.35 (6.99)	61.7 (6.85)	61 (7.20)	0.66
Oxygen saturation (SpO2 (%))	88.80 (2.06)	89 (2.05)	89.03 (2.07)	0.33

Table 7: Baseline clinical presentation in zinc and placebo group

Parameters	Total	Zinc		Placebo		*P* value
		Frequency	%	Frequency	%	
Lower chest indrawing	80	40	100.0%	40	100.0%	—
Wheeze	37	17	42.5%	20	50.0%	0.50
Cyanosis	0	0	0.0%	0	0.0%	—
History of fever	80	40	100.0%	40	100.0%	—
Irritability	18	10	25.0%	8	20.0%	0.59
Altered sensorium	0	0	0.0%	0	0.0%	—
Poor feeding	53	28	70.0%	25	62.5%	0.48

Table 8: Resolution of symptoms (mean hours) in zinc and placebo group

Parameters	Zinc	Placebo	Mean Difference	95% CI	*P* value
	Mean (SD)	Mean (SD)			
Duration of hospitalization (hours)	137.23(12.88)	132.98(13.92)	-4.250	(-)10.220-1.720	0.16
Duration of resolution of severe pneumonia (hours)	54.10(8.77)	53.83(7.75)	-0.275	(-)3.960-3.410	0.88
Duration of lower chest indrawing (hours)	54.10(8.77)	53.83(7.75)	-0.275	(-)3.960-3.140	0.88
Duration of fast breathing (hours)	69.65(10.83)	73.73(9.44)	4.075	(-)0.447-8.597	0.08
Time to start oral feeds (hours)	29.33(16.54)	26.00(16.70)	-3.325	(-)10.723-4.073	0.37
Duration of O2 therapy (hours)	22.63(11.95)	19.80(8.99)	-2.825	(-)7.532-1.882	0.24
Duration of IV fluids (hours)	60.08(12.18)	57.43(8.62)	-2.650	(-)7.348-2.048	0.27

Discussion:

Reasons behind inclusion and exclusion criteria:

We included cases of severe pneumonia between age groups of 3 months to 5 years. Lower age limit of 3 months was chosen to exclude children with bacteraemia who may otherwise present with fever and non specific respiratory symptoms. Young age of the child (<6-12 weeks) is associated with an increase risk of very severe disease because of poorly developed immune system, inactivity of respiratory center, anatomical features of upper airway that predispose to collapse and obstruction, a compliant rib cage and poorly developed respiratory muscles, so they frequently develop apnea, which has been associated with prolonged hospitalization, admission to intensive care and mechanical ventilation. This was another reason to exclude children less than 3 months from this study.

We included only severe cases of pneumonia in our study population as chances of getting a positive effect are always more in severe cases. Also, in previous trials (example-zinc in diarrhea causing severe dehydration), efficacy of treatment was always first tested in severe condition and if found to be effective in severe cases, then intervention was evaluated in children with mild and moderate disease severity.

To avoid including children with reactive airway disease, children who presented with wheeze were treated with salbutamol. However, because wheezing can be a part of symptoms of bronchopneumonia, we enrolled these children only if lower chest indrawing persisted after salbutamol nebulization. Children with history of associated allergic disorders and asthma were excluded as these children are at increased risk of reactive airway disease and it would have been difficult to diagnose bronchopneumonia in the setting of reactive airway disease.

We excluded cases that received micronutrients in last four weeks or were currently on micronutrient supplements as many of them contain zinc. We also excluded cases of diarrhea presenting along with cases of severe pneumonia, as zinc supplementation is routinely recommended for them. If child had received any micronutrient four weeks back, it should not affect results of our study. Four weeks zinc free gap should suffice our purpose to create baseline

similar groups and this will avoid micronutrient supplementation being a confounding factor.

We excluded cases where we suspected any cardiac or chronic pulmonary condition as course of disease can be prolonged in these conditions and it may behave differently in individual cases. We also excluded children with other co-existing morbid condition (example: meningitis, heart disease, severe malnutrition, severe anemia, tuberculosis) as the course and duration of bronchopneumonia will be different in existence with these conditions. Children who required intubation and artificial ventilation were also not included for ethical reasons.

We excluded children who have received parenteral antibiotics in past 48 hours prior to admission for current illness as this would have not fulfilled our aim to study the effect of zinc as an adjunct to antibiotics. We also excluded children requiring hospitalization in previous 21 days for any illness, as this illness may be a progression of past illness or any nosocomially acquired infection and course and duration of pneumonia will be different in such a scenario. Children with complicated pneumonia (pneumothorax, empyema) were also excluded as these cases have different course and duration of illness.

Zinc deficiency is prevalent in developing countries because of inadequate dietary intake or poor absorption. Limited bioavailability of zinc from local diets and high incidence of diarrheal infections also predispose children to zinc deficiency. It is thought to be one of the ten greatest factors contributing to disease burden among children in developing countries (21-22). We were not able to obtain serum zinc level in our enrolled cases. However based on population based studies in infants from Delhi, it can be safely presumed that majority of our study population were also zinc deficient. Study by Sazawal et al showed that around 40% children are deficient in zinc (23). Another study by Bhandari et al conducted in Delhi showed one third of cases are deficient in zinc (24).

The subjects in both the groups (zinc versus placebo) were comparable in terms of baseline personal characteristics such as age (15.7 months versus 15 months), sex distribution (55% male versus 63% male), present weight (8.34 kg versus 8.26 kg), present length (73.55 cm versus 73.21 cm) and head circumference (43.78 cm versus 43.97 cm). There was no clinically significant difference in proportion of exclusively breast fed children (45% versus 28%) and fully immunized children (55% versus 63%) in both the study groups.

Baseline clinical parameters on enrollement were also similar in both the study groups. Mean respiratory rate at enrollment was 61.35 breaths/minute in zinc group compared to 61.7 breaths/minute in placebo group (p value = 0.66). Mean SpO2 at enrollment in zinc group was 88.8% and in placebo group was 89% (p value = 0.33). Wheeze was present in 42.5% children in zinc group and 50% children in placebo group (p value = 0.50). There was no clinical or statistically significant difference in presence of fever, poor feeding, irritability, cyanosis and altered sensorium.

Thus we ensured inclusion of a homogenous population, which should behave in almost similar manner to administration of the drug or placebo. The homogeneity also facilitated valid interpretation of the observation so that results obtained could be generalized.

Outcome comparisons

During the stay at hospital following variables were examined: duration of hospitalization, time to resolution of severe pneumonia, duration of lower chest indrawing, duration of fast breathing, time to start oral feeds, duration of oxygen therapy and intravenous fluids

Duration of hospitalization

In our study the mean (SD) duration of hospitalize-tion in zinc group was 137.23 (12.88) hours with median (IQR) of 137 (132, 143) hours. The mean (SD) duration of hospitalization in placebo group was 132.98 (13.92) hours with median (IQR) of 135 (124, 143.5). The two groups were comparable in terms of duration of hospitalization (*P*=0.16).

These findings are consistent with the studies done by other authors (15-17,19,25). In the study by Shah et al (15), the median (IQR) duration of hospitalization was 73.5 (49.5, 107.5) hours in zinc group and 72 (48.0, 87.7) hours in placebo group. The difference between the two groups was not significant (*P*=0.193). In the study conducted by Valentiner-Branth et al (16), the median (IQR) duration of hospitalization was 3 (3,4 days), and this did not differ between the zinc and placebo groups (HR: 1.1; 95% CI: 0.77-1.5). Bansal et al (17) found that the median (IQR) duration of hospital stay was similar in zinc and placebo groups (5(4,5.5) days and 5(3,6.5) days, *P*=0.63). In the study by Bose et al (19) the median (95% CI) duration of hospitalization was 71.1 (68.1, 87.3) hours in zinc group and 72.3 (67.7, 79.6) hours in placebo group. The difference between the two groups was not significant (*P*=0.55). Fataki et al [25] found that the median (IQR) duration of hospitalization was comparable between zinc (74.2

(67.3, 117.5) hours) and placebo group (68.5 (47.8, 99.5) hours), (*P*=0.089).

Our results are in contrast to the findings of Valavi et al [12] and Brooks et al (14). Valavi et al (12) found that the mean (SD) duration of hospital stay was 126.74 (12.8) hours in zinc group and 137.74 (11.52) hours in placebo group. The children who received zinc supplementation required a shorter hospital stay ($p < 0.001$), than did the controls. Brooks et al (14) found that the median duration of hospitalization was 112 hours in both zinc and placebo groups (Relative hazard = 0.75, 95% CI: 0.57-0.99). When wheezing children were omitted the median duration of hospitalization was 112 hours in zinc group and 128 hours in placebo group (Relative hazard = 0.67, 95% CI 0.47-0.94). The study showed a mean reduction of 1 day in the duration of hospitalization in the two groups which was statistically significant.

Time to resolution of severe pneumonia

In our study, time to resolution of severe pneumonia, was defined as the period starting from enrollment to the beginning of a 24-hour consecutive period of absence of lower chest indrawing, hypoxia, and any danger signs. The mean (SD) time taken for resolution of severe pneumonia in zinc group was 54.10 (8.77) hours and in placebo group was 53.83 (7.75) hours. Median (IQR) time taken for resolution of severe pneumonia in zinc group was 54 (48.75, 59.75) hours and in placebo group was 52.5 (48, 59.25) hours. The two groups were comparable in terms of time to resolution of severe pneumonia (*P*=0.88).

Similar results were found in many studies (15-17,19,26-28). Shah et al (15) defined severe pneumonia as per WHO guidelines. The primary outcome measures were decrease in duration of severe pneumonia and pneumonia. The median (IQR) duration of severe pneumonia was comparable between zinc (34.2 (21.0, 48.0) hours) and placebo (26 (16.0, 46.0) hours) group (*P*=0.219). The median (IQR) duration of pneumonia was 40 (24, 54.2) hours in zinc group and 43 (18.5, 72.0) hours in placebo group. The difference between the two groups was not significant (*P*=0.943).Valentiner-Branth et al (16) defined recovery from severe pneumonia as the beginning of the first 24 hour period without lower chest indrawing, without grunting and with no nasal flaring. The median time to recovery from severe pneumonia was 2 days for infants and 1 day for toddlers. There was no difference in time to recovery between the zinc and placebo groups (HR: 1.1; 95% CI: 0.77, 1.5). In the study by Bansal et al (17) the median (IQR) time taken to become asymptomatic was 60 (24,78) hours in zinc group and 54 (30,72) hours in placebo group. The difference between the two groups was not significant (*P*=0.98). In the study conducted by Bose et al (19) the primary clinical outcome was the time to resolution of severe pneumonia. Three definitions of severe pneumonia were taken to evaluate recovery: 1) respiratory rate >50 breaths/minute and oxygen saturation <93%; 2) inability to drink, respiratory rate >50 breaths/minute and oxygen saturation <93%; and 3) chest indrawing, respiratory rate >50 breaths/minute and oxygen saturation <93%. The study found that irrespective of the definition used there was no significant difference between the zinc and placebo groups in the time to recovery from severe pneumonia. In the study by Sempertegui et al (26) the criteria for clinical resolution of pneumonia were remission of tachypnea and hypoxemia for at least 12 hours. In children with chest wall indrawing at baseline, resolution also included absence of this sign for at least 12 hours. The mean (SD) time taken for resolution of two signs (tachypnea and hypoxemia) was 101.3 (75.5) hours in zinc group and 93.2(69.5) hours in placebo group. The mean (SD) time taken for resolution of three signs (tachypnea, hypoxemia and chest wall indrawing) was 102.6 (76.1) hours in zinc group and 93.9 (69.8) hours in placebo group. *P* values were non-significant for both the comparisons.

In the study conducted by Wadhwa et al (27), resolution of severe pneumonia was considered when breathing, chest indrawing fast, and crepitations on chest auscultation were no longer present. Resolution of very severe pneumonia was defined as absence of the above signs along with absence of general danger signs such as cyanosis, lethargy, inability to drink or convulsions. The median (IQR) time to recovery in children with severe or very severe pneumonia was 78.5 (59, 122) hours in zinc group and 77.0 (58, 117) hours in placebo group. The difference between the two groups was not significant (HR: 0.98; 95% CI: 0.82, 1.17). In the stratified analysis, zinc was shown to be efficacious in reducing the time to recovery in children with very severe pneumonia (HR:1.52; 95%CI: 1.03,2.23); however, the effect was no longer statistically significant after adjustment for differences in severely underweight children in the two groups.

In the study by Basnet et al (28), the primary outcome, time to cessation of severe pneumonia, was defined as the period starting from enrollment to the beginning of a 24 hour consecutive period of absence of lower chest indrawing, hypoxia, and any danger signs. Median (IQR) time to cessation of severe pneumonia was comparable between zinc (49 (33, 77) hours) and placebo (49 (29, 91) hours) group, (*P*=0.22).

Contrast results were found in other studies (12,14). In the study by Valavi et al (12) resolution of severe pneumonia was defined as absence of all symptoms such as fever, tachypnea, chest indrawing and inability to feed. The mean (SD) time taken for resolution of all symptoms was 42.26 (6.66) hours in zinc group and 47.52 (7.15) hours in placebo group. The difference between the two groups was significant (P<0.001). In the study conducted by Brooks et al (14) severe pneumonia was said to be resolved when there was no chest indrawing, respiratory rate was less than 50 breaths/minute, and oxygen saturation was at least 95% on room air. Median time to resolution of severe pneumonia was 72 hours in zinc group and 96 hours in placebo group. The difference was statistically significant (Relative hazard = 0.70, 95% CI 0.51-0.98). When wheezing children were omitted the median time to resolution of severe pneumonia was 84 hours in zinc group and 96 hours in placebo group. The difference between the two groups was significant (Relative hazard =0.61, 95% CI 0.40-0.92).

Time to resolution of lower chest indrawing

We found that the median (IQR) time taken for resolution of lower chest indrawing in zinc group was 54 (48.75, 59.75) hours with mean (SD) of 54.10 (8.77) hours. The median (IQR) time taken for resolution of lower chest indrawing in placebo group was 52.5 (48, 59.25) hours with mean (SD) of 53.83 (7.75) hours. The two groups were comparable in terms of time to resolution of lower chest indrawing, (P=0.88).

These finding are in agreement with earlier studies (19,25-26). Bose et al (19) found that the median (95% CI) time taken for resolution of lower chest indrawing similar in zinc and placebo groups (88.1 (71.5, 99.9) hours versus 84.3 (73.2, 97.2) hours, P=0.563).

Fataki et al (25) found that the median (IQR) time taken for resolution of lower chest indrawing was comparable between zinc (48.7 (24.6, 74.3) hours) and placebo (46.5 (26.9, 68.5) hours) group, (P=0.176). In the study by Sempertegui et al (26) the mean (SD) time taken for resolution of lower chest indrawing was 43.1 (41.1) hours in zinc group and 45.7 (49.4) hours in placebo group. The difference between the two groups was not significant.

Contrast results were found in the study by Brooks et al (14). The median time taken for resolution of lower chest indrawing was 40 hours in zinc group and 48 hours in placebo groups (Relative hazard = 0.80, 95% CI 0.61-1.05). When wheezing children were omitted the median time taken for resolution of lower chest indrawing was 48 hours in both zinc and placebo groups (Relative hazard =0.68, 95% CI 0.48-0.96). The difference between the two groups was significant.

Time to resolution of fast breathing

In our study the median (IQR) time taken for resolution of fast breathing in zinc group was 70.5 (61.5, 79) hours with mean (SD) of 69.65 (10.83) hours. The median (IQR) time taken for resolution of fast breathing in placebo group was 73 (68, 80) hours with mean (SD) of 73.73 (9.44) hours. The two groups were comparable in terms of time to resolution of fast breathing (P=0.08).

These results are consistent with the findings of several studies (17,19,25,26,29). In the study by Fataki et al (25), the median (IQR) time taken for resolution of fast breathing was comparable between zinc and placebo groups (47.3 (28.7, 86.9) hours versus 32.5 (23.7, 56.3) hours, P=0.071). Sempertegui et al (26) found that the mean (SD) time taken for resolution of fast breathing was 69.2 (68.5) hours in zinc group and 69.5 (61.9) hours in placebo group. The difference between the two groups was not significant. Srinivasan et al (29) found that the median (95%CI) time to normalization of respiratory rate was 96.0 (83.0, 109.0) hours in zinc group and 86.0 (75.4, 96.6) hours in placebo group. The difference between the two groups was not significant (Hazard ratio (95%CI) = 0.88 (0.69, 1.13), P=0,306).

Contrast result was found in the study by Brooks et al (14). The median time taken for resolution of fast breathing (respiratory rate >50) was 48 hours in zinc group and 56 hours in placebo groups (Relative hazard=0.74, 95% CI: 0.57-0.98). When wheezing children were omitted the median time taken for resolution of lower chest indrawing was 48 hours in zinc group and 56 hours in placebo group (Relative hazard=0.65, 95% CI: 0.46-0.92). The difference between the two groups was significant.

Time to resolution of inability to feed

We found that the median (IQR) time taken for resolution of inability to feed in zinc group was 32 (13.5, 40.5) hours with mean (SD) of 29.33 (16.54) hours. The median (IQR) time taken for resolution of inability to feed in placebo group was 21(11.5, 40) hours with mean (SD) of 26.00 (16.70) hours. The two groups were comparable in terms of time to resolution of inability to feed (P=0.37).

Only two other studies assessed the effect of adjuvant zinc therapy on time taken for resolution of inability to feed. In the study by Shah et al (15) the median (IQR) duration of nil per orally was comparable between zinc (10 (0.0, 23) hours) and placebo (12 (0.0, 18) hours) group, (P=0.771). Bose et al (19)

found that the median (95% CI) time taken for resolution of inability to feed was 71.5 (68.1, 88.0) hours in zinc group and 72.3 (69.0, 79.8) hours in placebo group. The difference between the two groups was not significant (*P*=0.511).

Duration of oxygen therapy

In our study oxygen was discontinued when oxygen saturation (SpO2) was ≥ 92% while breathing room air for more than 30 minutes, respiratory rate was < 70 breaths/minute and there was absence of severe lower chest indrawing, grunting and cyanosis. The median (IQR) duration of oxygen therapy in zinc group was 23 (11.5, 30.5) hours with mean (SD) of 22.63 (11.95) hours. The median (IQR) duration of oxygen therapy in placebo group was 19.5 (12.25, 25) hours with mean (SD) of 19.80 (8.99) hours. The two groups were comparable in terms of duration of oxygen therapy (*P*=0.24).

Only one study assessed the effect of adjuvant zinc therapy on duration of oxygen therapy. In the study by Shah et al [15] the median (IQR) duration of oxygen therapy was 10 (0.0, 22.0) hours in zinc group and 11.0 (0.0, 23.5) hours in placebo group. The difference between the two groups was not significant (*P*=0.684).

However other studies did assess the effect of adjuvant zinc therapy on time to resolution of hypoxemia. In the study conducted by Bansal et al (17), the median (IQR) time taken to achieve oxygen saturation (SpO2) > 95% in room air was similar in zinc and placebo groups (0 (0–7) hours and 0 (0–6.5) hours, *P*=0.73). Bose et al (19) defined hypoxia as oxygen saturation (SpO2) < 93% on room air. The median (95% CI) time taken for resolution of hypoxia was comparable between zinc (70.7 (65.5, 87.2) hours) and placebo group (72.3 (67.7, 76.2) hours), (*P*=0.575).

Sempertegui et al (26) defined hypoxemia as oxygen saturation of less than 90% on room air. The mean (SD) time to resolution of hypoxemia was 100.5 (75.5) hours in zinc group and 92.5 (69.5) hours in placebo group. The difference between the two groups was not significant (*P*=0.24). In the study by Srinivasan et al (29) normalization of oxygen saturation was regarded as oxygen saturation above 92% while breathing room air for more than 15 minutes, and maintaining above 92% on subsequent readings. The median (95% CI) time to normalization of oxygen saturation was 24.0 (20.6, 27.4) hours in zinc group and 18.0 (10.6, 25.4) hours in placebo group. The difference between the two groups was not significant (*P*=0.823).

Contrast results were found in the study by Brooks et al (14). Hypoxia was defined as oxygen saturation of < 95% on room air. The median duration of hypoxia was 80 hours in zinc group and 88 hours in the placebo groups (Relative hazard = 0.79, 95% CI 0.61-1.04). The difference between the two groups was significant.

Duration of intravenous fluid therapy

In the present study the median (IQR) duration of intravenous fluids in zinc group was 63(50, 70) hours with mean (SD) of 60.08 (12.18) hours. The median (IQR) duration of intravenous fluids in placebo group was 56.5 (51.5, 63.25) hours with mean (SD) of 57.43 (8.62) hours. The groups were comparable in terms of duration of intravenous fluids (*P*=0.27).

Only one study assessed the effect of adjuvant zinc therapy on duration of intravenous fluid therapy. In the study by Shah et al (15), the median (IQR) duration of intravenous fluid therapy was comparable between zinc and placebo group (22.0 (12.0, 31.0) hours versus 16 (1.5, 32.5) hours, *P*=0.258).

Results of our study showed that clinical resolution in both the groups was comparable in terms of median duration of hospitalization (137.23 hours versus 132.98 hours), duration of resolution of severe pneumonia (54.1 hours versus 53.83 hours), resolution of lower chest indrawing (54.1 hours versus 53.83 hours), resolution of fast breathing (69.65 hours versus 73.73 hours), time to start oral feeds (29.3 hours versus 26 hours), duration of intravenous fluid therapy (60.08 hours versus 57.43 hours) and duration of oxygen therapy (22.63 hours versus 19.80 hours). Thus there was no difference in the primary or secondary outcome variables between the zinc and placebo groups.

Several speculations can be made about these results: Were these children zinc deficient at all? Micronutrient stores are depleted more in malnourished children compared to well-nourished children and we excluded children with severe malnourishment. So it may be possible that the children included in our study were not zinc depleted. This is an important question which we were unable to answer as we did not measure the serum zinc levels in our study participants. The second plausible explanation is on the extreme other end of the spectrum; may be the zinc deficiency was so severe and the given dose of supplementation and duration of supplementation were probably not enough. A recent Cochrane review which concluded that zinc supplementation in children is associated with a reduction in the incidence and prevalence of pneumonia, included trials in which zinc supplements were administered for at least three months and

outcome surveillance was carried out for at least four weeks.[30] Due to logistic and financial barriers and limited time frame we were not able to plan such study.

Summary

- Out of total eligible children, 80 participants were randomized into two groups (*n*=40 each) as per a computer generated randomization chart to receive oral zinc or placebo.
- The primary outcome of interest was duration of hospitalization. The secondary outcome measured were time to resolution of severe pneumonia, time taken for normalization of lower chest indrawing, fast breathing and inability to feed, duration of oxygen therapy, duration of intravenous fluids and recurrence of pneumonia within 3 months of discharge.
- The subjects in both the groups (zinc versus placebo) were comparable in terms of baseline personal characteristics such as age (15.7 months versus 15 months), sex distribution (55% male versus 63% male), present weight (8.34 kg versus 8.26 kg), present height (73.55 cm versus 73.21 cm) and head circumference (43.78 cm versus 43.97 cm). There was no significant difference in proportion of exclusively breast fed children (45% versus 28%) and fully immunized children (55% versus 63%) in both the study groups.
- Baseline clinical parameters on enrollment were also similar in both the study groups. Mean duration of symptoms was 4.1 days in zinc group and 4.4 days in placebo group (*P*=0.34). Mean respiratory rate at enrollment was 61.35 breaths/minute in zinc group compared to 61.7 breaths/minute in placebo group (*P*=0.66). Mean SpO2 at enrollment in zinc group was 88.8% and in placebo group was 89% (*P*=0.33). Wheeze was present in 42.5% children in zinc group and 50% children in placebo group (*P*=0.50). There was no clinical or statistically significant difference in presence of fever, poor feeding, irritability, cyanosis and altered sensorium.
- No major adverse effects were noted. Only two children had vomiting immediately after giving the drug. One of them belonged to the zinc group while the other belonged to the placebo group.
- When children were classified in accordance with WHO criteria into ‘severe pneumonia’ and ‘very severe pneumonia’ 27 children (12 (30%) in zinc and 15 (37.5%) in placebo group) had severe pneumonia and 53 children (28 (70%) in zinc and 25 (62.5%) in placebo group) had very severe pneumonia. Proportion of children with severe pneumonia and very severe pneumonia was comparable in the two groups (*P*=0.48).
- The proportion of children who required second line antibiotics was comparable between zinc (27.5%) and placebo (32.5%) group, (*P*=0.63).
- Results of our study showed that clinical resolution in both the groups (zinc versus placebo) was comparable in terms of median duration of hospitalization (137.23 hours versus 132.98 hours), duration of resolution of severe pneumonia (54.1 hours versus 53.83 hours), resolution of lower chest indrawing (54.1 hours versus 53.83 hours), resolution of fast breathing (69.65 hours versus 73.73 hours), time to start oral feeds (29.3 hours versus 26 hours), duration of intravenous fluid therapy (60.08 hours versus 57.43 hours) and duration of oxygen therapy (22.63 hours versus 19.80 hours). Thus there was no difference in the primary or secondary outcome variables between the zinc and placebo groups.
- All children enrolled in the study completed 14 days of zinc and placebo treatment and none of them had any recurrence of pneumonia or any other reason of hospitalization within three months of discharge

Conclusions and Recommendations:

In this randomized controlled trial, conducted to study the efficacy of zinc supplementation, as an adjunct to antibiotics, in the treatment of severe pneumonia, we conclude that short term zinc supplementation, given during the course of illness does not shorten the duration of hospitalization in children aged 3 months to 5 years. Zinc supplementation also does not shorten the time to resolution of severe pneumonia, lower chest indrawing, fast breathing and inability to feed. Zinc supplementation also does not shorten the duration of oxygen therapy and intravenous fluid therapy.

Though our study did not show any beneficial effect of zinc in severe pneumonia there were certain limitations in our study which mandates a further research. Implications for future studies include study with a larger sample size and estimation of serum zinc levels to evaluate the baseline zinc status of study population. Additional research is also needed in specific subgroups such as children with very severe pneumonia with stratification for severely underweight. A longer duration of zinc supplementation and a long term follow up is

required to see the impact of zinc supplementation in prevention of recurrence of pneumonia.

Key Message

What is already known on this topic?

Zinc supplementation in treatment of severe pneumonia in children, aged 2 months to 60 months, demonstrated inconsistent results.

What this study adds:

Zinc therapy does not shorten the duration of severe pneumonia in hospitalized children aged 3 months to 5 years.

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