Original Article

DOI: 10.7860/JCDR/2018/37215.12277

Paediatrics Section

Effect of Zinc Supplementation in Children with Severe Pneumonia: A Randomised Controlled Study

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ABSTRACT

Introduction: Pneumonia is one of the leading cause of mortality among children under five years of age globally and responsible for 18 % of all deaths. Zinc is thought to help in decreasing the susceptibility to acute lower respiratory infections by regulating various immune functions.

Aim: To evaluate the effect of zinc supplementation on clinical resolution, duration of hospital stay and recurrence in next three months in children with severe pneumonia.

Materials and Methods: This was a randomised, double-blind, placebo-controlled trial done in the Department of Paediatrics of a tertiary care hospital, where in a total of 560 children, aged 2-60 months, admitted with the diagnosis of severe pneumonia {according to WHO case definition i.e., fever, cough, fast breathing (respiratory rate ≥50/minute in 2-12 month and ≥40/minute in 1-5 years of age) and lower chest indrawing}, between November 2013 to October 2015, were included in this study. Subjects were randomised blindly into zinc and placebo group in 1:1 ratio. Zinc or placebo supplementation was given (10 mg in 2-6 months and 20 mg in 7-60 months of age) orally daily once for two weeks, to each child according to randomisation. Outcome measures were calculation of time taken for clinical resolution of pneumonia, duration of hospital stay in completed days and counting the number of episodes of pneumonia in the next three months from the date of admission. Statistical analysis was done using Microsoft Excel 2007. Outcome measures were compared between zinc and placebo group by calculating p-value (p-value <0.05 was taken as significant), odds ratio and 95% confidence interval. Other variables were analysed by calculating mean, standard deviation and p-value.

Results: When compared among zinc group and placebo group, zinc group showed significant acceleration in clinical resolution of pneumonia (p=0.042) and reduction in the duration of hospital stay (p=0.035). However, zinc supplementation and recurrence of pneumonia showed no significant association (p=0.52).

Conclusion: Zinc supplementation can be considered in the treatment of severe pneumonia in children to accelerate the clinical resolution and thereby to reduce the hospital stay. However, zinc supplementation has no role in the prevention of pneumonia in next three months.

Keywords: Adjuvant, Child, Pneumonia, Zinc

INTRODUCTION

Every year, an estimated 1.4 million children under the age of five years die because of pneumonia, accounting for 18% of all deaths of children under five-year-old worldwide [1]. Zinc regulates various immune functions and protects the health and integrity of the respiratory cells during lung inflammation or injury; thus decreasing susceptibility to acute lower respiratory infections [2]. IAP National Task Force recommended zinc for the treatment of acute diarrhoea [3]. Consensus as to whether zinc supplementation provides a similar therapeutic benefit to children with severe pneumonia has not yet been established [4]. Many studies were done by different authors [4-11] on zinc supplementation in severe pneumonia in children but the results of this supplementation on recovery from pneumonia or on the duration of hospital stay were conflicting. Some studies found no role of zinc in clinical recovery and reduction of hospital stay in children with pneumonia [4,5,8-10] while others stated that zinc supplementation enhanced the recovery from severe pneumonia and reduced the duration of hospital stay [6,7]. One meta-analysis concluded that zinc supplementation in children was associated with a reduction in the incidence and prevalence of pneumonia [11] while others showed no effect either in treatment or in prevention [12,13].

Since, there is no consensus about the role of zinc in the treatment of pneumonia, this study was conducted with the aim of evaluating the effect of zinc supplementation given to the children, admitted for severe pneumonia, along with the standard antimicrobial therapy, daily for 14 days, on the time taken for clinical resolution of pneumonia, on duration of hospital stay and on the recurrence of pneumonia in the next three months, with the hypothesis that zinc supplementation in children with severe pneumonia accelerates recovery, reduces duration of hospital stay and prevents recurrence in the next three months.

MATERIALS AND METHODS

This was a randomised double-blind placebo-controlled study (CTRI/2012/11/003105) conducted in the Department of Paediatrics of a tertiary care centre of Assam in North East India, from November 2013 to October 2015. Children aged 2-60 months admitted with the diagnosis of severe pneumonia {according to WHO case definition of severe pneumonia i.e., fever, cough and fast breathing (respiratory rate ≥50/minute in 2-12 month and ≥40/minute in 1-5 years of age) and lower chest indrawing} [14] were included in this study.

A total of 560 children, after fulfilling the inclusion and exclusion criteria, were randomised into zinc group and placebo group with 280 children in each arm i.e., in 1:1 ratio. Children with very severe pneumonia (according to WHO case definition) [14], severe acute malnutrition, tuberculosis (of any system), congenital heart disease, present episode with allergic disease or asthma, history of intake of zinc in the past three months, associated with diarrhea and those not giving consent for participation, were excluded. Children who were not able to take medication orally were excluded.

The sample size was calculated to detect a minimum of 25% reduction in time taken for clinical resolution of severe pneumonia between two treatment groups. Average time taken for clinical resolution of severe pneumonia was taken as five days. The figure assumes 80% power and a 2-sided Type 1 error of 5%.

After enrolling, the children were assessed for eligibility and after taking parental informed consent they were assigned for intervention. Ethical Clearance from the Institutional Ethics Committee was obtained to conduct this study. Standard Operating Procedures (SOP) like whom to contact for enrollment whenever a resident admits a child with severe pneumonia, how to enrol the children for the study etc., were kept both in the OPD and emergency room of the department for the knowledge of the residents. After inclusion into the study, a detailed history was taken from each child (with parent) and recorded in a predesigned proforma. General examination and systemic examination findings were recorded. Blood samples were taken for serum zinc estimation, routine blood examination, CRP and serum total protein and fraction. Other investigations done were Chest X-ray, throat swab culture and sensitivity. Serum zinc estimations were done by the colorimetric method in the Department of Biochemistry by an automated auto-analyser.

Zinc or placebo-supplementation was given as 10 mg (2.5 mL) in 2-6 months and 20 mg (5 mL) in 7-60 months of age orally once daily for two weeks (as recommended by IAP national task force for treatment of diarrhoea) to the children according to the randomisation [3].

Random numbers were generated from www.randomiser.org. The allocation sequence was done by an office assistant in the department who is not related to the study and that was kept in an almirah under lock and key till the end of the study. Zinc was given as Zn 20 syrup (zinc gluconate) manufactured by Wallace Pharmaceuticals Ltd., containing 20 mg of elemental zinc per 5 mL. Placebo was prepared by the same company without the zinc molecule. Both preparations were indistinguishable from one another in colour, consistency and taste, and packed in brown coloured 100 mL bottles. Bottles were again covered with brown paper and sequentially numbered from 1 to 560. The residents enrolled the participants according to SOP. The project staff assigned the participants to interventions. Both the patients, caregivers and investigator/project staff were blinded to the intervention till the end of the study.

The First dose of zinc/placebo was started within 24 hours of admission. Doses of zinc/placebo were repeated if the child vomited the dose. Each patient was monitored daily for intervention by the project staff and 12 hourly for clinical parameters i.e., presence of fever, chest indrawing and respiratory rate by the resident staffs under the supervision of investigators and recorded. All the patients were given Amoxycillin and Clavulanic acid combination as the first line antibiotic and changed to 3rd generation Cephalosporins if there was deterioration.

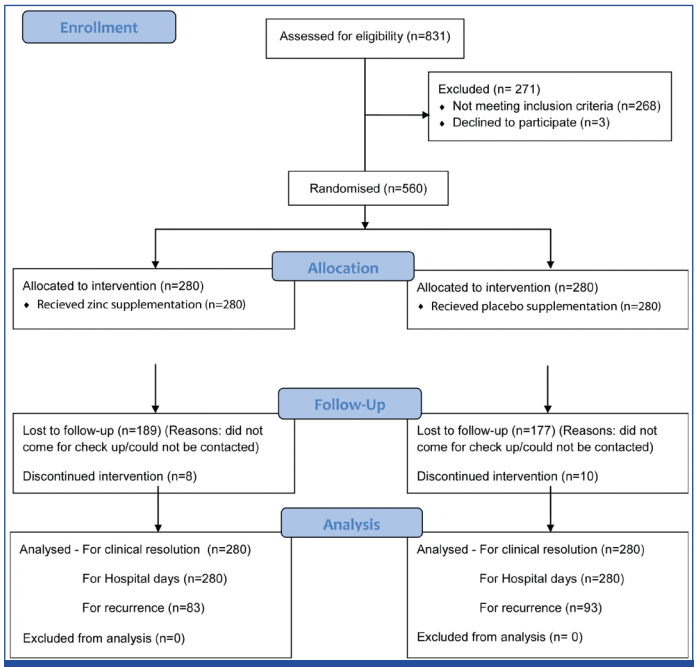
Outcome measures were clinical resolution of pneumonia, duration of hospital stay in completed days and recurrence of pneumonia in the next three months (from the date of admission). Clinical resolution of pneumonia was defined as no fever, no chest indrawing and respiratory rate <50/minute in 2-12 months and <40/minute in 1-5 years of age. After discharge, they were asked to come for check up after two weeks and were then followed up every 2-4 weekly, till three months from the date of admission, for further episodes of pneumonia. Patients were contacted over phone to know about any episode of pneumonia, if they did not turn up for check-ups. At three month follow-up visit, blood samples were taken for second serum zinc estimation.

STATISTICAL ANALYSIS

Statistical analysis was done using Microsoft Excel 2007. Outcome measures were compared between zinc and placebo group by calculating p-value (p-value <0.05 was taken as significant), the odds ratio and 95% confidence interval. Other variables were analysed by calculating mean, standard deviation and p-value.

RESULTS

A total of 831 children with severe pneumonia were enrolled and 560 children were included in the study after fulfilling the inclusion and exclusion criteria. A total of 280 children received zinc suspension (cases) and 280 children received placebo suspension (controls) as allocated [Table/Fig-1]. Baseline variables like age and sex were comparable between two groups (p-value 0.52 and 0.29 respectively) [Table/Fig-2]. Majority of the children (79.6%) were between 2 to 12 months [Table/Fig-3].



[Table/Fig-1]: Consort flow diagram of the study.

Variables	Zinc (n=280)	Placebo (n=280)	p-value
Mean Age in months (SD)	9.3 (9.9)	9.8 (9.5)	0.52
Sex			
Male (n=358)	185 (66.1%)	173 (61.8%)	0.29
Female (n=202)	95 (33.9%)	107 (38.2%)	
Mean initial serum zinc level in ug/dL (SD) (n=560)	139.5 (47.9) (n=280)	139.3 (66.2) (n=280)	0.98

[Table/Fig-2]: Age, sex and serum zinc levels in zinc and placebo group.

Age	2mo-12mo	13mo-24mo	25mo-60mo	Total
Number of cases (%)	446 (79.6%)	84 (15%)	30 (5.4%)	560

[Table/Fig-3]: Age distribution of the children.

There was no significant difference between the mean serum zinc levels of zinc and placebo group (p=0.98) [Table/Fig-2]. Serum zinc estimation at three months after admission was done in 55 children in zinc supplementation group and in 67 children of the placebo group. Mean serum zinc levels of zinc and placebo group taken at three months after admission were 137.6 µg/dL±76.4 and 137.3 µg/dL±41.9 respectively (p=0.97). So there was no significant difference between serum zinc levels of the two groups at three months after admission as well.

Taking zinc supplementation as the exposure variable and different recovery times as outcome variables, the logistic regression revealed that zinc supplementation significantly accelerated clinical resolution, as in 24.6% controls and 32.5% cases clinical resolution occurred in less than three days; and in 75.4% controls and 67.5% cases clinical resolution occurred in ≥3 days, with p-value of 0.04 and 95% CI of 0.68 (0.47-0.98). Zinc supplementation significantly reduced the duration of hospital stay also, as 45.4% controls and 54.3% cases were discharged in five days and 54.6% controls and 45.7% cases were discharged in more than five days, with a p-value of 0.035 and 95% CI of 0.70 (0.50-0.97). Recurrence of pneumonia was observed in 15.7% controls and 19.4% cases and no recurrence in 84.3% controls and 80.6% cases (p=0.52) [Table/Fig-4]. So zinc supplementation and recurrence of the disease showed no significant association.

Outcome measures	Categories		p-value	Unadj OR (95% CI)
Time for clinical resolution of Pneumonia	<3 days	≥3 days		
Placebo (n=280)	69 (24.6%)	211 (75.4%)	0.040	1
Zinc (n=280)	91 (32.5%)	189 (67.5%)		0.68 (0.47-0.98)
Hospital stay (day)	upto 5 days	>5 days		
Placebo (n=280)	127 (45.4%)	153 (54.6%)	0.035	1
Zinc (n=280)	152 (54.3%)	128 (45.7%)		0.70 (0.50-0.97)
Recurrence of pneumonia in next three months	No	Yes		
Placebo (n=83)	70 (84.3%)	13 (15.7%)	0.52	
Zinc (n=93)	75 (80.6%)	18 (19.4%)		

[Table/Fig-4]: Showing effect of zinc supplementation on outcome measures like clinical resolution, hospital stay and recurrence of pneumonia in next 3 months.

Eight children vomited after taking the first dose of zinc but accepted subsequently. No other side effects of zinc were observed in the present study.

DISCUSSION

In this randomised controlled trial, authors studied the effects of zinc supplementation in children with severe pneumonia on time taken for clinical resolution, duration of hospital stay and recurrence of pneumonia within three months of admission. Authors found that, zinc supplementation significantly accelerated clinical resolution of pneumonia in comparison to the placebo group (p=0.04) which was in accordance with some previous studies [6,7,10]. However, Bose A et al., and Shah GS et al., found no statistically significant reduction in the duration of severe pneumonia in children while giving zinc supplementation along with standard antimicrobial therapy [4,8]. In the study done by Shah GS et al., zinc-supplementation was given as 10 mg daily to all the children from two months to five years age which may not be sufficient for the required effect.

Duration of hospital stay was found to be significantly reduced in the zinc-supplemented group in comparison to the placebo group which was similar to other studies [6,7]. But Bose A et al., Shah GS et al., and Chang AB et al., found no effect of zinc supplementation on reducing the duration of hospital stay [4,8,9]. However, zinc supplementation and recurrence of pneumonia in next three months showed no significant association in this study. A similar result was seen by Chandyo RK et al., where it was stated that zinc supplementation does not reduce the incidence of pneumonia in the next six months [15]. Mathew JL et al., also found no role of zinc both in treatment and prevention of pneumonia in children [13], though Lassi ZS et al., stated that zinc supplementation in children was associated with a reduction in the incidence and prevalence of pneumonia [11]. Sakulchit T et al., stated in their meta-analysis that zinc-supplementation for longer than three months in children younger than five years of age was effective in preventing pneumonia and evidence related to supplementation for less than three months duration is not as strong [12]. In the present study, zinc-supplementation was given for two weeks only, which may be the reason for no effect of zinc supplementation in prevention of pneumonia episodes in near future.

Age and sex were comparable between two groups. In present study, out of total 560 children, 79.6% were between two months to 12 months of age, indicating that occurrence of severe pneumonia was highest during infancy (excluding neonatal period) contributing more than 70-80% of the pneumonia cases occurring in under 5 children.

No significant differences were observed in mean serum zinc levels between two groups at the initial enrollment as well as at three months after admission. Bose A et al., showed an increase in serum zinc level after giving zinc for two weeks but they did not specify the time of zinc estimation [4]. Yuan X et al., stated that serum zinc level increased in the zinc treatment group and returned to normal level on day 12±2 [5]. They also did not mention on which day serum zinc level was estimated. In the present study, there was no increase in serum zinc level in zinc group at three months after admission i.e., two and a half months after supplementation. So it can be opined that zinc supplementation given for two weeks may not be sufficient to sustain the increase in serum zinc level after two and a half months.

LIMITATION

Authors could not assess recurrence and estimate serum zinc level at three months, in all the children due to loss to follow-up, in spite of taking various measures. Hence, reduced sample size, might have affected present results on recurrence of pneumonia and serum zinc levels at three months.

CONCLUSION

It can be concluded from present study that zinc supplementation can be considered in the treatment of children suffering from severe pneumonia, along with standard antimicrobial therapy and supportive management, as it accelerates the time for clinical resolution as well as decreases the duration of hospital stay.

ACKNOWLEDGEMENTS

Authors are grateful to the Head of the Department of Paediatrics for allowing authors to conduct the study and to the Head of the Department of Biochemistry for allowing authors to do the serum zinc estimation in their Department and Wallace Pharmaceuticals Ltd for supplying the placebo free of cost. Authors are thankful to the Indian Council of Medical Research, for funding the present project.

Funding: Indian Council of Medical Research

CTRI registration no: CTRI/2012/11/003105

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FINANCIAL OR OTHER COMPETING INTERESTS: As declared above.

Date of Submission: **Jun 06, 2018**
Date of Peer Review: **Jul 23, 2018**
Date of Acceptance: **Aug 29, 2018**
Date of Publishing: **Nov 01, 2018**