Original Article

Zinc as an Adjuvant Therapy in Treating Pneumonia in Under Five Hospitalized Children

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Abstract

Pneumonia is a leading cause of illness and death in children < 5 yrs of age. Zinc may have role in treatment of pneumonia as it contributes to the body immunity. This study was aimed to find out the use of zinc as an adjuvant therapy in treating pneumonia in under five hospitalized children. This interventional study was conducted in the Department of Paediatrics, Institute of Child and Mother Health, Matuail, Dhaka from July 2020 to June 2021. A total 60 children of 2 months to 5 years of age with pneumonia were included in the study. All patient was randomized into two groups, Group A (Experimental group) children got zinc with antibiotics and Group B (control group) children got only antibiotics until discharge. The zinc recipients showed early resolution of symptoms and signs. Among the signs chest indrawing resolved significantly faster in experimental group (P=0.019), other signs including fast breathing, restlessness, crepitation also resolved early in experimental group in comparison to control group but not significant. The findings of this study might be beneficial among the physician involving in treating pneumonia.

Key words: *Pneumonia, Zinc.*

Introduction

Pneumonia, defined as an inflammation of the lung parenchyma, is the leading infectious cause of death among children younger than 5 year, accounting for an estimated 920,000 death globally per year. Mortality due to pneumonia is closely linked to poverty. More than 99% of pneumonia deaths are in low and middle-income countries, with the highest pneumonia mortality rate occurring in poorly developed countries in Africa and South Asia[1]. In Bangladesh, pneumonia is responsible for around 28% of the deaths of children under five years of age. Around 50,000 children die of pneumonia every year [2].

Zinc affects multiple aspects of the immune system. It is crucial for normal development and function of cells mediating innate immunity, neutrophils, and natural killer cells. Macrophages are also affected by zinc deficiency. Phagocytosis, intracellular killing and cytokine production all are affected by zinc deficiency. Its deficiency also 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 [3].

In a meta analysis of clinical trials evaluating the preventive role of zinc, it was suggested that a daily supplementation of zinc led to 14% and 8% reductions in the risk of diarrhea and pneumonia respectively [4]. The World Health Organization (WHO) 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 diarrhoeal episode [6]. The benefit of zinc in the treatment of pneumonia is however unclear, but its role in cellular growth and immune defence is well established and its deficiency is associated with increased susceptibility to various infectious pathogens [7]. To establish the beneficial role of zinc, we therefore intended to perform this RCT .

Materials and Methods

This research was Randomized controlled trial (RCT). The study was carried out at Department of Pediatrics, Institute of Child and Mother Health (ICMH), Matuail, Dhaka-1362 and the period was from July, 2020 to June, 2021. 60 Children of 2 months to 5 years of age with clinically diagnosed pneumonia admitted in the pediatric ward was enrolled in this study.

Inclusion criteria:

i. Age: 2 months to 5 years
ii. Fast breathing (50 per minute or more if infant 2 months up to 12 months; 40 per minute or more if child 12 months up to 5 years) and or
iii. Chest indrawing.

Exclusion criteria:

i. Congenital heart disease having murmur.
ii. Severe anemia (defined as hemoglobin <7 gm/dL).
iii. Concurrent diarrhea receiving zinc therapy.
iv. Tuberculosis in any form including pulmonary tuberculosis.
v. Those who receiving zinc therapy in last 15 days.

60 patients who meet the criteria were randomly allocated into two group. Randomization was done by purposive sampling method by lottery.

I) Group A (Experimental group)

This group was consist of 30 patients, of children under 5 with pneumonia who were got zinc (10 mg in 2 to 11 months old and 20 mg in older children) along with antibiotic (inj. Ampicillin 200 mg/kg/day every 6 hours) until discharged.

II) Group B (Control group)

This group was consist of 30 patients, of children under 5 with pneumonia who got only antibiotic (inj. Ampicillin 200 mg/kg/day every 6 hours) therapy until discharged.

Children with clinically diagnosed pneumonia, aged between two months to five years who were admitted in inpatient department (IPD), ICMH were enrolled after fulfill the inclusion criteria.Informed written consent was taken from every parents. After selection of pneumonia cases a thorough history was taken clinical examination was done and recorded on the questionnaire then investigations was done. After that all patient were randomized into two groups. Group A and group B by lottery method. Group A (Experimental group) children got zinc (10 mg in 2 to 11 months old and 20 mg in older children) along with antibiotic (inj. Ampicillin 200 mg/kg/day every 6 hours) and group B

(Control group) children got only antibiotic (inj. Ampicillin 200 mg/kg/day every 6 hours) therapy until discharge.Data on respiratory rate, chest indrawing, auscultation finding (crepitations), fever, general well being and oxygen saturation was obtained at admission and every 12 hourly follow up by trained physician on a structured sheet.The day of recovery from severe pneumonia was defined as the beginning of the first 24 hour period without lower chest indrawing. Patients who failed to improve after 48 hours of antibiotics or whose condition became worse(fast breathing, high grade fever and feeding difficulty persist) their antibiotic was changed to ceftriaxone (50 mg/kg/day I/V every 12-24 hours).Treatment failure, was defined as a requirement for change in antibiotics, development of complications such as pleural effusion, empyema or pneumothorax requiring surgical intervention or admission to the ICU for ventilator or ionotropic support. Children was discharged from hospital once respiratory rate was fall to less than 50 per min (2-12 months) and less than 40 per min (12 months to 5 years) for 24 consecutive hours with no recurrence of respiratory distress, other danger signs or fever. Duration of clinical symptoms and signs of pneumonia and duration of hospital stay, duration of I/V fluid and duration of oxygen therapy was compared in both groups.

Although oral zinc supplementation was well tolerate, zinc can cause gastrointestinal symptoms, including nausea,vomiting,diarrhoea. Oral zinc supplementation is safe in children when used in dosages 10 mg in 2 to 11 months old and 20 mg in older children.

Descriptive analytical techniques including percentage, mean, SD etc were used. Chi square test was used for categorical variables. Unpaired t-test was used for continuous variables. P-value <0.05 was considered significant.

Results

This was a randomized controlled trial (RCT) study conducted in the Department of Paediatrics, ICMH, Matuail, Dhaka during the period of July 2020 to June 2021. A total 60 children of 2 months to 5 years of age with pneumonia were included in this study. After that all patients were randomized into two groups. Group A and group B by lottery method. Group A (Experimental group) children got zinc (10 mg in 2 to 11 months old and 20 mg in older children) along with antibiotic and group B children (Control group) got only antibiotic therapy until discharge. The results were as follows:

Table I: Baseline Distribution of the study patients by clinical variables (n=60)

Clinical variables	Experimental group (n=30)		Control Group (n=30)		P value
	n	%	n	%	
Fever	30	100	30	100.0	-
Cough	30	100.0	30	100.0	-
Feeding difficulty	21	70.0	23	76.7	0.559
Sleeping difficulty	21	70.0	23	76.7	0.559
Fast breathing	30	100.0	30	100.0	-
Chest indrawing	30	100.0	28	93.3	0.150
Restlessness	25	83.3	21	76.7	0.221
Crepitation	30	100.0	30	100.0	-

P value reached from Chi square test

Table I showed that all patients had fever, cough, fast breathing, crepitation in both groups. Feeding difficulty was 21(70.0%) in experimental group and 23(76.7%) in control group. Sleeping difficulty was 21(70.0%) and 23(76.7%) in experimental and control group respectively. Chest indrawing was 30(100.0%) in experimental group and 28(93.3%) in control group. Restlessness was found 25(83.3%) in experimental group and 21(76.7%) in control group. The difference was not statistically significant (p>0.05) between two groups.

From admission to discharge every day two times follow up was given. Morning follow up was given at 10 am and night follow up was given at 10 pm. Fever was measured by recording axillary temperature other symptoms were measured on the basis of mothers opinion. All data were recorded in a structured questionnaire. Finally mean comparison of resolution of symptoms of pneumonia were done between two study groups.

Table II: Resolution of symptoms (mean hours) in experimental and control group

Resolution of symptoms	Total n	Study group			P value
		Experimental group Mean ±SD	Total n	Control Group Mean ±SD	
Duration of fever (hrs)	30	88.8(±30.5)	30	92.8(±26.7)	0.590
Duration of cough (hrs)	30	100.4(±29.3)	30	104.4(±26.9)	0.583
Duration of sleeping difficulty (hrs)	21	50.1(±25.7)	23	53.7(±27.0)	0.652
Duration of feeding difficulty (hrs)	21	55.4(±18.8)	21	59.4(±22.6)	0.536

P value reached from unpaired t-test

Table II showed that regarding resolution of symptoms, mean duration of fever 88.8(±30.5) hours in experimental group and 92.8(±26.7) hours in control groups, mean duration of cough 100.4(±29.3) hours in experimental group and 104.4(±26.9) hours in control groups, mean duration of sleeping difficulty 50.1(±25.7) hours in experimental group and 53.7(±27.0) hours in control groups, mean duration of feeding difficulty 55.4(±18.8) hours in experimental group and 59.4(±22.6) hours in control groups. That difference was not statistically significant but less duration of symptoms was found in experimental group in comparison to controls.

From admission to discharge every day two times signs of pneumonia were evaluated. Morning evaluation was done at 10 am and night evaluation at 10 pm. Fast breathing, chest indrawing and crepitation on auscultation of lung were evaluated by clinical observation, restlessness was evaluated on the basis of mothers opinion and recorded in a structured questionnaire. Finally mean comparison of resolution of signs of pneumonia were done between two study groups.

Table III: Resolution of signs (mean hours) in experimental and control group

Resolution of signs	Total n	Study group			P value
		Experimental group Mean ±SD	Total n	Control Group Mean ±SD	
Duration of fast breathing (hrs)	30	84.4(±31.8)	29	93.1(±32.6)	0.303
Duration of chest indrawing (hrs)	30	54.0(±24.7)	28	72.8(±34.1)	**0.019**
Duration of restlessness (hrs)	23	47.0(±16.1)	21	48.0 ±(22.4))	0.864
Duration of c repitation (hrs)	30	77.2(±24.1)	29	81.1(±29.5)	0.579

P value reached from unpaired t-test

Table III showed that regarding resolution of signs, mean duration of fast breathing (hrs) 84.4(±31.8) hours in experimental group and 93.1(±32.6) hours in control groups, mean duration of chest indrawing 54.0(±24.7) hours in experimental group and 72.8(±34.1) hours in control groups ($p<0.05$) that was statistically significant. The mean duration of restlessness 47.0(±16.1) hours in experimental group and 48.0±(22.4) hours in control groups, mean duration of crepitation 77.2(±24.1) hours in experimental group and 81.1(±29.5) hours in control groups.

Duration of chest indrawing was significantly less in experimental group in comparison to controls, other signs were not statistically significant but less duration was found in experimental group in comparison to controls.

Discussion.

This study showed, regarding resolution of symptoms, mean duration of fever 88.8(±30.5) hours in experimental group and 92.8(±26.7) hours in control groups, mean duration of cough 100.4(±29.3) hours in experimental group and 104.4(±26.9) hours in control groups, mean duration of sleeping difficulty 50.1(±25.7) hours in experimental group and 53.7(±27.0) hours in control groups, mean duration of feeding difficulty 55.4(±18.8) hours in experimental group and 59.4(±22.6) hours in control groups. The difference was not statistically significant but less duration was found in experimental group in comparison to controls.

This study observed regarding resolution of signs, mean duration of fast breathing 84.4(±31.8) hours in experimental group and 93.1(±32.6) hours in control groups, mean duration of chest indrawing 54.0(±24.7) hours in experimental group and 72.8(±34.1) hours in control groups ($p<0.05$) that was statistically significant, the mean duration of restlessness 47.0(±16.1) hours in experimental group and 48.0±(22.4) hours in control groups, mean duration of crepitation 77.2(±24.1) hours in experimental group and 81.1(±29.5) hours in control groups. Duration of chest indrawing was significantly less in experimental group in comparison to controls, other signs were not statistically significant but overall less duration of signs was found in experimental group in comparison to controls.

Qasemzadeh MJ, Fathi M, Tashvighi M et al.[8] reported that compared to the comparison group, a significant decrease was found in the recovery from pneumonia symptoms in zinc receiving children. This result was consistent with the results of current study.

Brooks WA, Yunus M, Santosham M et al.[9] showed that prescription of zinc in 2 to 23-month children suffering from severe pneumonia leads to significant reduction in the severity of fast breathing, feeding difficulty, restlessness. A similar study in India done by Coles CL, Bose A, Mose PD et al.[10] on 299 children aged 2–23months and hospitalized due to severe pneumonia showed that, compared to the comparison group, disease symptoms were improved faster significantly in the zinc-receiving patients. Both the studies showed similar result with the precent study.

Another study in India conducted by Mahalanabis D, Lahiri M, Paul D et al.[11] on 153 children aged 2–24 months, hospitalized due to acute lower respiratory infection were divided into two groups (one taking 10mg of zinc plus vitamin A daily and the other taking placebo plus vitamin A). It was shown that the recovery time was significantly faster in the treatment group than in the control group. Overall, zinc therapy can reduce the duration of symptoms and acute clinical condition. This finding was consistent with the findings of our study.

In contrast Valentiner-Branth P, Shrestha PS, Chandyo RK et al.[12] observed adjuvant zinc neither reduced the risk of treatment failure nor hasten the recovery from non-severe or severe pneumonia in Nepalese children in the age group of 2-35 months of age.

Basnet S, Shrestha PS, Sharma A et al.[13] observed a modest but not statistically significant effect of daily zinc administration in reducing time to cessation of severe pneumonia defined as a 24-hour consecutive period of absence of lower chest indrawing, hypoxia, and any other danger sign.

Conclusion

Zinc as an adjuvant therapy in treating pneumonia in under five hospitalized children reduced the duration of clinical symptoms and signs of pneumonia. The findings of this study might be beneficial among the physician involving in treating pneumonia.

References

1. Kliegman RM, Geme ST, Blum NJ, Shah SS, Tasker RC and Wilson KM. Nelson, Textook of Pediatrics. 21st edition. Elsevier. 2020:2266

2. Lozano R, Naghabi M, Foreman K, Lim S, Shibuya K, Aboyans V et al. Global and regional mortality from 235 causes of death for 20 age groups in 1990 and 2010: a systematic analysis for the Global Burden of diseases study 2010.Lancet. 2012; 380(9859):2095-2128.

3. Prasad AS. Zinc in human health: effect of zinc on immune cells.Molecular Medicine. 2008;*14*(5) :353-357.

4. Aggarwal R, Sentz J and Miller MA et al. Role of zinc administration in prevention of childhood diarrhea and respiratory illnesses: a meta-analysis.Paediatrics. 2007; *119*(6):1120-1130.

5. World Health Organisation(WHO); United nations children's fund; Johns Hopkins Bloomberg school of public health; USAID. Implementing the new recommendations on the clinical management of Diarrhoea. Guidelines for policy makers and programme Manegers.Geneva, Switzerland:World Health Organisation, 2006.

6. Fontaine O. Effect of zinc supplementation on clinical course of acute diarrhoea.Journal of Health, Population and Nutrition. 2001; *19*(4):339-346.

7. Basnet S, Mathisen M and Strand TA. Oral zinc and common childhood infections- An update.Journal Of Trace Elements In Medicine and Biology. 2015; 31(2015):163-166.

8. Qasemzadeh MJ, Fathi M, Tashvighi M, Gharehbeglou M, Yadollah-Damavandi S, Parsa Y

et al . The effect of adjuvant zinc therapy on recovery from pneumonia in hospitalized children: a double-blind randomized controlled trial. Scientifica. *2014*:1-4.

9. Brooks WA,Yunus M, Santosham M, Wahed MA, Nahar K, Yeasmin S et al. Zinc for severe pneumonia in very young children: double-blind placebo-controlled trial.Lancet. 2004;363(9422) :1683-1688.

10. Coles CL, Bose A, Mose PD, Mathew L, Agarwal I, Mammen T et al. Infectious etiology modifies the treatment effect of zinc in severe pneumonia.The American Journal of Clinical Nutrition. 2007; *86*(2) :397-403.

11. Mahalanabis D, Lahiri M, Paul D, Gupta S, Gupta A, Wahed MA. et al. Randomized, double-blind, placebo-controlled clinical trial of the efficacy of treatment with zinc or vitamin A in infants and young children with severe acute lower respiratory infection.The American journal Of clinical Nutrition. 2004;*79*(3):430-436.

12. Valentiner-Branth P, Shrestha PS, Chandyo RK, Mathisen M, Basnet S, Bhandari N, Adhikari RK et al. A randomized controlled trial of the effect of zinc as adjuvant therapy in children 2–35 mo of age with severe or nonsevere pneumonia in Bhaktapur, Nepal.The American Journal Of Clinical nutrition.2010; *91*(6):1667-1674.

13. Basnet S, Shrestha PS, Sharma A, Mathisen M, Prasai R, Bhandari N et al. A randomized controlled trial of zinc as adjuvant therapy for severe pneumonia in young children.Paediatrics. *2012; 129(4):701-708*