

Effect of Zinc as an adjunct to antibiotic on the duration of hospitalization of sever pneumonia patients among 6-59 months of children in Debretabor General Hospital, Amhara, Ethiopia

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Abstract

Introduction: Zinc deficiency is an important driver of mal nutrition in children under 5 years of age and is associated with stunting, lower respiratory tract infections and diarrhea. Pneumonia is the most common causes of death for children in low-income countries. Studies evaluating the impact of zinc supplementation as an adjunct in the management of pneumonia are limited. In Ethiopia, pneumonia is the leading cause of child mortality, which accounts 17% of all under five mortality.

Objective: To determine the effect of Zinc as an adjunct to antibiotic on the duration of Hospitalization of sever pneumonia among 6-59 months of Children in Debretabor General Hospital.

Methods:total sample size were 152 young both experimental and placebo groups, 50% of children visiting the hospital was taken as sample size, Double-blinded, randomized, placebo-controlled trial study was conducted at Debretaboar General Hospital, Northwest Ethiopia 2017. The follow up and data collection were taken February 1 to May 1, 2017. The treatment and the control groups were received Zinc tablet and placebo from the enrolment till to discharge time. SPSS version 22 statistical package was used for analysis.

Result: The mean day duration of hospitalization in zinc treated group 3.4(1.17) is significantly shorter than placebo groups 4(1.27). Median (IQR) time taken for resolution of severe pneumonia in zinc group was 52(32, 64) hours and in placebo control group was 56(48, 72) hours. The two groups were comparable in terms of time to resolution of severe pneumonia ($p = 0.047$). The mean (SD) time taken for resolution of severe pneumonia in zinc group was 52.6(24.5) hours and in placebo group was 61.4(26.7) hours.

Conclusion: In this study, zinc supplementation as adjunct to standard antibiotic shortens the median duration of hospital stay, and duration of resolution of severe pneumonia sign symptoms.

Key words: Zinc, pneumonia, placebo control, randomized control and duration

Introduction

Pneumonia is the leading infectious cause of hospitalization and death in the world which results an enormous cost in economic and human terms. In 2015, 5.9 million children died before reaching their fifth birthday that's more than 2500 per day (Muhammed et al. 2015). Approximately, 95% of the pneumonia related deaths occur in the developing countries and children less than 2 years of age have the highest risk of death. In sub-Saharan Africa, 1 child in 12 dies before his or her fifth birthday and 1 child in 19 in south Asia. In the world's high-income countries, that ratio is 1 in 147(Kate 2016). If levels of under-five mortality for each country remain at today's levels, 94 million under five children will die between 2016 and 2030. Although pneumonia can occur in anyone, it occurs with increased frequency in individuals whose immune systems are deficient. Under nourished children, especially those who are not exclusively breastfed or with inadequate zinc intake, are at a higher risk of

developing pneumonia (Ellison 2015). Zinc is a component for more than 300 enzymes. Thus zinc plays an important role in biological functioning of body and its deficiency affects human health a lot (Gabriel 2015). Zinc deficiency can impair macrophage and neutrophil functions, natural killer cell activity, and complement activity (Ellison 2015). The body requires zinc to develop and activate T-lymphocytes (Sandstead 1994). Zinc deficiency can impairs the immune system and can increase the rate of serious infections such as pneumonia (Prasad 1998). Infants and very young children are highly vulnerable, to this increased risk relates impaired immunity. Individuals with a serious impairment of their immune system become susceptible to pneumonia. Zinc supplementation may also reduce the incidence of lower respiratory infections, pneumonia (Christine et al. 2015).

Various studies conducted over years have provided evidence that zinc deficiency is a worldwide public

health problem. World Health Organization (WHO) estimates that zinc deficiency affects 31 % with the prevalence rates ranging from 4 to 73 %. In developing countries, zinc deficiency is one of the ten significant factors contributing to the burden of disease. According to a report on global and regional child mortality and burden of disease attributable to zinc deficiency, 58 % of child deaths in Africa is attributed to zinc deficiency. Ethiopia is one of the five countries who together contribute 47 % of the child deaths attributable to zinc deficiency in Africa (Tesfahun et al. 2015). According to Ethiopia Demographic and Health Survey (EDHS 2016), nearly 38 % of the under-five children are stunted. Stunting in children is considered as an indirect indicator of zinc nutritional status (Brown 2004).

The effect of zinc as adjunct to antibiotics, on the treatment of severe pneumonia in under five children demonstrated inconsistent results and is still under debate, to resolve the heterogeneous conflict it is necessary to carry out this clinical trial. Therefore, this study aimed at determining the effect of zinc as an adjunct to antibiotic on the duration of Hospitalization of severe pneumonia among 6-59 months of children in Debreabor General Hospital.

Materials and Methods

An institution based double-blinded, randomized, placebo-controlled clinical trial was conducted on 152 under five years children with severe pneumonia at

Debreabor General Hospital pediatric ward, between February 1, 2017 and July 2017, 2017. A pediatrician was collecting data using Standardized format. The quality of the data was controlled using Standardized format, checking completeness and consistency, cleaning and using EPI info and SPSS for the data entry as well analysis. Ethical clearance was obtained from Scientific and Ethical Review Committee of Bahirdar University and Regional Health Bureau.

Results

Characteristics of children in the zinc and placebo group: One hundred and fifty two children who were included in the study. Among these, 76 were randomly assigned to take Zinc tablet and 76 were assigned to take placebo which was not known as it was randomized, double blind controlled trial. Around 32% patients were younger than 12 months, and 53.3% of participants were male, from which 43.2% were assigned in zinc treated group. There was no clinically significant difference between the two arms. Mean duration of symptoms was 3.4 days in zinc group and 3.6 days in placebo group ($P=0.831$). The Mean respiratory rate at enrollment was zinc 58.7 breaths/minute in zinc group compared to 60.3 breaths/minute in placebo group ($P=0.240$) with IQR of 58(52, 65) and 60(52, 68) respectively. Mean oxygen saturation at enrollment in zinc group was 82.2 (6.41) and in placebo group was 80.9(6.56) ($P=0.323$) (Table 1).

Table 1: Mean time to recovery from symptoms among zinc treatment and placebo control groups at Debreabor Hospital, 2017

Outcome variable	Zinc group		placebo group		Mean	
	Mean (SD)	IQR	Mean(SD)	IQR	Differences	p value
Duration of hospitalization (Days)	3.4(1.2)	3.3(3,4)	4(1.3)	4(3,4,7)	-0.481	0.019
Duration of resolution of severe pneumonia (hours)	52.6(24.5)	52(32,64)	61.4(26.7)	56(48,72)	-8.42	0.047
Duration of lower chest indrawing (hours)	15.7(9.3)	16(8,16)	20.4(13.2)	22(16,24)	-4.75	0.03
Duration of fast breathing (hours)	38.9(20.7)	32(24,48)	44.7(26.2)	40(28,63)	-5.80	0.221
Time to start oral feeds (hours)	48.2(27.2)	48(28,56)	50.7(27.5)	48(32,64)	-2.48	0.496
Duration of O2 therapy (hours)	16(9.1)	16(8,24)	22.5(11.3)	24(16,24)	-5.58	0.00
Duration of IV fluids (hours)	33.7(17.7)	32(24,4)	42.2(22.1)	40(24,56)	-8.5	0.11
Duration of fever(Hour)	15.58(12.46)	16(8,24)	14.32(15.98)	8(0,24)	-1.26	0.156

Lower chest indrawing was evident in children of zinc treated arm 96.1 % and 98.7 % of patients in placebo arm. A similar result was recorded for patients presented with Vomiting assigned in zinc treated arm was 21.1% and placebo treated group 26.3 %. Wheeze was pragmatic in 32. % children in zinc group and 40.8% children in placebo group ($P=0.237$). In the same fashion there was no clinically statistically significant difference in presence of irritability, cyanosis, altered sensorium, fever and poor feeding.

Mean time to recovery from symptoms among zinc treatment and placebo control groups: The main outcome findings were evident, that the mean day

duration of hospitalization in zinc treated group 3.4 (1.17) is significantly shorter than placebo groups 4(1.27), so the two groups were dissimilar in terms of duration of hospitalization (Table 2). The mean (SD) time taken for resolution of severe pneumonia in zinc group was 52.6(24.5) hours and in placebo group was 61.4 (26.7) hours. Median (IQR) time taken for resolution of severe pneumonia in zinc group was 52 (32, 64) hours and in placebo group was 56(48, 72) hours. The two groups were comparable in terms of time to resolve severe pneumonia ($P=0.047$). A similar analysis was evident that the median (IQR) time taken to resolve lower chest indrawing in zinc group was 16 (8, 16) hours with mean (SD) of 15.7(9.27) hours.

Table 2: Age adjusted hazard ratio of severe pneumonia among zinc treatment and placebo control groups at Debreabor Hospital, 2017.

Outcome	Median Duration at 95% CI		P value	Outcome of RH (95% CI)
	Zinc (N=76)	Placebo (N=76)		
Duration of hospitalization(Days)	4.5(4-5)	4.46(4.2-4.2)	.628	.85(0.6-1.3)
Duration of resolution of sever pneumonia (Hour)	70.4(62-79)	71(63-80)	.874	1(.99-1)
Duration of fast breathing (Hour)	54.4(48-61)	54.5(48-62)	.986	1(0.99-1)
Duration of Fever (Hour)	27.3(22-32)	22.2(16-29)	.558	1(0.99-1)
Duration of lower chest in drawing (Hour)	29.0(22-36)	29.5(22-37)	.200	.98(0.95-1)
Duration of oxygen therapy(Hour)	31.3(25-38)	27.8(24-32)	.473	.99(0.96-1)
Time to start oral feeds (Hours)	71.9(60-83)	61(53-70)	.738	1(0.96-1)
Duration of IV fluids(Hours)	49.6(42-57)	51.5(45-58)	.326	1(0.97-1)

The median (IQR) time taken for resolution of lower chest indrawing in placebo group was 16(16, 24) hours with mean (SD) of 20.4(13.2) hours. The two groups were comparable in terms of time to resolve lower chest indrawing ($P = 0.03$). In the same fashion the median (IQR) time taken for resolution of fast breathing in zinc group was 32(24, 48) hours with mean (SD) of 38.9(20.7) hours. The median (IQR) time taken to solve fast breathing in placebo group was 40(28, 63) hours with mean (SD) of 44.7(26.2) hours. The two groups were comparable in terms of time to resolution of fast breathing ($P = 0.221$). The median (IQR) duration of oxygen therapy in zinc

group was 16(8, 24) hours with mean (SD) of 16(9.05) hours. The median (IQR) duration of oxygen therapy in placebo group was 24(16, 24) hours with mean (SD)

of 22.5(11.3) hours. The two groups were had absolute significant difference in terms of duration of oxygen therapy ($P = 0.00$). In this study the median (IQR) duration of intravenous fluids in zinc group was 32(24, 4) hours with mean (SD) of 33.7(17.7) hours. The median (IQR) duration of intravenous fluids in placebo group was 40(24, 56) hours with mean (SD) of 42.2(22.1) hours. The groups were comparable in terms of duration of intravenous fluids ($P = 0.11$).

Age adjusted hazard ratio between placebo and zinc group: Since nearly 60% of the children in the study were younger than 24 months, all hazard calculated modeling controlled for age as a continuous variable. After age was controlled for, each severe pneumonia outcome variable revealed no improvement in zinc supplemented children compared with those receiving placebo (Table 3).

Table 3: Age adjusted hazard ratio of severe pneumonia among zinc treatment and placebo control groups at Debreabor Hospital, 2017

Outcome	Median Duration at 95% CI		P value	Outcome of RH (95% CI)
	Zinc (N=76)	Placebo (N=76)		
Duration of hospitalization(Days)	4.5(4-5)	4.46(4.2-4.2)	.628	.85(0.6-1.3)
Duration of resolution of sever pneumonia (Hour)	70.4(62-79)	71(63-80)	.874	1(.99-1)
Duration of fast breathing (Hour)	54.4(48-61)	54.5(48-62)	.986	1(0.99-1)
Duration of Fever (Hour)	27.3(22-32)	22.2(16-29)	.558	1(0.99-1)
Duration of lower chest in drawing (Hour)	29.0(22-36)	29.5(22-37)	.200	.98(0.95-1)
Duration of oxygen therapy(Hour)	31.3(25-38)	27.8(24-32)	.473	.99(0.96-1)
Time to start oral feeds (Hours)	71.9(60-83)	61(53-70)	.738	1(0.96-1)
Duration of IV fluids(Hours)	49.6(42-57)	51.5(45-58)	.326	1(0.97-1)

When adjusted for confounders like age, the HR model (HR: 0.85; 95% CI: 0.6-1.3) showed that the probability of shortening the duration of hospital stay in zinc treated group is 15% less likely lower than the placebo treated group at any study time between adjusted age group, however the result is not statistically significant ($p = 0.628$). Similarly there is no significant difference between zinc treated patients and placebo treated groups with $p = (0.874)$ for shorter recovery from sign and symptoms of severe pneumonia patients with the HR model (HR: 1; 95% CI: 0.99-1). Generally There were no shorter durations of chest indrawing, fast breathing, fever, oxygen therapy, time to start oral feeds and duration of IV fluids, leading to no shorter overall duration of improvement of variable as age group is considered as the potential confounder (table 7), as well as total hospital stay (tables 6 and

5). Median (IQR) time to discharge: zinc, 3.6(4, 3) day); placebo, 4 day (6, 3) days). HR (95% CI): 0.77 (0.053, 1.1); $P = 0.053$ (time-to event analyses by using a Cox proportional hazards regression model). Median (IQR) time to discharge: zinc, 59.2 hour (51.58, 66.87 hour); placebo, 76.79 (65.95, 87.6 hour). HR (95% CI): 0.97(0.67, 1.42); $P = 0.892$ (time-to event analyses by using a Cox proportional hazards regression model). Reduction in the time to recovery of severe pneumonia was not also comparable in the hazards model (HR: 0.97; 95% CI: 0.67, 1.42) (Figure 3). When adjusted for pre specified potential confounders age, effect of zinc on the time to resolution of symptoms in subjects with severe pneumonia (HR: 0.97; 95% CI: 0.67, 1.42) continued to be not significant.

Discussion

At the time of hospital hang about the subsequent variables were taken into consideration: duration of hospitalization, time to resolution of severe pneumonia, duration of lower chest in drawing, duration of fast breathing, time to start oral feeds, duration of oxygen therapy and intravenous fluids. The main outcome of this research was evident, that the mean day duration of hospitalization in zinc treated group 3.4(1.17) is significantly shorter than placebo groups 4(1.27). This result is in line with to the findings of Nazia in which the Duration of hospital stay was 128.31+3.71 hours in zinc Group is shorter compared to non-zinc Group was 137.67+2.56 with (p-value 0.001) which is highly significant (Nazia 2015).

Our results were in line with the findings of Valavi (2011); Brooks et al. (2004); Arun et al. (2012), who were 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. 2004) 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. (Arun et al. 2012) Explores similarly zinc supplementation of children suffering from pneumonia resulted in mean reduction of 25% in hospital stay ($p=0.04$). The two groups were comparable in terms of duration of hospitalization ($P=0.16$) (Vinayak, 2015). In the study by (Shah et al. 2012), 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 ($P=0.193$). Analogous results were found in other studies. In the study by (Arun et al. 2012) resolution of severe pneumonia was defined as absence of all symptoms such as fever, tachypnea, chest in drawing 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 (Bose et al. 2006) severe pneumonia was said to be resolved when there was no chest in drawing, 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). 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 ($P=0.943$). Generally heterogeneous results were recorded due to the following reason, zinc status of children, the differences in etiologies, treatment protocol of antibiotics, definitions of pneumonia, recovery time and Timing of zinc supplementation in the course of the illness are some of the possibilities that may explain the variation in results (Arun et al. 2012).

Conclusions and Recommendations

This randomized clinical trial in children with severe pneumonia patients in supplementation of zinc to shorten duration of hospitalization. A zinc supplementation shortening median (IQR) duration of hospitalization (3.4 Day versus placebo arm was 4 Day), duration of resolution of severe pneumonia (52 hours versus 56 hours). So Evidence provided in this clinical trial is sufficient to recommend the use of zinc as an adjunct to standard antibiotic therapy for severe pneumonia in children aged 6 to 59 months. Further research should be done in zinc status of severe pneumonic children in relation to duration of hospitalization without external zinc supplementation.

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Competing interest: The authors declare that they have no competing interest.

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