https://doi.org/10.29309/TPMJ/2022.29.07.6545

The Professional Medical Journal
www.theprofesional.com
2022, Volume, 29 Issue, 07

ORIGINAL ARTICLE

The efficacy of zinc as an adjuvant therapy in the treatment of severe pneumonia in children between 2 months to 2 years of age.

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Article Citation: Hashmi MB, Kaleem Ullah, Imran A, Khan I, Shabbir S. The efficacy of zinc as an adjuvant therapy in the treatment of severe pneumonia in children between 2 months to 2 years of age. Professional Med J 2022; 29(7):1028-1034. https://doi.org/10.29309/TPMJ/2022.29.07.6545

ABSTRACT… Objective: To compare the efficacy of zinc as an adjuvant therapy in the treatment of severe pneumonia in children between 2 months to 2 years of age. **Study Design:** Case Control study. **Setting:** Department of Paediatrics, Mayo Hospital Lahore. **Period:** 20 February 2019 to 20 August 2019. **Material & Methods:** After approval of Institutional Review board of King Edward Medical University Lahore Pakistan total 200 cases were selected by Consecutive (non probability) sampling and were divided into 2 groups each containing 100 cases. Group A children were given 20 mg elemental zinc per day plus Ampicillin plus cloxacillin while Group B patients were given only on Ampicillin plus cloxacillin. Mean + Standard deviation were calculated for continuous variables like age, base line zinc level and duration of fever. Post stratification chi square test was applied in which P value ≤0.05 will be considered as significant value. **Results:** Mean Age was recorded as 09 Months ± 5.54 in Group A while in Group B it was recorded as 12 Months ± 6.47. In Group A, 56 (56%) infants showed improvement who were administered zinc while 44 (44%) did not. Similarly, in Group B, 38 (38%) infant patients showed improvement who were not administered zinc whereas 62 (62%) did not show any improvement. This improvement was statistically significant P Value = 0.010. **Conclusion:** This study revealed a statistically significant efficacy estimate for zinc in the resolution of severe pneumonia.

Key words: Zinc, Pneumonia, Mortality, Morbidity, Children.

INTRODUCTION

Pneumonia is defined as inflammation of the parenchyma of the lungs. Childhood pneumonia is the one of the leading single cause of mortality in children with age less than 5 years.[1] The incidence in this age group is estimated to be 0.29 episodes per child per year in developing and 0.05 episodes per child per year in developed countries. This account to about 156 million new episodes each year worldwide, of which 151 million episodes are in the developing world.[2] Most cases occur in India approximately 43 million, China approximately 21 million and Pakistan approximately 10 million with additional high numbers in Bangladesh, Indonesia and Nigeria (6 million each).[3] World Health Organization has estimated that each year pneumonia kills up to 2.4 million children which accounts for 19% of all deaths in the under-five age group. Recent studies have identified Streptococcus pneumoniae, Hemophilus influenzae and respiratory syncytial virus as the main pathogens associated with childhood pneumonia.[4]

While much emphasis is placed on protein-energy status and vitamin A, it has been proposed that zinc has a real potential in the prevention of pneumonia morbidity and mortality.[5] Zinc modulates host response to infection by enhancing skin and mucous membrane barriers, leukocyte function and cytokine expression. Children with good zinc status have a more robust immune response whereas low plasma zinc concentration has been found to be associated with a greater susceptibility to infections.[6]

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Article received on: 22/04/2021
Accepted for publication: 10/01/2022

Zinc-supplemented children have been found to have lower rates of diarrhoea, pneumonia and malaria in comparison with children not given zinc. In a study done by Jyoti et al, zinc supplementation reduced the incidence of acute lower respiratory tract infections by approximately 15%.[7] In another study conducted by Kumar et al, the time taken for all the symptoms to resolve in the zinc-supplemented group was significantly lesser then that in the placebo group (42.26 [6.66 %] vs. 47.52 [7.15%] respectively, P < 0.001). The zinc-treated group had a significantly shorter duration of fever (23.29 [6.67 %] vs. 26.6 [6.26%], P=0.024), lower respiratory distress (32.87 [7.85%] vs. 37.37 [4.43%], P = 0.001), required a shorter hospital stay (126.74 [12.8%] vs. 137.74 [11.52%], P < 0.001) as compared to the controls.[8]

In another study by Marangu et al, the cardinal features of pneumonia improved significantly in both study groups. Normal breathing was observed after 1 week of treatment in 49% subjects in zinc supplemented vs 43% in placebo group(P=0.685). However, there were no appreciable intergroup differences. The clinical cure rate favoured zinc, but the difference from placebo was modest and statistically insignificant P>0.05. Chest in-drawing was present in 5 subjects (10.20%) on zinc and 8 (16.33%) on placebo at baseline (p=0.553). By day 7, the frequency had dropped to 2 (4.08%) and 7(14.29%), respectively in the two arms (P=0.159).[9]

Another study conducted by Mazari et al, have shown clinically and statistically significant reductions in recovery time from severe pneumonia and overall hospital stay in children less than 2 years old given zinc with standard antimicrobial therapy. In study conducted by Rajagembeeran V the efficacy of zinc supplement was found to be 57.1% where as 19% in non-zinc adjuvant therapy.[10]

This study is designed to highlight the role of Zinc in terms of its efficacy by comparing the different parameters of severe pneumonia in the two groups of children. The objective of this study is to compare the efficacy of zinc as an adjuvant therapy in the treatment of severe pneumonia in children between 2 months to 2 years of age.

MATERIAL & METHODS

It was a Case Control study done in the Department of Paediatrics, Mayo Hospital Lahore. The duration of the study was six months, from 1st September 2019 to 29th February 2020. This study was approved by Institutional Review Board of King Edward Medical University Lahore, Pakistan (IRB No 248/RC/KEMU) on 2nd February 2019.

Sample size calculated was 200 (100 in each group) keeping proportion of efficacy of zinc supplements 57.1% and non-zinc (placebo) 19%, keeping confidence interval of 95% and power of test 80% using WHO calculator.[11] Sampling technique used was consecutive non probability technique. All children of either gender with minimum age of 2 months and maximum age of 2 years with severe pneumonia as per operational definition were included in this study. While all those children with any congenital heart disease, congenital lung disease, with aspiration pneumonia, with history of recurrent cough, wheezing and recurrent chest infection and children already taking zinc supplements were excluded from this study.

Severe pneumonia was defined as “any child who presents with history of cough and fever of more than 100-degree Fahrenheit and having respiratory rate of more than 50 per minute and lower chest wall indrawing during inspiration on inspection”.[12] Efficacy for each group was assessed by improvement in the respiratory rate to normal i.e., less than 50 per minute and absence of lower chest wall indrawing in 48 hours. All infants meeting the inclusion criteria having pneumonia (fever, fast breathing, chest indrawing) will be included in the study. The purpose and benefits of the study will be explained to the parents of the baby, they will be explained that all the information will be kept confidential and this study is designed purely of data review and publication purpose and a written informed consent will be obtained.

Patient’s demographic characteristics will be

noted including name, age, sex and address. All the information will be extracted from the parents in full privacy and patient will be put on standard treatment for pneumonia. Before starting the therapy, the time will be recorded. Children will then be randomly allocated in two groups by lottery method. Children in Group A will receive 20 mg elemental zinc per day (10 mg zinc per 5 mL syrup) as acetate plus Ampicillin plus cloxacillin (150–200 mg/kg per day, given intravenously every 8 h). Children in Group B will be put only on Ampicillin plus cloxacillin (150–200 mg/kg per day, given intravenously every 8 h) but without zinc supplementation.

Patients who failed to improve after 48 hours of antibiotics or whose condition worsened, their antibiotic would be changed to Clarithromycin (20mg/kg/day i/v). Failure to improve or worsening condition would be established clinically by respiratory rate count and appearance of signs of severe pneumonia i.e., chest indrawing, decreasing saturation of oxygen and inability to take feeds. All the children will be constantly monitored for resolution of symptoms every 8 hourly till the resolution of all the symptoms related to pneumonia. Children would be observed for at least another 48 hours after the resolution of signs and symptoms of pneumonia. All the above-mentioned data will be recorded in a predesigned proforma and strictly exclusion criteria will be followed so as to control confounders and bias in the study results.

Data was analysed using SPSS version 26. Mean + Standard deviation were calculated for continuous variables like age, base line zinc level and duration of fever. Frequencies and percentages were calculated for categorical variables like gender, education level of mother, socio economic status, residence and efficacy. Chi Square test was applied to compare efficacy between the two groups keeping the p-value of ≤ 0.05 as significant. Efficacy was stratified among age, gender, duration of fever, baseline zinc level, education level of mother, socio economic status and residence. Post stratification chi square test was applied in which P value ≤ 0.05 will be considered as significant value.

RESULTS

As per Descriptive Statistics the Mean Age was recorded as 09 Months ± 5.54 in Group A while in Group B it was recorded as 12 Months ± 6.47. Mean duration of fever was 5 Days + 0.88 in Group A while in Group B it was recorded as 5 Days ± 0.92. In Group A, Mean Baseline Zinc Level was recorded as 68 ug/dl + 3.12 whereas in Group B Mean Baseline Zinc was recorded as 69 ug/dl ±2.86.

As per frequencies and percentages for age wise distribution in Group A, 39 (39%) infants belonged to 02-08 months of age group whereas 61 (61%) patients belonged to 09-24 months age group. In the same manner, in Group B, 39 (39%) infants belonged to 02-08 months of age group whereas 61 (61%) patients belonged to 09-24 months age group.

As per frequencies and percentages for gender wise distribution in Group A, 68 (68%) infants were Males whereas 32 (32%) patients were Females. Similarly, in Group B, 70 (70%) were Males while 30 (30%) patients were Female.

As per frequencies and percentages for Exclusive Breast Feeding, in Group A, 36 (36%) infants were given exclusive breast feeding while 64 (64%) were not given exclusive breast feeding. Similarly, in Group B, 72 (72%) infants were given exclusive breast feeding while 28 (28%) infants were not given exclusive breast feeding.

The efficacy in both groups is shown in Table-I. As per efficacy, in Group A, on 56 (56%) infants showed improvement who were administered zinc while 44 (44%) did not. Similarly, in Group B, 38 (38%) infant patients showed improvement who were not administered zinc whereas 62 (62%) did not show any improvement. This improvement was statistically significant. (P Value = 0.010).
The stratification of efficacy with respect to age, gender, duration of fever, baseline zinc level, residence, exclusive breast feeding is shown in Table-II.

Efficacy	Group A (with zinc) (n=100)		Group B (without zinc) (n=100)		P-Value
	Frequencies	Percentages	Frequencies	Percentages	
Yes	56	28%	38	19%	0.010
No	44	22%	62	31%	

Table-I. Efficacy in both groups

		Efficacy	Group A (with zinc) (n=100)	Group B (without zinc) (n=100)	P-Value
Age	02 -08 months	Yes	22	14	0.069
		No	17	25	
	09 – 24 months	Yes	34	24	0.069
		No	27	37	
Gender	Male	Yes	38	29	0.089
		No	30	41	
	Female	Yes	18	09	0.037
		No	14	21	
Duration of fever	Less than 3 days	Yes	09	02	0.019
		No	04	08	
	More than 3 days	Yes	47	36	0.061
		No	40	54	
Baseline Zinc Level	Less than 66 ug/dl	Yes	23	02	0.0175
		No	18	06	
	More than 66 ug/dl	Yes	33	36	0.043
		No	26	56	
Residence	Rural	Yes	26	15	0.057
		No	22	24	
	Urban	Yes	30	26	0.067
		No	22	38	
Breast feeding	Exclusive	Yes	21	30	0.101
		No	15	42	
	Inclusive	Yes	35	08	0.020
		No	29	20	

Table-II. Stratification of efficacy with respect to age, gender, duration of fever, baseline zinc level, residence, exclusive breast feeding

DISCUSSION

This study on zinc as adjuvant therapy in children with severe pneumonia showed statistically significant effect of daily zinc administration along with standard antimicrobial treatment by showing improvement in the respiratory rate i.e., less than 50 breaths per minute and absence of lower chest indrawing in 48 hours. In the study by Rerksuppaphol et al, there was no significant difference in normalization of respiratory rate, temperature and oxygen saturation between children receiving placebo and zinc which as compared our study where the efficacy, in Group A,56 (56%) infants showed improvement who were administered zinc while 44 (44%) did not. Similarly, in Group B, 38 (38%) infant patients showed improvement who were not administered zinc whereas 62 (62%) did not show any improvement. This improvement was statistically significant. P Value = 0.010.[13]

Sabeen et al reported that there is no significant reduction in duration of severe pneumonia or reduction in hospital stay instead the duration has increased in zinc group.[14] This is contradictory to our study which as compared our study where the efficacy, in Group A, 56 (56%) infants showed improvement who were administered zinc while 44 (44%) did not. Similarly, in Group B, 38 (38%) infant patients showed improvement who were

not administered zinc whereas 62 (62%) did not show any improvement. This improvement was statistically significant. P Value = 0.010.
In a study undertaken in Bangladesh by Somji et al, children who received zinc recovered faster and fewer had treatment failure and duration of severe pneumonia lasting 72, 96 or 120 hours[15] which also gave similar results like our study where the improvement was also statistically significant, P Value = 0.010. This also reported that in children without wheezing, administration of zinc resulted in earlier resolution of clinical signs. The effect of zinc was not modified by wheezing status in our subgroup analysis, a finding similar to that reported from South India.[16] However, because there were only 9 children without wheezing, we had insufficient power to detect an effect of zinc in this subgroup. Furthermore, other recent trial by Sazawal et al, showed that zinc therapy can reduce resistance caused by antibiotic therapies and inferred that zinc can hasten the recovery from pneumonia and quickly resolve symptoms in children. There were no differences in the time to resolution of respiratory signs either combined or individually between the zinc and placebo groups in Ecuadorian children.[17]

In another study by Goodman et al, the cardinal features of pneumonia improved significantly in both study arms. Fast breathing was present after 1 week of treatment in 49 % subjects in zinc supplemented vs 43 % on placebo (p=0.685). However, there were no appreciable intergroup differences. The clinical cure rate favoured zinc, but the difference from placebo was modest and statistically insignificant p > 0.05[18]. Chest in-drawing was present in 5 subjects (10.20%) on zinc and 8 (16.33%) on placebo at baseline (p=0.553). By day 7, the frequency had dropped to 2 (4.08%) and 7(14.29%), respectively in the two arms (p=0.159) which as compared to our study where the efficacy, in Group A, 56 (56%) infants showed improvement who were administered zinc while 44 (44%) did not. Similarly, in Group B, 38 (38%) infant patients showed improvement who were not administered zinc whereas 62 (62%) did not show any improvement. This improvement was statistically significant. P Value = 0.010.

In study conducted by Kumar et al the efficacy of zinc supplement was found to be 57.1% where as 19% in non-zinc adjuvant therapy [19] which is comparable to our study in which 56 (56%) infants showed improvement who were administered zinc while 44 (44%) did not. Similarly, in Group B, 38 (38%) infant patients showed improvement who were not administered zinc whereas 62 (62%) did not show any improvement. Thus, the improvement recorded in our study was statistically significant. P Value 0.010.

There are certain limitations to this study. First the sample size is small and secondly it is a single centre study. More national and international multicentre studies are required on this topic to ascertain the beneficial role of zinc in the treatment of severe pneumonia.

CONCLUSION

This study revealed a statistically significant efficacy estimate for zinc in the resolution of severe pneumonia. In light of conflicting study results, additional large studies in different local settings are required to help clarify the role of zinc and its efficacy in the treatment of severe pneumonia.

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AUTHORSHIP AND CONTRIBUTION DECLARATION

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1	M. Basit Hashmi	Substantial contributions to the design of the work, revising it critically for important intellectual content, final approval of the version to be published and agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.	
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