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EFFICACY OF ZINC AS ADJUNCT THERAPY IN CHILDHOOD PNEUMONIA ADMITTED IN A TERTIARY CARE HOSPITAL

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Abstract

Background: *Pneumonia is a leading cause of morbidity and mortality in children, particularly in developing countries. Zinc, known for its immune-modulating properties, has been suggested as an adjunct therapy to improve recovery outcomes in childhood pneumonia.*

Objective: *To evaluate the efficacy of zinc supplementation as an adjunct therapy in reducing recovery time and hospital stay in children with pneumonia.*

Study Design and Setting: *This randomized, double-blind, placebo-controlled trial was conducted at Department of Paediatrics Sughra Shafi Medical Complex, Narowal over duration of 6 months from 14 November 2022 to 14 May 2022.*

Methods: *Total 128 children aged 2 months to 5 years, diagnosed with pneumonia were included. Participants were randomly assigned to receive either zinc supplementation (n=64) or placebo (n=64), alongside standard antibiotic treatment. The zinc group received zinc sulfate (20 mg/day for children over 12 months and 10 mg/day for infants) for 7-10 days. Primary outcomes were time to clinical recovery, duration of hospital stay, and need for second or third-line treatments. Secondary outcomes included respiratory rate, oxygen saturation, and laboratory findings such as hemoglobin levels and serum zinc levels. Data were analyzed using appropriate statistical tests, with p-values <0.05 considered significant.*

Results: *The zinc group had a significantly shorter recovery time (64.6 ± 8.51 hours) compared to the placebo group (82.5 ± 9.55 hours, $p < 0.001$). The duration of hospital stay was also shorter in the zinc group (72.7 ± 6.99 hours vs. 89.2 ± 10.84 hours, $p < 0.001$). No significant differences were observed in treatment failure rates.*

Conclusion: *Zinc supplementation significantly improves recovery time and reduces hospital stay in children with pneumonia, supporting its role as an effective adjunct therapy.*

INTRODUCTION

Pneumonia remains one of the leading causes of mortality and morbidity among children under the age of five, particularly in low- and middle-income countries.[1] Each year, numerous children are affected by pneumonia, with approximately 11.5% advancing to severe pneumonia, posing a significant threat to their health and survival.[2] According to the World Health Organization (WHO), pneumonia is responsible for 15% of all fatalities in children under the age of five, resulting in approximately 922,000 deaths in 2015.[3] Globally, around 156 million new cases of childhood pneumonia are reported each year, with 151 million of these occurring in low- and middle-income countries. India experiences 43 million cases annually, followed by 21 million in China, and 10 million in Pakistan.[4] The incidence of invasive pneumococcal disease is estimated to be 25 cases per 100,000 children each year. In Pakistan, the rate of pneumonia is 0.26 episodes per child annually, with the highest incidence in infants under 12 months, at 0.42 episodes per child per year. As children age, the likelihood of pneumonia decreases. In the neonatal stage, pneumonia accounts for 28% of infant deaths.[5]

Despite significant advances in medical care and the development of effective antibiotic treatments, the burden of childhood pneumonia continues to strain healthcare systems, highlighting the need for innovative approaches to treatment and prevention.[6] One such approach involves the use of zinc as an adjunct therapy in managing childhood pneumonia. Zinc, an essential micronutrient, plays a crucial role in maintaining immune function, enhancing the body's ability to fight infections, and promoting healthy growth and development in children. Zinc deficiency has been associated with an increased susceptibility to infections, including respiratory tract infections such as pneumonia. This has led to growing interest in zinc as a therapeutic agent, particularly in resource-limited settings where pneumonia is a major public health concern. Zinc's role in immune function, particularly in the maintenance of mucosal integrity and the modulation of inflammatory responses, suggests that it may enhance the body's ability to recover from infections like pneumonia.[7]

Zinc's immunomodulatory effects, including its ability to reduce inflammation and oxidative stress, may help improve clinical outcomes in children with pneumonia by reducing the severity and duration of the illness. Pneumonia is a contagious illness that leads to the inflammation of the alveoli and airways in the lungs, and it plays a major role in causing illness and death among infants and children. Typical symptoms of pneumonia include fever, coughing, stridor, wheezing, rapid breathing (tachypnea), and respiratory distress. Several factors increase the likelihood of pneumonia, such as poor socioeconomic conditions, crowded indoor environments, pollution, exposure to individuals with acute respiratory infections, limited access to medical care, and lower levels of maternal education.[8]

Several clinical trials have been conducted to evaluate the efficacy of zinc as an adjunct therapy for childhood pneumonia, yielding mixed but largely positive results. The use of zinc as an adjunct therapy in pneumonia treatment remains conflicted. Meta-analyses conducted in 2011, 2012, and 2016 did not show a significant impact, whereas a 2018 study reported a notable reduction in mortality (risk ratio 0.43, 95% CI 0.22 to 0.83) but no significant effect on treatment failure rates.[9-11] The 2018 study incorporated research up until October 2015, four years prior to the current analysis. Furthermore, this meta-analysis focused solely on cases involving severe pneumonia at the time of randomization, which represent only a small portion of all pneumonia cases. Even minor improvements in treating non-severe pneumonia could have considerable public health benefits.[12]

Our study aims to resolve the conflicting findings regarding the role of zinc as an adjunct therapy in childhood pneumonia. Previous studies have provided mixed results, with some reporting no significant effect and others demonstrating a reduction in mortality but no change in treatment failure rates. This study will build on existing research by focusing on both severe and non-severe pneumonia cases, which have not been thoroughly addressed in earlier studies. By incorporating more recent data, our study seeks to offer new insights into the potential of zinc therapy and its broader

implications for improving treatment outcomes in pneumonia, particularly in resource-limited settings.

MATERIALS AND METHODS

This study was a randomized, double-blind, placebo-controlled trial conducted at Department of Paediatrics Sughra Shafi Medical Complex, Narowal over duration of 6 months From 14 November 2022 to 14 May 2022. The sample size was determined to be 128 children (64 in each group) based on an assumed zinc supplement efficacy of 57.1% and a placebo efficacy of 19%, with a 95% confidence interval and 80% power. The WHO sample size calculator (www.openepi.com) was utilized for this purpose. A consecutive non-probability sampling technique was employed to recruit children.[13] A total of 128 children aged between 2 months and 5 years, diagnosed with pneumonia, were enrolled in the study. Inclusion criteria were children aged 2 months to 5 years with clinical signs of pneumonia (fever ≥38°C, cough, tachypnea ≥50 breaths/min for infants or ≥40 breaths/min for children, and chest indrawing) as per WHO guidelines. Exclusion criteria were severe malnutrition (weight-for-age Z score < -3), chronic illnesses (e.g., congenital heart disease, immunodeficiency), or prior zinc supplementation within the last 3 months. The participants were randomly assigned to two groups: the zinc group (n=64) and the placebo group (n=64). Children in the zinc group were administered zinc sulfate (20 mg/day for children older than 12 months and 10 mg/day for infants) in addition to standard antibiotic therapy, while the placebo group received standard treatment along with a placebo. The supplementation was given for a period of 7 to 10 days, depending on the recovery rate.

Data were collected on demographic characteristics, clinical signs and symptoms, and laboratory findings such as oxygen saturation, hemoglobin levels, C-reactive protein (CRP), leukocyte count, serum zinc levels, and blood culture results. Variables such as gender, age, weight, height, respiratory rate, and oxygen saturation were recorded. Additionally, clinical features including chest indrawing, wheezing, stridor, and fever were documented. Laboratory parameters, including hemoglobin levels, C-reactive protein (CRP), leukocytosis, serum zinc levels, and blood cultures, were analyzed. The primary outcome variable was the time to recovery from pneumonia, while secondary outcome variables included the duration of hospital stay and duration of oxygen therapy.

Data were analyzed using SPSS software (version 27.0). Continuous variables, such as age, weight, height, respiratory rate, oxygen saturation, hemoglobin levels, C-reactive protein (CRP), and serum zinc levels, were presented as mean ± standard deviation (SD) and compared between the zinc and placebo groups using Mann-Whitney U test. Categorical variables, such as gender, presence of chest indrawing, wheezing, stridor, fever, oxygen saturation <90%, hemoglobin <11 g/dL, leukocytosis, positive blood cultures, and treatment failure rates, were expressed as frequencies and percentages. Comparisons between groups for categorical data were performed using the Chi-square test or Fisher's exact test, as appropriate. A p-value of less than 0.05 was considered statistically significant.

RESULTS

A total of 128 children were enrolled in the study, with 64 participants in each of the zinc and placebo groups. The demographic characteristics of the enrolled children are summarized in Table 1. The distribution of gender was relatively similar between the groups, with 23 (35.9%) females in the zinc group compared to 27 (42.2%) in the placebo group. The majority of the participants were aged between 2-12 months, comprising 50 (78.1%) of the zinc group and 45 (70.3%) of the placebo group. The mean age was 10.9 ± 11.92 months in the zinc group and 13.7 ± 12.99 months in the placebo group. The mean weight and height were also comparable between the groups, with the mean weight being 7.8 ± 2.16 kg in the zinc group and 8.0 ± 2.46 kg in the placebo group. The mean height was 70.9 ± 7.82 cm in the zinc group and 74.1 ± 10.74 cm in the placebo group.

Table 1: Demographic characteristics of the enrolled children in the zinc and placebo groups

	Zinc group (n=64)		Placebo group (n=64)	
	n	%	n	%
Gender				
Female	23	35.9%	27	42.2%
Male	41	64.1%	37	57.8%
Age groups				
2-12 months	50	78.1%	45	70.3%
13-24 months	9	14.1%	11	17.2%
25-60 months	5	7.8%	8	12.5%
Age (months), mean ± SD	10.9 ± 11.92		13.7 ± 12.99	
Weight (kg), mean ± SD	7.8 ± 2.16		8.0 ± 2.46	
Height (cm), mean ± SD	70.9 ± 7.82		74.1 ± 10.74	

Clinical characteristics, including signs, symptoms, and laboratory findings, are detailed in Table 2. Chest indrawing and fever were present in nearly all participants in both groups, with 64 (100.0%) of the children in the zinc group showing chest indrawing compared to 63 (98.4%) in the placebo group. Wheezing was observed in 49 (76.6%) of the zinc group and 45 (70.3%) of the placebo group. Stridor was noted in 9 (14.1%) of the zinc group and 7 (10.9%) of the placebo group. The mean respiratory rate was 65.1 ± 7.46 breaths per minute in the zinc group and 60.3 ± 9.07 breaths per minute in the placebo group. Oxygen saturation below 90% was more frequent in the placebo group, with 36 (56.3%) of the children affected compared to 27 (42.2%) in the zinc group. Laboratory findings indicated that hemoglobin levels below 11 mg/dl were more common in the zinc group, affecting 51 (79.7%) children compared to 47 (73.4%) in the placebo group. Leukocytosis was observed in 8 (12.5%) of the zinc group and 7 (10.9%) of the placebo group. Positive blood culture results were seen in 5 (7.8%) of the zinc group and 7 (10.9%) of the placebo group. The mean serum zinc level was 9.4 ± 3.69 µmol/L in the zinc group and 9.2 ± 3.59 µmol/L in the placebo group.

Table 2: Clinical characteristics of the enrolled children in the zinc and placebo groups

	Zinc group (n=64)		Placebo group (n=64)	
	n	%	n	%
Signs and symptoms				
Chest indrawing	64	100.0%	63	98.4%
Wheeze	49	76.6%	45	70.3%
Stridor	9	14.1%	7	10.9%
Fever	64	100.0%	64	100.0%
Respiratory rate	65.1 ± 7.46		60.3 ± 9.07	
Laboratory findings				
Oxygen saturation < 90%	27	42.2%	36	56.3%
Hemoglobin < 11 mg/dl	51	79.7%	47	73.4%
Leukocytosis	8	12.5%	7	10.9%
CRP (mg/L)	13.2 ± 6.80		10.4 ± 4.16	
Positive blood culture	5	7.8%	7	10.9%
Serum zinc level (µmol/L)	9.4 ± 3.69		9.2 ± 3.59	

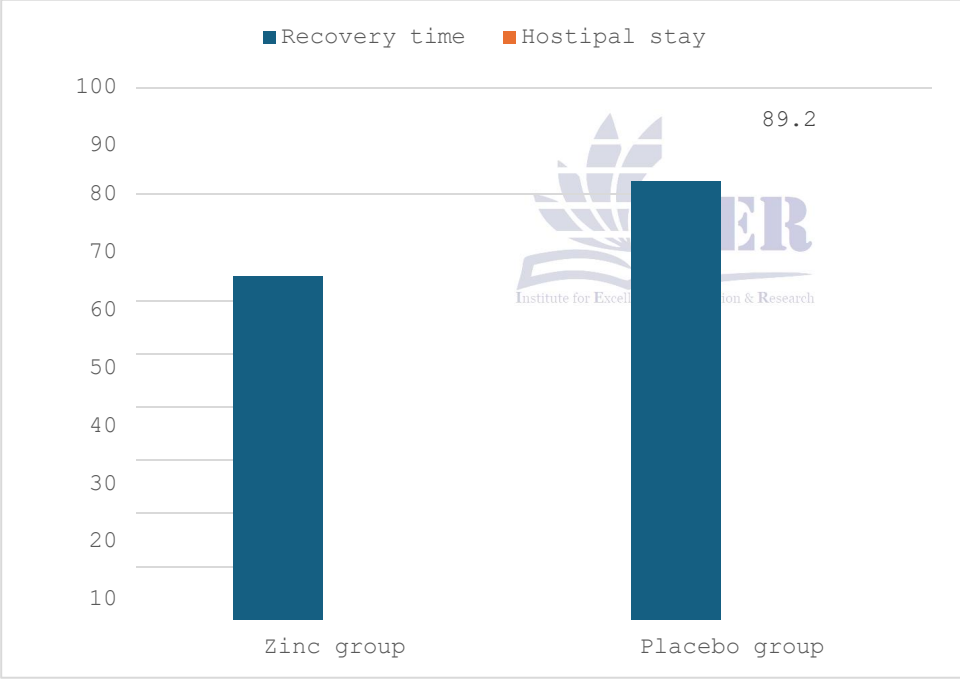
The comparison of outcomes between the zinc and placebo groups is presented in Table 3. The zinc group demonstrated a significantly shorter time to recovery, with a mean duration of 64.6 ± 8.51 hours compared to 82.5 ± 9.55 hours in the placebo group ($p < 0.001$). Similarly, the duration of hospital stay

was significantly shorter in the zinc group, with a mean of 72.7 ± 6.99 hours compared to 89.2 ± 10.84 hours in the placebo group ($p < 0.001$). The mean duration of oxygen therapy was also reduced in the zinc group (9.6 ± 4.07 hours) compared to the placebo group (11.2 ± 3.32 hours) with a p-value of 0.029. Treatment failure requiring second-line drugs occurred in 15 (23.4%) of the children in the zinc group and 20 (31.3%) in the placebo group, though this difference was not statistically significant ($p = 0.321$). Similarly, the need for third-line drugs was low in both groups, with 1 (1.6%) in the zinc group and 2 (3.1%) in the placebo group, with no significant difference observed ($p = 0.559$).

Table 3: Comparison of outcomes in zinc and placebo groups

	Zinc group (n=64)		Placebo group (n=64)		p value
Time to recovery (hours), mean ± SD	64.6 ± 8.51		82.5 ± 9.55		< 0.001[a]
Duration of hospital stay (hours), mean ± SD	72.7 ± 6.99		89.2 ± 10.84		< 0.001[b]
Duration of oxygen therapy (hours), mean ± SD	9.6 ± 4.07		11.2 ± 3.32		0.029 [b]
Treatment failure requiring 2nd line drugs, n (%)	15	23.4%	20	31.3%	0.321 [c]
Treatment failure requiring 3rd line drugs, n (%)	1	1.6%	2	3.1%	0.559 [c]

[a] Student t-test; [b] Mann-Whitney U test; [c] Chi square test.



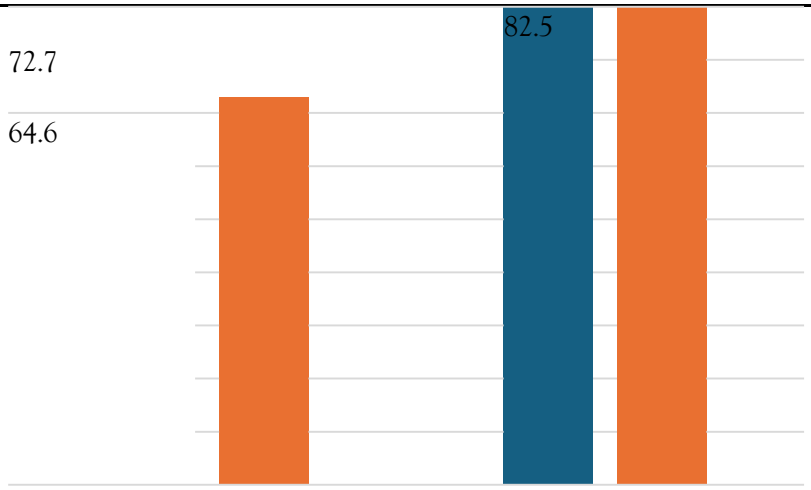


Figure 3: Recovery time of children in zinc and placebo group

DISCUSSION

Pneumonia is a leading cause of morbidity and mortality in children worldwide, particularly in low- and middle-income countries. Zinc, an essential micronutrient crucial for immune function, has been investigated as an adjunct therapy to standard pneumonia treatments due to its role in reducing inflammation and enhancing immune response. Despite promising results, the effectiveness of zinc supplementation in improving recovery from childhood pneumonia remains a subject of ongoing research. Our study aimed to evaluate the efficacy of zinc as an adjunct therapy in the treatment of childhood pneumonia. The results demonstrate a significant reduction in recovery time and hospital stay in the zinc group compared to the placebo group, highlighting the potential benefits of zinc supplementation in managing pneumonia in children.

Our study found that the distribution of gender and age was relatively similar between the zinc and placebo groups, consistent with findings by Khan et al. (2023). In our study, 35.9% of the zinc group and 42.2% of the placebo group were female, compared to 23.3% and 46.7% in the study by Khan et al. Additionally, both studies reported comparable respiratory rates, with a mean of 65.1 breaths per minute in our zinc group and 50 bpm in Khan's Group-I. Oxygen saturation levels were lower in our placebo group (56.3%) compared to 94.5% in Khan's Group-II. Hemoglobin levels below 11 mg/dL were observed in 79.7% of our zinc group and 73.4% of the placebo group, similar to Khan et al.'s reported levels of 11.8 g/dL in Group-I and 11.4 g/dL in Group-II.[14] Our study found that the majority of participants were in the 2-12 month age group, with 78.1% in the zinc group and 70.3% in the placebo group, which aligns with the findings of Ahmed et al. (2023), where most patients were aged 6 months to 2 years (65.6% in the zinc group and 60.0% in the placebo group). The mean age in our study was

10.9 ± 11.92 months for the zinc group and 13.7 ± 12.99 months for the placebo group, comparable to the study by Ahmed et al., which reported a mean age of 11.49 ± 9.73 months in the zinc group and 11.62

± 11.13 months in the placebo group.[15] Similar age distributions were also observed by Sempertegui et al. (2018) and Srinivasan et al. (2022), with mean ages ranging from 12.99 to 18.1 months in both placebo and zinc groups. These consistent findings reinforce the representative age distribution of pneumonia in young children across various studies.[16,17]

Our study demonstrated a significantly shorter time to recovery in the zinc group, with a mean of 64.6 ± 8.51 hours compared to 82.5 ± 9.55 hours in the placebo group ($p < 0.001$), which aligns with the findings of Priya et al. (2022), who reported a similar reduction in recovery time, although their results (66.44 ± 34.75 hours vs. 87.20 ± 38.65 hours, $p = 0.055$) were not statistically significant.[18] Additionally, Laghari et al. (2019) found a significantly reduced duration of hospital stay (3.12 ± 0.99 hours in the zinc group vs. 3.57 ± 0.81 hours,

p = 0.01), which mirrors our findings.[19] The mean hospital stay in our study was significantly shorter in the zinc group (72.7
± 6.99 hours) compared to the placebo group (89.2 ± 10.84 hours, p < 0.001), consistent with Singh et al. (2017), who reported a mean hospital stay of 3 ± 1 days in the zinc group versus 7 ± 3 days in the placebo group (p < 0.05), further supporting the benefit of zinc supplementation.[20]

Our study results is also consistent with findings from Hashemian et al. (2021), who reported a shorter duration of fever (2.1 vs. 2.84 days, p < 0.05) and tachypnea (1.75 vs. 2.1 days, p = 0.011) in the zinc group.[21] In contrast, Hashemian et al. did not observe a significant difference in the overall length of hospital stay (p = 0.728), while our study showed a notable reduction in hospital stay duration for the zinc group (72.7 ± 6.99 hours vs. 89.2 ± 10.84 hours, p < 0.001).[22] Similarly, Farahat et al. (2024) observed a statistically significant reduction in the mean duration of hospitalization (p = 0.004) and tachypnea (p = 0.026), reinforcing the effectiveness of zinc supplementation.[23]

This study is strengthened by its randomized, double-blind, placebo-controlled design, ensuring robust comparisons between the zinc and placebo groups. Additionally, the large sample size and inclusion of both severe and non-severe pneumonia cases provide a comprehensive understanding of zinc's potential effects on recovery. One limitation is the lack of long-term follow-up to assess the sustained impact of zinc supplementation. Furthermore, the study's focus on a specific age group and setting may limit the generalizability of findings to other populations or regions.

CONCLUSION

Zinc supplementation as an adjunct therapy significantly reduced the recovery time and hospital stay duration in children with pneumonia. These findings support the potential role of zinc in improving clinical outcomes and accelerating recovery in pediatric pneumonia cases.

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