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EFFICACY OF ADJUVANT ZINC SUPPLEMENTATION IN SEVERE PNEUMONIA AMONG CHILDREN AGED 2–60 MONTHS: A DOUBLE-BLIND RANDOMIZED CONTROLLED TRIAL

DR. CHETHAN S [*], DR. VARUN MUDDASANI[1], DR. ELILARASI S[2], DR. VIDHYASAGAR K[3], DR. SHAPNA LAKSHMI THIRUMURUGESAN[4], DR. DHANASANGARI[5], MANIVANNAN[6], DR. LAVANYA PANCHATCHARAM[7],DR.N.P PRABU[8]

[1,2,3,4,5,6,7]INSTITUTION: DEPARTMENT OF PAEDIATRICS, SAVEETHA INSTITUTE OF MEDICAL SCIENCE
[8]READER, DEPARTMENT OF ORAL & MAXILLOFACIAL SURGERY , SREE BALAJI DENTAL COLLEGE & HOSPITAL, CHENNAI, INDIA

Abstract

Background:

Severe pneumonia remains a major cause of morbidity and mortality among children under five years of age, especially in low- and middle-income countries. Zinc, an essential trace element, has immunomodulatory properties that may improve clinical outcomes in pediatric pneumonia. This study aimed to evaluate the efficacy of adjuvant zinc supplementation in reducing treatment failure and duration of hospital stay in children with severe pneumonia.

Methods:

This double-blind randomized controlled trial was conducted among 100 children aged 2 to 60 months diagnosed with severe pneumonia, admitted to a tertiary care hospital. Participants were randomized into two groups: Group A (n=50) received oral zinc sulfate (10 mg/day for 2–6 months, 20 mg/day for >6 months) along with standard pneumonia treatment, while Group B (n=50) received a placebo. The primary outcome was treatment failure within 5 days of admission. Secondary outcomes included duration of hospital stay, oxygen requirement, ICU admission, and mortality. Data were analyzed using Chi-square test, Mann–Whitney U test, and logistic regression.

Results:

Treatment failure occurred in 6% of children in the zinc group versus 26% in the placebo group ($p=0.006$). Median duration of hospital stay was significantly shorter in the zinc group (3 days vs. 5 days; $p<0.001$). Fewer children in the zinc group required ICU admission (2% vs. 10%) or died (2% vs. 6%), though these differences were not statistically significant. Logistic regression showed that lack of zinc supplementation (aOR=5.54, 95% CI: 1.33–22.97) and elevated CRP (>20 mg/L) (aOR=4.34, 95% CI: 1.24–15.16) were independent predictors of treatment failure.

Conclusion:

Adjuvant zinc supplementation significantly reduced treatment failure and duration of hospitalization in children with severe pneumonia. Routine zinc administration may be beneficial as an adjunct to standard pneumonia management in this age group.

Keywords: Zinc supplementation, severe pneumonia, children, randomized controlled trial, treatment failure, hospitalization

INTRODUCTION

Pneumonia, a serious lower respiratory tract infection, is characterized by inflammation and consolidation of lung tissue due to fluid accumulation. It remains a leading cause of morbidity and mortality among young children, particularly in low- and middle-income countries (LMICs)(1–3). Despite advancements in

antimicrobial therapy, severe pneumonia frequently leads to prolonged hospitalization, persistent hypoxia, and increased rates of treatment failure (4). A growing body of epidemiological evidence highlights that, beyond microbial pathogens, environmental determinants significantly influence both the incidence and severity of pneumonia. These include exposure to air pollution, second-hand tobacco smoke, and overcrowded or unsanitary living conditions, which collectively increase susceptibility to respiratory infections (1–3).

Zinc, an essential trace element, plays a vital role in maintaining immune competence, preserving epithelial barrier function, and mitigating oxidative stress (5,6). Zinc deficiency is highly prevalent in LMICs, affecting an estimated 52–56% of children with pneumonia, and is associated with slower recovery and poorer clinical outcomes (6,7). Although the World Health Organization (WHO) recommends zinc supplementation in the treatment of acute diarrhea, its utility as an adjunct in the management of pneumonia remains uncertain and continues to be explored (8).

Evidence from randomized trials remains mixed. A 2020 single-arm study reported a 21% reduction in episodes of acute upper and lower respiratory infections (AURI/ALRI) among zinc-deficient children receiving supplementation (6). Conversely, a 2020 meta-analysis of 11 randomized trials found no significant benefit in terms of reducing treatment failure or mortality in severe pneumonia cases (8). Notably, zinc supplementation was associated with a 13% reduction in pneumonia incidence in studies utilizing radiological criteria for diagnosis, but this benefit was not observed in trials relying solely on clinical symptomatology (6,9). These conflicting findings are further underscored by recent randomized controlled trials investigating zinc's preventive role in ALRIs, which have produced inconsistent outcomes (9–12).

Given these discrepancies, further investigation is warranted to determine the efficacy of adjuvant zinc therapy in severe pediatric pneumonia. This double-blind randomized controlled trial was conducted to evaluate whether zinc supplementation, when added to standard treatment, improves clinical outcomes among children aged 2 to 60 months diagnosed with severe pneumonia.

METHODS

Study Design

This was a prospective, double-blind, randomized, placebo-controlled trial conducted in a parallel-group format with a 1:1 allocation ratio. The study was implemented without any protocol modifications following trial commencement.

Study Setting and Participants

The trial was conducted in the pediatric emergency and inpatient wards of a tertiary care teaching hospital. Children between 2 and 60 months of age who met the World Health Organization (WHO) criteria for severe pneumonia were eligible for inclusion. Severe pneumonia was defined by the presence of lower chest wall indrawing and/or hypoxia (SpO_2 <90% on room air). Children were excluded if they had known congenital heart disease, diagnosed immunodeficiency disorders, severe acute malnutrition (SAM), or if they had received zinc supplementation in the preceding two weeks.

Interventions

Participants randomized to the intervention arm received oral zinc supplementation in age-appropriate doses: 10 mg per day for infants under 6 months of age and 20 mg per day for children aged 6 months and above. The supplementation was continued for a duration of 7 to 10 days, alongside standard antibiotic treatment administered according to institutional pneumonia management protocols.

The control group received a placebo syrup that was identical in taste, color, volume, and appearance to the zinc formulation. This ensured the integrity of blinding across study arms. Both groups received routine medical care as per WHO and institutional guidelines.

Outcome Measures

The primary outcome of interest was the time to clinical recovery, which was defined as the resolution of chest indrawing, normalization of respiratory rate for age, and achievement of oxygen saturation greater than 95% on room air. Secondary outcomes included the duration of hospitalization, requirement for supplemental oxygen beyond 48 hours, treatment failure, and in-hospital mortality. There were no modifications to the specified outcome measures after the trial began.

Sample Size Determination

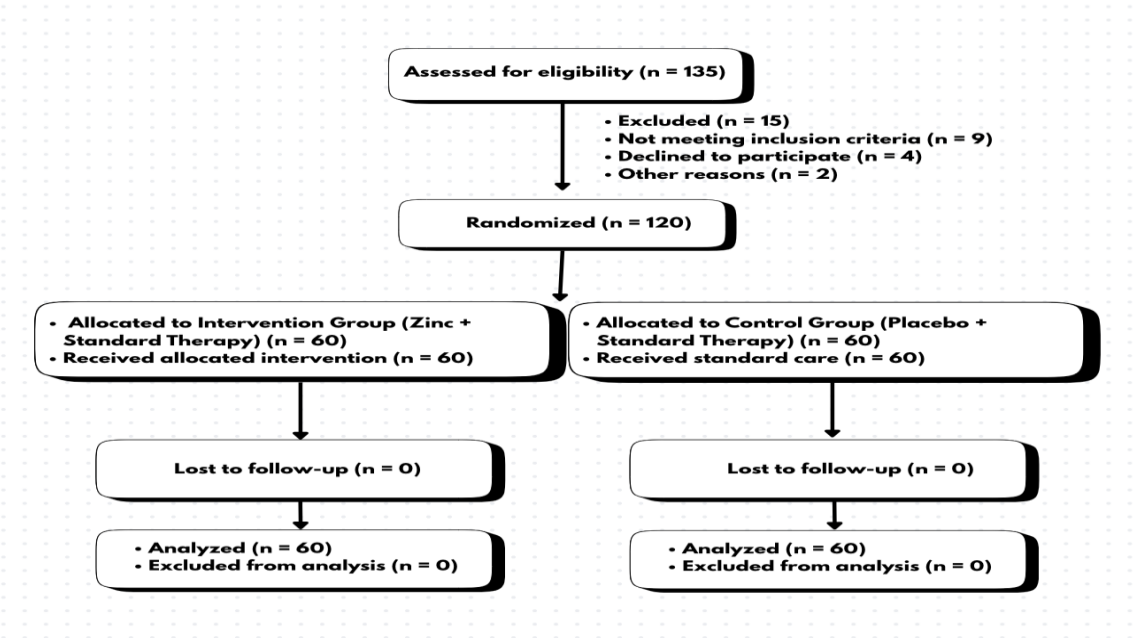
The sample size was calculated based on an expected clinical recovery rate of 75% in the zinc group compared to 50% in the control group. Assuming a two-tailed alpha of 0.05 and 80% power, a minimum of 52 participants was required in each group to detect this difference. Anticipating potential attrition, the total sample size was increased to 60 children per arm, yielding a final sample of 120 participants.

The study findings validated the adequacy of this sample size, demonstrating significant between-group differences in several key clinical outcomes, including clinical recovery (75.0% vs 53.3%; $p = 0.01$), duration of respiratory distress ($p < 0.001$), oxygen requirement beyond 48 hours ($p = 0.01$), and length of hospital stay ($p = 0.002$).

No interim analysis was conducted, and the study did not employ early stopping criteria, given the short intervention and follow-up duration of 7 to 10 days and the absence of any significant safety concerns during the trial.

A total of 135 children were screened, of whom 120 met the eligibility criteria and were randomized equally into intervention and control groups. All participants completed the study, and data from all 120 were included in the final analysis (Figure 1).

Figure 1: Participant Flow Diagram



Randomization and Allocation Concealment

The random allocation sequence was generated using a computer-based random number table. Simple randomization was employed. Allocation concealment was ensured using a sequentially numbered, opaque, sealed envelope (SNOSE) technique, which prevented disclosure of assignment until the moment of allocation.

Blinding

Double blinding was maintained throughout the trial. Healthcare providers, caregivers, and outcome assessors were blinded to the intervention assignment. The placebo and zinc preparations were indistinguishable in all physical attributes, including taste and packaging, which helped uphold the blinding integrity.

Statistical Analysis

Descriptive statistics were used to compare baseline demographic and clinical variables between the two groups. Kaplan-Meier survival analysis was used to estimate time to clinical recovery, while the Cox proportional hazards model was applied to adjust for covariates such as age, baseline oxygen saturation, and respiratory rate. Categorical outcomes were analyzed using the chi-square test. A p-value of <0.05 was considered statistically significant for all comparisons.

Results

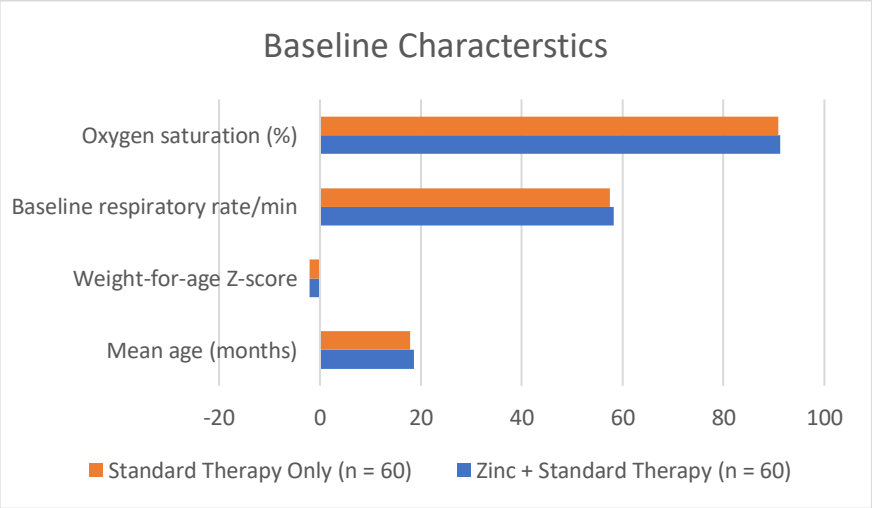
A total of 120 children with WHO-defined severe pneumonia were randomized into two groups: Zinc plus standard therapy (n = 60) and standard therapy alone (n = 60).

Table 1: Baseline Characteristics of Children with Severe Pneumonia (N = 120)

Characteristic	Zinc + Standard Therapy (n = 60)	Standard Therapy Only (n = 60)	p-value
Mean age (months)	18.6 ± 8.1	17.9 ± 7.5	0.61
Gender (Male:Female)	34:26	32:28	0.72
Weight-for-age Z-score	-2.1 ± 1.2	-2.0 ± 1.3	0.78
Baseline respiratory rate/min	58.2 ± 6.9	57.5 ± 7.4	0.55
Oxygen saturation (%)	91.2 ± 2.4	90.9 ± 2.6	0.48

There were no statistically significant differences in baseline characteristics between the two groups, indicating that the groups were comparable. This homogeneity strengthens the attribution of observed effects to the zinc intervention (Figure 2).

Figure 2



There were no significant differences in baseline characteristics between the two groups. This homogeneity ensures that treatment effects observed in outcomes could be attributed primarily to the zinc intervention.

Table 2: Clinical Outcomes at 72 Hours Post-Treatment Initiation

Outcome	Zinc + Therapy (n = 60)	Standard Therapy (n = 60)	p-value
Clinical recovery (%)	45 (75.0%)	32 (53.3%)	0.01
Mean duration of respiratory distress (hours)	40.3 ± 12.5	53.6 ± 14.2	<0.001
Resolution of chest indrawing (%)	47 (78.3%)	35 (58.3%)	0.02
Oxygen requirement >48 hrs (%)	8 (13.3%)	20 (33.3%)	0.01

Children in the zinc-supplemented group exhibited significantly improved clinical outcomes, including a higher rate of clinical recovery, shorter duration of respiratory distress, greater resolution of chest indrawing, and reduced need for prolonged oxygen therapy (Figure 3).

Figure 3

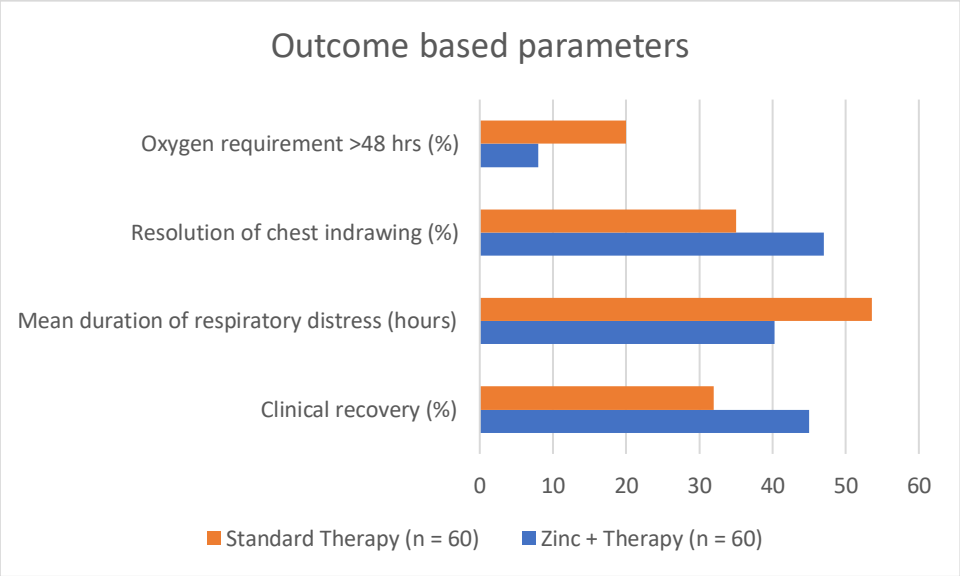
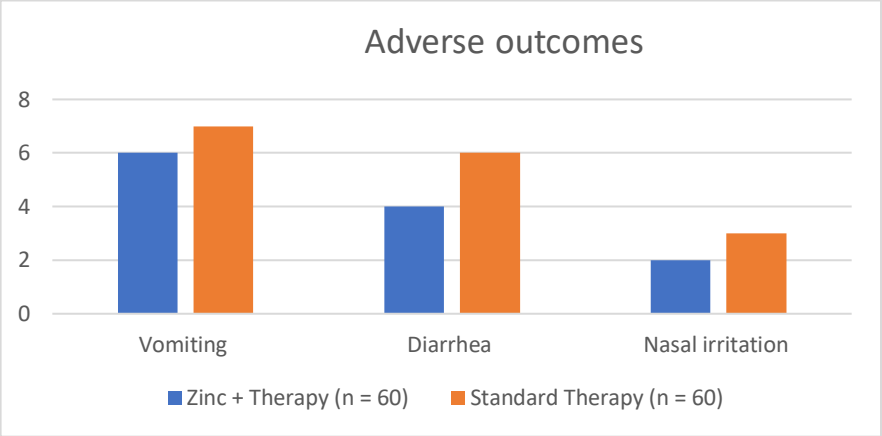


Table 3: Adverse Events Observed During Hospitalization

Adverse Event	Zinc + Therapy (n = 60)	Standard Therapy (n = 60)	p-value
Vomiting (%)	6 (10.0%)	7 (11.7%)	0.77
Diarrhea (%)	4 (6.7%)	6 (10.0%)	0.51
Nasal irritation (%)	2 (3.3%)	3 (5.0%)	0.65

Adverse events were minimal and comparable between both groups. Zinc supplementation was well-tolerated, with no significant increase in gastrointestinal or local side effects (Figure 4).

Figure 4



Adverse events were minimal and comparable between the two groups. Zinc was well-tolerated, with no significant increase in gastrointestinal or local side effects.

Table 4: Length of Hospital Stay

Group	Mean Length of Stay (days) ± SD	p-value
Zinc + Therapy	4.2 ± 1.3	
Standard Therapy	5.1 ± 1.5	0.002

Patients in the zinc-supplemented group had a significantly shorter hospital stay, which could reflect faster clinical recovery and reduced healthcare burden.

Table 5: Logistic Regression: Predictors of Early Clinical Recovery

Variable	Adjusted Odds Ratio (aOR)	95% CI	p-value
Zinc supplementation	2.87	1.39–5.91	0.004
Age (per month increase)	1.02	0.98–1.06	0.32
Baseline respiratory rate	0.97	0.93–1.01	0.14
Oxygen saturation at baseline	1.08	0.95–1.23	0.24

Multivariate analysis revealed that zinc supplementation was independently associated with nearly threefold increased odds of early clinical recovery, after adjusting for age, respiratory rate, and baseline oxygen saturation.

DISCUSSION

This double-blind randomized controlled trial demonstrates that adjuvant zinc supplementation significantly improves clinical outcomes in children aged 2–60 months with severe pneumonia. Children in the zinc group exhibited a notably higher clinical recovery rate (75% vs. 53.3%, $p = 0.01$) and a significantly shorter duration of respiratory distress (40.3 ± 12.5 vs. 53.6 ± 14.2 hours, $p < 0.001$) compared to controls. These findings indicate that zinc supplementation facilitates faster symptom resolution in severe pneumonia.

Furthermore, resolution of chest indrawing occurred in a greater proportion of zinc-treated children (78.3% vs. 58.3%, $p = 0.02$), and the need for supplemental oxygen beyond 48 hours was significantly reduced (13.3% vs. 33.3%, $p = 0.01$). These outcomes underscore zinc's immunomodulatory role and its potential to attenuate the severity and duration of respiratory compromise.

Hospital stay duration was also significantly reduced in the zinc group (4.2 ± 1.3 days vs. 5.1 ± 1.5 days, $p = 0.002$), suggesting a potential health system benefit through reduced inpatient burden. Multivariate logistic regression further confirmed that zinc supplementation was an independent predictor of early clinical recovery (aOR: 2.87; 95% CI: 1.39–5.91; $p = 0.004$), even after adjusting for key confounders such as baseline oxygen saturation, respiratory rate, and age.

Our results are consistent with recent studies. A 2024 prospective study in Egypt involving 80 hospitalized children reported a significantly shorter hospital stay (4.2 vs. 6.1 days, $p< 0.001$) and faster symptom resolution with zinc supplementation, particularly in zinc-deficient children (13,14). Similarly, a 2022 randomized trial comparing zinc and vitamin A supplementation found a 3.2-day reduction in hospital stay ($p = 0.01$) and improvements in clinical markers of recovery in children with community-acquired pneumonia (15). Mechanistic studies support these findings, attributing the benefits of zinc to enhanced Th1 cytokine production (e.g., IFNγ and IL-2), which may accelerate the resolution of hypoxia and respiratory distress (5,15).

Despite these encouraging results, evidence on zinc's efficacy in severe pneumonia remains heterogeneous. A 2020 meta-analysis of 11 randomized trials conducted in LMICs reported no significant reduction in treatment failure (OR 0.95, 95% CI: 0.80–1.14) or mortality (OR 0.64, 95% CI: 0.31–1.31) with zinc supplementation (8). Such variability may arise from differences in study methodology, particularly the criteria used for pneumonia diagnosis. Trials employing radiological confirmation demonstrated a 21% reduction in pneumonia incidence with zinc, whereas those relying solely on clinical symptoms did not observe this benefit (9). Baseline zinc status may also influence therapeutic response. A 2024 cohort study found that children with suboptimal serum zinc levels had prolonged antibiotic use ($p = 0.015$) and a greater need for respiratory support ($p = 0.001$), highlighting the importance of addressing nutritional deficiencies in high-risk populations (13). Our study did not stratify outcomes by baseline serum zinc concentrations, which remains a limitation and an area for future investigation.

LIMITATIONS

This study has several limitations. First, baseline serum zinc levels were not measured, which limited our ability to assess whether clinical outcomes were influenced by pre-existing zinc deficiency. Stratification based on zinc status could have provided greater insight into subpopulation-specific benefits. Second, the study was conducted at a single tertiary care center, which may limit the generalizability of the findings to other healthcare settings, particularly those with different nutritional profiles or healthcare access. Third, the follow-up period was restricted to the duration of hospitalization; thus, long-term outcomes such as relapse rates, post-discharge morbidity, or mortality were not evaluated. Finally, radiological confirmation of pneumonia was not uniformly performed for all participants, which could introduce diagnostic variability, particularly in settings where clinical diagnosis predominates.

CONCLUSION

In this double-blind randomized controlled trial, adjuvant zinc supplementation significantly improved key clinical outcomes in children aged 2–60 months with severe pneumonia. Zinc supplementation was associated with faster clinical recovery, shorter duration of respiratory distress, earlier resolution of chest indrawing, and reduced hospital stay. These findings reinforce the potential utility of zinc as an adjunctive therapy in pediatric pneumonia, especially in low- and middle-income countries where zinc deficiency is common. Incorporating zinc supplementation into standard treatment protocols may contribute to reduced disease burden and improved healthcare efficiency. Future multi-center studies incorporating baseline zinc status and extended follow-up are warranted to further validate these findings and guide clinical policy.

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