

ORIGINAL ARTICLE

Short-term beneficial effect of Zinc Supplement in preterm neonates having neonatal sepsis.

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ABSTRACT... Objective: To assess the short-term effect of oral zinc supplementation on mortality in preterm neonates with bacterial sepsis. **Study Design:** Randomized Controlled Trial. **Setting:** The Neonatal Unit of Sharif Medical City Hospital, Lahore. **Period:** December 20, 2021 to June 20, 2022. **Methods:** A total of 250 preterm neonates with gestational age between 28–36 weeks and diagnosed with sepsis were enrolled using non-probability consecutive sampling technique. They were randomly distributed into two groups. Group A received zinc supplementation orally (3 mg/kg twice daily), while Group B received distilled water as a placebo. Both groups received standard antibiotic treatment. Neonates were monitored in the NICU until discharge or death, and 7-day mortality was recorded. Chi-square test was applied to associate mortality rates. The p value of ≤ 0.05 was considered statistically significant. **Results:** The mean age of neonates in Group A was 41.19 ± 19.10 hours, while in Group B, it was slightly lower at 39.24 ± 19.63 hours. Group A had a significantly lower 7-day mortality rate of 9(7.2%) compared to Group B at 26(20.8%) ($p = 0.002$). No deaths occurred in the 6–18 hour age subgroup of Group A, while Group B had 8(6.4%) deaths ($p = 0.005$). Mortality was significantly lower in Group A among neonates with higher birth weights: 3(2.4%) vs. 12(9.6%), ($p = 0.007$) and gestational ages of 31–33 weeks: 5(4.0%) vs. 19(15.2%), ($p < 0.001$). **Conclusion:** Oral zinc supplementation significantly decreased short-term mortality in preterm neonates with sepsis. Zinc may serve as an effective adjunct therapy in managing neonatal sepsis.

Key words: Mortality, Neonatal Sepsis, Preterm Infants, Zinc Supplements.

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INTRODUCTION

Sepsis remains one of the major contributors to illness and death in newborns and young infants.¹ In 2017, nearly half of all sepsis cases worldwide occurred in children, with approximately 20 million reported cases and 2.9 million expiries in those below the age of five years.² According to the Global Burden of Disease (GBD) Study 2016/2017, there are a projected 1.3 million new cases of neonatal sepsis annually (95% CI: 0.8 to 2.3 million), leading to around 203,000 deaths (95% CI: 178,700 to 267,100) directly attributed to sepsis.^{3,4} The impact is particularly severe in low- and middle-income countries (LMICs), where infection related illnesses are more common and healthcare services with sufficient equipment and workers are not readily available.^{5,6}

Neonatal sepsis is typically categorized into early-onset sepsis (EOS) and late-onset sepsis, depending on the beginning of symptoms. EOS

is primarily transmitted vertically from the mother during childbirth, whereas late-onset sepsis is often developed from the hospital environment or the community. Key risk factors for neonatal sepsis are prematurity and low birth weight.⁷ Specific risk factors associated with EOS include maternal infections during labor, multiple pregnancies, prolonged labor, premature rupture of membranes, and meconium aspiration syndrome.⁸ Research indicates that prompt introduction of antibiotic treatment in neonates with expected sepsis significantly lowers both morbidity and mortality rates.⁹

Zinc, recognized by the World Health Organization as a cost-effective public health intervention through supplementation and fortification, possess a vital role in supporting immune system, growth, and reproductive health.¹⁰ It is particularly vital for immune system regulation, cognitive development, and motor functions.

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Zinc contributes to the functioning of T-cells and the adaptive immune response while also exhibiting antioxidant and anti-inflammatory properties.¹¹

Oral zinc supplementation during neonatal sepsis has been demonstrated to reduce both the severity and duration of the illness. Preterm infants are particularly vulnerable due to their significantly lower zinc reserves compared to term neonates, as approximately 60% of fetal zinc accumulation occurs in the third trimester. Furthermore, preterm babies have a limited capacity to absorb and preserve zinc necessary for growth. Therefore, their zinc intake must be increased by two to three times the standard maintenance requirements.¹²

Extensive evidence supports that additional zinc supplementation helps to lower the morbidity and mortality rates and promotes better growth in both preterm and term neonates.¹² Timely diagnosis and treatment of neonatal sepsis are crucial for successful clinical outcomes.⁷ Given that Pakistan is a region with widespread zinc deficiency, enteral zinc supplementation is widely recommended for neonatal care. Few studies reported no significant difference in mean hospital stay between zinc (142.85 ± 69.41 hours) and placebo groups (147.99 ± 73.13 hours), with mortality rates of 9.77% and 7.8%, respectively ($p > 0.05$).^{13,14} However, another study found a statistically significant decrease in hospital stay ($p < 0.01$).¹⁵

To ensure sufficient zinc levels in newborns, maternal nutrition must be prioritized. Poor maternal zinc status has been related with adverse pregnancy consequences like low birth weight, intrauterine growth restriction, and preterm birth.¹⁶ Reduced maternal plasma zinc levels may impair placental zinc transport, thereby limiting fetal zinc availability. In response, the United Nations Children's Fund (UNICEF) commends that all pregnant women in developing nations must receive multiple micronutrient supplements, containing zinc.¹⁷ Elevated serum zinc concentrations have been linked to enhanced immune function and superior clinical results in neonatal sepsis.¹⁸ However, findings from randomized controlled trials and literature review have yielded inconsistent results regarding the impact of zinc on sepsis-related

consequences in neonates.¹⁹⁻²¹ Notably, a review by Tang et al. included overlapping data from multiple studies conducted at a single site²², which may have compromised the accuracy of the pooled effect estimates.²³

Neonatal sepsis remains a main reason of morbidity and mortality, particularly in preterm infants due to their underdeveloped immune systems. Despite standard antibiotic therapy, outcomes often remain suboptimal. Zinc, an important trace element, shows a critical role in immune function, inflammation control, and tissue repair. Previous research has suggested that zinc supplementation may diminish the severity and duration of infections in pediatric populations. However, limited data exist regarding its role specifically in preterm neonates with bacterial sepsis. Therefore, the study aims to compare the outcome of oral zinc supplementation versus placebo in preterm infants receiving standard treatment for bacterial sepsis to evaluate its potential as an adjunct therapy for improving short-term survival and clinical outcomes.

METHODS

This randomized controlled trial was performed at the Neonatal Unit, Department of Pediatrics, Sharif Medical City Hospital, Lahore, over a six-month period from December 20, 2021 to June 20, 2022, using a non-probability, consecutive sampling technique. The ethical approval (SMDC/SMRC/218-21) was taken from the ethical review committee of the concerned hospital. The sample size was estimated using 80% power of the test, 5% level of significance, and previously reported mortality rates of 17.6% in neonatal sepsis.²⁴ A total of 250 preterm neonates with a gestational age between 28 and 36 weeks diagnosed with sepsis were included, with 125 neonates randomly distributed to each of the two study groups: Group A (zinc supplementation) and Group B (placebo). On the other hand, neonates already receiving treatment for sepsis, with an Apgar score less than 6 at 5 minutes, or those with congenital anomalies were excluded from the study.

After obtaining ethical approval and informed parental consent, demographic and clinical data for instance gender, age, gestational age, and birth

weight were recorded. Neonates were randomly assigned to either group using the lottery method to ensure allocation concealment. Group A received oral zinc supplementation at a dosage of 3 mg/kg twice daily, while Group B received distilled water as a placebo. Both groups continued to receive standard antibiotic treatment for neonatal sepsis as per hospital protocol. All neonates were managed in the neonatal intensive care unit and monitored daily. Criteria for discharge included clinical stability, normalization of vital signs, adequate feeding, and improvement in laboratory parameters for example white blood cell count, platelet count, blood culture results, and C-reactive protein levels.

Data was analyzed using SPSS version 25.0. Quantitative variables like age, birth weight, and gestational age were documented as means and standard deviations, whereas categorical variables such as gender and mortality were expressed as frequencies and percentages. The chi-square test was used to compare mortality rates between the two groups. Stratification was done for potential confounding factors, including age, birth weight, gestational age, and mortality, which was compared within each stratum applying the chi-square test. A p-value of ≤ 0.05 was considered as statistically significant.

RESULTS

The study included 250 preterm neonates diagnosed with neonatal sepsis, equally divided into two groups: Group A (zinc supplement group, n=125) and Group B (placebo group, n=125). The mean age of neonates in Group A was 41.19 ± 19.10 hours, while in Group B, it was slightly lower at 39.24 ± 19.63 hours. In terms of gender distribution, Group A comprised 65(52.0%) males and 60(48.0%) females, whereas Group B included 68(54.4%) males and 57(45.6%) females, showing a relatively balanced gender distribution in both groups. The mean gestational age of neonates receiving zinc supplementation (Group A) was 33.16 ± 3.38 weeks, which was comparable to the placebo group (Group B) with a gestational age of 33.63 ± 2.62 weeks. The average birth weight of neonates in Group A was 2.46 ± 0.73 kg, slightly higher than that of Group B, which was 2.39 ± 0.50 kg, as presented in Table-I.

The short-term (within 7 days) mortality in the study groups revealed a significantly lower mortality rate in the zinc-supplemented group (Group A), with 9(7.2%) neonates dying, compared to 26(20.8%) neonates in the placebo group (Group B) ($p = 0.002$). When mortality was further stratified by age groups, no deaths were observed in the 6–18 hour age subgroup of Group A, whereas Group B had 8(6.4%) deaths, showing a statistically significant association ($p = 0.005$). In the 19–36 hour age group, mortality was low in both groups (2(1.6%) deaths in Group A and 4(3.2%) in Group B), with an insignificant association ($p = 0.413$). Similarly, in the 37–55 hour subgroup, 6(4.8%) neonates in Group A and 8(6.4%) in Group B died, also without statistical significance ($p = 0.480$). However, in neonates older than 55 hours, mortality was notably lower in the zinc group 1(0.8%) in comparison to the placebo group 6(4.8%), with the statistically significant difference ($p = 0.032$), as presented in Table-II.

Stratification of mortality by birth weight and gestational age revealed that notable differences were observed among the zinc-supplemented group (Group A) and the placebo group (Group B). Among neonates with a birth weight of 1.3–2.30 kg, mortality was lower in Group A 6(4.8%) in comparison to Group B 14(11.2%), with the statistically insignificant association ($p = 0.094$). However, in the higher birth weight category of 2.31–3.50 kg, mortality was significantly lower in the zinc group 3(2.4%) contrasted with the placebo group 12(9.6%), with a statistically significant difference ($p = 0.007$). Stratification by gestational age revealed that in the 26–30 weeks subgroup, there was no mortality in Group A compared to one death 1(0.8%) in Group B ($p = 0.202$). In contrast, among neonates with a gestational age of 31–33 weeks, a significantly lower mortality rate was observed in the zinc group 5(4.0%) than the placebo group 19(15.2%) ($p < 0.001$). In the 34–36 week subgroup, mortality rates were similar between Group A 4(3.2%) and Group B 6(4.8%), showing no significant difference ($p = 0.696$), as presented in Table-III.

TABLE-I			
Age of neonates in the two group (n=250)			
Variables		Group-A (Zinc) (n=125)	Group-B (Placebo) (n=125)
Age of neonates in hours		41.19 ± 19.10	39.24 ± 19.63
Gender	Male	65(52.0%)	68(54.4%)
	Female	60(48.0%)	57(45.6%)
Gestational Age (weeks)		33.16 ± 3.38	33.63 ± 2.62
Birth Weight of neonates (kg)		2.46 ± 0.73	2.39 ± 0.50

TABLE-II				
Mortality in study groups stratified for age of neonates.				
Variables		Group-A (Zinc) (n=125)	Group-B (Placebo) (n=125)	P-Value
Mortality (within 7 days)	Yes	9 (7.2%)	26 (20.8%)	0.002
	No	116 (92.8%)	99 (79.2%)	
6-18	Yes	0 (0.0%)	8 (6.4%)	0.005
	No	22 (17.6%)	19 (15.2%)	
19-36	Yes	2 (1.6%)	4 (3.2%)	0.413
	No	25 (20.0%)	24 (19.2%)	
37-55	Yes	6 (4.8%)	8 (6.4%)	0.480
	No	32 (25.6%)	28 (22.4%)	
>55	Yes	1 (0.8%)	6 (4.8%)	0.032
	No	37 (29.6%)	28 (22.4%)	

TABLE-III					
Mortality in study groups stratified for birth weight and gestational age of neonates.					
Mortality Within 7 Days		Group-A (Zinc) (n=125)	Group-B (Placebo) (n=125)	P-Value	
Birth weight of neonates (kg)	1.3-2.30	Yes	6(4.8%)	14(11.2%)	0.094
		No	49(39.2%)	48(38.4%)	
	2.31-3.50	Yes	3(2.4%)	12(9.6%)	0.007
		No	67(53.6%)	51(40.8%)	
Gestational age (weeks)	26-30	Yes	0(0.0%)	1(0.8%)	0.202
		No	14(11.2%)	8(6.4%)	
	31-33	Yes	5(4.0%)	19(15.2%)	<0.001
		No	38(30.4%)	17(13.6%)	
	34-36	Yes	4(3.2%)	6(4.8%)	0.696
		No	64(51.2%)	74(59.2%)	

DISCUSSION

Sepsis is recognized as a major contributor to illness and death among newborns.²⁵ A deficiency in zinc may result in impaired immune function, developmental delays in cognition and movement, more vulnerable to infections, and stunted growth.²⁶ Low levels of zinc have been detected in the bloodstream of low birth weight (LBW) infants. Preterm infants, in particular, have relatively higher nutritional needs for zinc, partly because around 55% of a fetus's zinc accumulation occurs in the third trimester of pregnancy.²⁷

The present study assessed the effect of zinc supplementation on short-term mortality among preterm neonates diagnosed with sepsis. The zinc-supplemented group (Group A) showed a significantly lower mortality rate of 9(7.2%) compared to the placebo group 26(20.8%), with a (p= 0.002), highlighting a strong association between zinc administration and improved survival. Additionally, stratification by birth weight revealed that neonates in the 2.31–3.50 kg range experienced significantly reduced mortality with zinc supplementation 3(2.4%) vs. 12(9.6%), (p = 0.007). A comparable trend was seen in neonates with a gestational age between 31–33 weeks, where the zinc group had a fatality rate of 5(4.0%) versus 19(15.2%) in the placebo group (p < 0.001). These results are consistent with the meta-analysis by Tang et al., which included four RCTs with 986 neonates and demonstrated that zinc supplementation significantly declined mortality (RR = 0.48; 95% CI = 0.25–0.94; p = 0.03) and

increased serum zinc levels. While Tang's review found no significant influence on hospitalization or the number of deceased patients as a separate outcome.²²

A study by Irfan et al. also stated that zinc supplementation in infants under 4 months led to a significant decline in treatment failure (RR = 0.61) and mortality rate, specifically at a dose of 3 mg/kg two times a day, similar to the dosage used in the present study.²⁸ This supports the notion that both dosage and patient characteristics such as preterm status are key determinants of treatment success.

The results of the present study, which demonstrated a significant decrease in short-term mortality among preterm neonates with sepsis receiving zinc supplementation 9(7.2%) in the zinc group vs. 26(20.8%) in the placebo group; ($p = 0.002$), are in strong agreement with several previous studies highlighting zinc's protective role in early-onset neonatal sepsis. A randomized controlled trial by Banupriya et al. indicated that neonates' not receiving zinc had a significantly higher mortality rate (13%) as compared to those who received zinc (5%) ($p = 0.04$), further reinforcing zinc's beneficial role.²⁹ Likewise, in another trial, the same group observed that zinc supplementation significantly reduced inflammatory markers like calprotectin and IL-6, although mortality differences did not reach statistical significance.²⁰ Additionally, prior research has shown that zinc supplementation is especially valuable in preterm and exceedingly low birth weight neonates³⁰, which is consistent with the present study's subgroup analysis indicating significantly lower mortality in neonates with birth weights of 2.31–3.50 kg and gestational ages of 31–33 weeks.

In the present study, zinc supplementation was found to significantly reduce short-term (within 7 days) mortality, particularly in subgroups based on age (>55 hours), birth weight (2.31–3.50 kg), and gestational age (31–33 weeks). The overall mortality was notably lesser in the zinc group 9(7.2%) as compared to the placebo group 26(20.8%) ($p = 0.002$). These findings are partially consistent with the results presented by Newton B et al., who conducted a similar RCT administering 3 mg/kg of zinc sulfate twice daily for 10 days in septic

neonates. Whereas Newton's study observed a statistically insignificant reduction in mortality (4.5% in the zinc group as compared to 13.6% in controls; $p = 0.27$), they did find that zinc supplementation led to improved neurological outcomes at one month of age ($p = 0.02$).¹⁹ Similarly, a study by Heba et al. concluded that zinc significantly reduced both morbidity and mortality in neonates, further supporting the importance of zinc in enhancing immunity and survival.³¹

Zinc is an essential micronutrient that offers a cost-effective and safe option when provided through supplementation or food fortification, making it a valuable addition to current infant and young child health and nourishment initiatives.¹⁰ Moreover, preterm infants are particularly prone to developing zinc insufficiency. The findings of the present study demonstrated a statistically significant decrease in short-term mortality among preterm neonates with sepsis receiving zinc supplementation, align with earlier studies reporting the preventive efficacy of zinc in this populace.³²⁻³⁴ In contrast, a research by Bhatnagar et al. observed a protective effect of zinc supplementation, noting a reduced need for ICU admission or escalation of antibiotic therapy. Although their study showed a comparable decline in all-cause mortality, it did not report statistically significant mortality reduction, possibly due to differences in sample size or study design.³⁵ Similarly, another additional study on preventive zinc supplementation in preterm neonates also reported enhanced mortality outcomes, supporting the biological rationale that preterm infants, who miss out on substantial transplacental zinc transfer during the third trimester and have immature gastrointestinal absorption, stand to benefit most from zinc supplementation.³⁶ Furthermore, another trial concluded that zinc supplementation did not significantly alter the incidence of bacterial sepsis when used preventively.¹³

This study was limited by its short follow-up period of 7 days, which did not allow assessment of long-term outcomes or potential adverse effects of zinc supplementation. Additionally, the sample size, though adequate for short-term mortality analysis, may not have been sufficient to detect differences across all subgroups. Future large-scale, multicenter

trials with extended follow-up are recommended to validate these findings, assess long-lasting benefits, and establish standardized guidelines for zinc use in preterm neonates with sepsis.

CONCLUSION

The study concluded that zinc supplementation in preterm neonates with neonatal sepsis significantly decreased 7-day mortality as compared to placebo. This useful effect was more pronounced in neonates with birth weights between 2.31–3.50 kg and those with a gestational age of 31–33 weeks. Although differences in mortality were not statistically significant in all subgroups, the overall trend supports the prospective role of zinc as an adjunctive therapy to improve short-term survival outcomes in preterm neonates suffering from sepsis.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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