

OUTCOME OF ZINC SUPPLEMENTATION AS ADJUVANT THERAPY IN TREATMENT OF HIGH PROBABLE NEONATAL SEPSIS

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ABSTRACT

Background: Neonatal sepsis is a primary cause of morbidity and mortality all over the world, especially low and middle income countries. Zinc is a vital trace mineral that plays a role in immune function, cellular structure, antioxidant and inflammatory processes. It could be used as an adjunctive treatment to conventional antimicrobial treatment to enhance healing in neonates with sepsis. **Objective:** To compare outcome of zinc supplementation as adjuvant therapy to antibiotic than antibiotic alone in treatment of high probable neonatal sepsis. **Methods:** This was a randomized controlled trial that was carried out at Department of Pediatrics, Ghurki Trust Teaching Hospital, Lahore from July 2025 to October 2025. 102 neonates meeting the pre-established criteria for HPNS were recruited and randomly assigned to intervention groups who received a course of standard antibiotic treatment plus oral/nasogastric zinc sulphate (2–3 mg/kg/day) or control groups who received a course of standard antibiotic treatment alone. The primary outcome was resolution of sepsis, defined as “no sepsis,” and evaluated on days 5, 10 and 15 based on clinical and laboratory parameters. Data was analysed with SPSS version 26. **Results:** No sepsis was recorded for 19.6% of the neonates in the zinc group and 11.8% of the neonates in the control group at day 5 ($p=0.276$). The corresponding rates increased to 45.1% versus 23.5% on day 10 ($p=0.022$) and 68.6% versus 39.2% on day 15 ($p=0.003$). **Conclusion:** When combined with conventional antibiotic treatment, there was a significant difference in favour of adjunctive zinc in sepsis resolution at day 10 and 15. Additional well powered multi-centre studies are necessary to validate and validate the role of zinc in the treatment of neonatal sepsis.

KEYWORDS: Neonatal Sepsis, Zinc Supplementation, Adjuvant Therapy, High Probable Neonatal Sepsis, Antibiotic Therapy, Treatment Outcome.

1. INTRODUCTION

Neonatal sepsis is a systemic infection, which is caused by the invasion and proliferation of pathogenic microorganisms, causing inflammatory response that can be associated with significant morbidity and mortality in neonates [1]. Its clinical manifestations include mild or non-specific symptoms, and may be either focal or systemic, caused by either intrauterine or maternal pathogens, or by pathogens acquired from the hospital or community [2]. The impact of neonatal sepsis is highly varied and tends to be worse in developing countries, especially in Pakistan [3,4]. Low gestational age and prematurity were found to be significant risk factors for neonatal sepsis and were correlated with vulnerability to poor neonatal outcomes [5]. Also, prolonged rupture of membranes is a significant perinatal risk factor, and associated with elevated risk for early onset neonatal sepsis [6].

Although the world has made strides in the treatment of sepsis, neonatal intensive care, supportive care and detecting risk factors, neonatal sepsis remains a significant cause of neonatal morbidity and mortality. The diagnosis is often difficult, as the clinical signs are not specific and may include respiratory distress, lethargy or irritability, feeding difficulty, temperature instability, convulsions, jaundice, bleeding, abdominal distension, and other systemic abnormalities [7]. For this reason laboratory tests may be necessary to aid in the clinical diagnosis, and therapy may be started prior to the results of microbiological testing. When neonatal sepsis is suspected, empirical antibiotic therapy is often used, which can lead to significant use of antibiotics in a baby and underlines the importance of effective adjunctive therapeutic strategies [8].

Zinc is an indispensable micronutrient and a cofactor for many enzymes; it also has important functions in immune-regulation, cellular function and host defense. It has immunomodulatory activity and is of interest for use as an adjunctive therapy in neonatal infections. The frequency of “no sepsis” was significantly higher among neonates with high probability of sepsis who were given adjunctive zinc and antibiotics than among those who were only given antibiotics (48% vs. 20%, $p=0.002$) [9]. Likewise, El Frargy et al. investigated the supplementation of zinc in preterm neonates with late onset sepsis and found that a higher number of neonates who were supplemented with zinc were classified as “no sepsis” than those treated with antibiotic therapy alone [10].

These results indicate a possible adjunctive effect of zinc in the therapy of these patients, but the evidence is still limited and local evidence of effectiveness in neonates with high probability of neonatal sepsis is scarce. Thus, more clinical studies should be conducted in the local community to assess the clinical benefits of zinc supplementation as an adjunct therapy. The aim of the present study was to compare the efficacy of conventional antibiotic treatment with and without adjunctive use of zinc in neonates with high likelihood of neonatal sepsis and to give some evidence to guide future practice.

2. OBJECTIVE

To compare outcome of zinc supplementation as adjuvant therapy to antibiotic than antibiotic alone in treatment of high probable neonatal sepsis.

3. METHODOLOGY

This was a randomized controlled trial that was carried out at Department of Pediatrics, Ghurki Trust Teaching Hospital, Lahore from July 2025 to October 2025. The non-probability consecutive sampling method was used to enroll a total of 102 neonates who met the predetermined criteria for HPS. Sample size was determined with the WHO sample size calculator, using 80% power, 5% significance level and frequencies of the outcomes in the zinc and control groups of 48% and 20%, respectively. Neonates who met the inclusion criteria were randomly allocated by lottery into two groups of equal numbers. Group A had standard antibiotic treatment and zinc sulphate (2–3 mg/kg/day) via oral or nasogastric route while Group B had only standard antibiotic treatment. The clinical and laboratory results were evaluated prospectively.

3.1 INCLUSION CRITERIA

Neonates (up to 28 days old) who fulfilled the operational criteria for high probable neonatal sepsis were included.

3.2 EXCLUSION CRITERIA

Neonates known allergy to the study antibiotics; inborn errors of metabolism; neurological problems that resembled sepsis; or had major congenital abnormalities, or were severely preterm (<24 weeks) were excluded.

3.3 DATA COLLECTION PROCEDURE

After obtaining informed written consent from their parents/legal guardians, eligible neonates admitted to NICU were recruited after securing ethical clearance. There were 102 neonates, who were randomly allocated to two equal groups by lottery. Both Group A and Group B were treated with standard intravenous antibiotic therapy and zinc sulfate was administered to Group A at 2–3 mg/kg/day, orally or via a nasogastric tube. Both groups received the same supportive and nursing care following institutional protocols. At enrolment, demographic and clinical data, such as gestational age, birth weight, chronological age, sex, mode of delivery and presenting clinical symptoms were obtained. Laboratory values such as Hs-CRP, T-LC, platelet count and serum lactate were recorded. The response to treatment was evaluated at baseline and at days 5, 10 and 15. The final outcome "no sepsis" was achieved based on predetermined clinical and laboratory criteria and by a senior paediatrician who was unaware of treatment allocation.

3.4 DATA ANALYSIS PROCEDURE

After acquiring the data, it was entered, coded and analyzed using software package Statistical Package for the Social Sciences (SPSS) version 26. Continuous variables such as gestational age, birth weight, chronological age, Hs-CRP, total leukocytes, platelets and serum lactate were expressed as mean and standard deviation (SD). The categorical variables such as treatment outcome, sex, mode of delivery, clinical manifestations were reported as frequencies and percentages. To determine comparability of the two treatment groups, baseline characteristics were compared. The Chi-square test was used to compare groups on the primary outcome, "no sepsis." A p value of ≤ 0.05 was set as a threshold for statistical significance. Post-stratification analysis was carried out for comparison of treatment effects by gestational age, chronological age and mode of delivery to see if any of these factors had an effect on the observed treatment effect. All statistical tests were 2-tailed.

4. RESULTS

In the end, 102 neonates, whose clinical characteristics matched the criteria established for HPNS, were analyzed. The subjects were randomly divided into two groups: Group A (antibiotic + zinc, n=51) and Group B (antibiotic alone, n=51). Demographic and laboratory parameters were similar, and did not differ significantly between the groups in terms of gestational age, birth weight, chronological age, mode of delivery or baseline Hs-CRP level (all p>0.05).

Table 1. The study population consisted of the baseline demographic and laboratory characteristics.

Parameter	Group A: Antibiotic + Zinc (n=51)	Group B: Antibiotic Alone (n=51)	p-value
Gestational age (weeks), mean $\pm$ SD	35.4 $\pm$ 2.1	35.1 $\pm$ 2.3	0.498
Birth weight (kg), mean $\pm$ SD	2.31 $\pm$ 0.45	2.28 $\pm$ 0.48	0.745
Chronological age (days), mean $\pm$ SD	8.4 $\pm$ 4.2	8.1 $\pm$ 4.6	0.732
Cesarean delivery, n (%)	28 (54.9%)	30 (58.8%)	0.689
Baseline Hs-CRP (mg/dL), mean $\pm$ SD	12.4 $\pm$ 3.1	11.9 $\pm$ 3.4	0.439

Demographic and baseline laboratory parameters were similar in the two treatment groups.

No statistically significant differences were found at baseline for any of the variables measured (all p>0.05).

This suggests that there is a satisfactory baseline comparability between the treatment groups.

Table 2. Compares the outcome of "No Sepsis" between treatment groups.

Follow-up Time	Group A: Antibiotic + Zinc (n=51)	Group B: Antibiotic Alone (n=51)	χ^2	p-value
Day 5	10 (19.6%)	6 (11.8%)	1.185	0.276

Day 10	23 (45.1%)	12 (23.5%)	5.257	0.022
Day 15	35 (68.6%)	20 (39.2%)	8.870	0.003

In both groups, the percentage of neonates that did not develop sepsis in the follow-up group was found to be gradually increased. The difference between the groups was not significant on day 5, but was significant on days 10 and 15. The zinc group had a “no sepsis” rate of 68.6% at day 15, whereas the antibiotic-only group had a rate of 39.2%.

Table 3. The difference in “No Sepsis” rate (absolute difference) between treatment groups.

Follow-up Time	Group A: No Sepsis, n (%)	Group B: No Sepsis, n (%)	Absolute Difference
Day 5	10 (19.6%)	6 (11.8%)	7.8 percentage points
Day 10	23 (45.1%)	12 (23.5%)	21.6 percentage points
Day 15	35 (68.6%)	20 (39.2%)	29.4 percentage points

The “no sepsis” percentages were found to be getting further apart over time: from 7.8 percentage points apart on day 5, to 29.4 percentage points apart on day 15. The biggest inter-group difference was on day 15 at the end of the assessment. The difference in progressive increases shows that the zinc-supplemented group had a higher degree of responders over time.

Table 4. Persistence of Sepsis at Follow-up

Follow-up Time	Group A: Sepsis Present, n (%)	Group B: Sepsis Present, n (%)	Between-Group Difference
Day 5	41 (80.4%)	45 (88.2%)	7.8 percentage points
Day 10	28 (54.9%)	39 (76.5%)	21.6 percentage points
Day 15	16 (31.4%)	31 (60.8%)	29.4 percentage points

Septicemia decreased steadily in both treatment groups in the follow-up period. 31.4% of the zinc group had sepsis at day 15 versus 60.8% of the antibiotic-only group. As the difference between the “no sepsis” rates between the groups increased, the decrease in persistent sepsis was observed.

Post-stratification Analysis

Post-stratification analysis by the mode of delivery (vaginal versus cesarean) and gestational age (≤ 36 weeks versus >36 weeks) was carried out. The percentage of neonates that achieved “no sepsis” was not statistically different ($p>0.05$) in any of the subgroups reported, but remained higher in the zinc-supplemented group. The results suggest that this difference in outcome of treatment remained within the categories of gestational-age and delivery mode examined.

Safety Outcome

No serious adverse drug effects or clinically significant gastrointestinal toxicity were reported over the 15 days of observation associated with zinc supplementation. No clinically significant treatment-related adverse events were noted in neonates that were taking the zinc as an adjuvant.

5. DISCUSSION

Neonatal sepsis is still an important cause of neonatal morbidity and mortality and a big problem in low and middle income countries. It's sometimes said to have non-specific clinical symptoms, such as mild feeding difficulties, changes in body temperature, but more severe respiratory, cardiac and neurological issues. This diversity can cause delays in recognition and prompt treatment especially if microbiological confirmation of diagnosis is delayed or unavailable [1]. Sepsis in the neonate can be maternal, intrauterine or acquired in the healthcare setting or community. Both clinical burden and gestational age, birth weight, delivery factors and local microbiological environment are factors that influence gestational age [2]. Sepsis in the neonatal period is still a significant clinical issue in Pakistan with different organisms reported to be the cause of sepsis and their antimicrobial sensitivity in different health care

services. The results highlight the need for proper empirical antibiotic use and regular evaluation of response to antibiotics [3].

In the present randomized controlled trial the effect of Zinc, when used as an adjunctive therapy, for the treatment of neonates with high probability of having neonatal sepsis was assessed. A total of 122 neonates were randomly divided into two equal size groups (zinc and control). There were no differences between the two groups at baseline with regard to gestational age, birth weight, chronological age or mode of delivery, or baseline Hs-CRP. This initial comparability enhances the internal validity of the study as any differences at follow-up may be less related to large baseline differences. Neonatal sepsis is often diagnosed late, in resource-poor settings, there is limited microbiological facilities, limited access to specialized neonatal care and antimicrobial resistance make the management of neonatal sepsis challenging [4]. Given that neonatal sepsis is a major cause of morbidity and mortality in children, the clinically relevant identification of safe and potentially effective adjunctive interventions is of great importance.

Infants born prematurely are at a higher risk for neonatal infection because of several factors including immature immune responses, decreased barriers and increased exposure to invasive procedures. The average gestational age was approximately 35 weeks in both groups with most participants being at high risk for infection. Previous studies have identified that neonatal sepsis is a serious problem even in term and after 35 weeks gestated infants [5]. Further, other peripartum risk factors have been found to impact the risk of infection: Rupture of membranes for more than 12 hours is a risk factor for early-onset neonatal sepsis [6]. Therefore, the baseline information from this study is clinically relevant baseline characteristics that should be taken into account when assessing treatment response.

The most important finding from this study was that neonates in the “no sepsis” category increased with time in both groups and were always significantly higher in the zinc group. Sepsis was noted in 19.6% of neonate who received zinc while 11.8% of neonate in the control group had sepsis, no significant difference ($p=0.276$) was observed on day 5. The percentage was 21.6 higher at day 10 in the zinc group (45.1%) versus the control group (23.5%) ($P=0.022$). The difference between groups was 29.4 percentage points in favour of the zinc group ($p=0.003$) with 68.6% of neonates in zinc group and 39.2% of neonates in control group having no evidence of sepsis by day 15 and 39. The difference in groups increased as a result of the treatment and follow-up.

The difference was not significant on Day 5 which may be due to the early time for the first evaluation of the outcome. Sepsis in the newborn is an evolving process and clinical parameters and inflammatory abnormalities may remain after treatment for the 4 cardinal signs of sepsis. The current management is still focused on the proper use of antimicrobial therapy and supportive neonatal care, and recognition of presumed infection [7]. The mainstay of therapy is therefore antibiotics, and different alternative therapies should be implemented in addition to, not instead of, the current therapy. As with all medicines, however, appropriate antimicrobial treatment and re-assessment is particularly important and unnecessary and excessive exposure to antimicrobials can also cause issues arising from antimicrobial resistance [8].

There are a number of biological properties that zinc has and provide a sound argument for using zinc as an adjunctive treatment in neonatal sepsis. It participates in immune regulation, maintaining the integrity of cells, anti-oxidant and anti-inflammatory functions. During systemic infection, zinc may move from the bloodstream to tissues and this may impact the host's immune response. The use of zinc supplementation in combination with the standard treatment has been beneficial in neonatal sepsis in a previous study [9]. There is also unresolved and limited evidence that zinc supplementation can benefit both the clinical and laboratory outcomes of the management of late onset sepsis (LOS) in preterms [10].

Recent literature provides more evidence for the biological basis of zinc supplementation. Banupriya et al. mentioned zinc has role in host defence and immune regulation, and very few clinical studies are conducted on zinc supplementation in sepsis in neonates [11]. A preliminary study of neonates with sepsis showed that zinc supplementation was correlated with a change in the relative expression of genes related to an immune response, suggesting that zinc might affect immune pathways in the process of infection [12]. Based on the above observations the zinc group could have a beneficial mechanism in the present study that could account for the progressive improvement in clinical benefits as the zinc group increased. In the clinical results described below, however, the first

thing that needs to be taken into account is the clinical outcome, and molecular effects do not necessarily translate into clinical benefit.

Neonatal sepsis is difficult to diagnose as clinical features can mimic non-septic neonatal illness. Additionally, low income neighbourhoods might compound the problems associated with microbiological testing and laboratory services, and raise the requirement for clinical examination and supportive testing [13].

Biomarkers can help with the diagnosis of suspected sepsis and surveillance of inflammatory response, but no single biomarker is robust enough to use to make or rule out neonatal sepsis in all neonates [14]. The present study, therefore, evaluated treatment response by a predefined clinical and laboratory criteria and not through a single laboratory parameter. A series of assessment on days 5, 10 and 15 also allowed the recovery trajectory to be assessed.

Clearly defined outcomes, especially in the research of neonatal sepsis, are important because diagnostic criteria for sepsis and measures of outcomes vary among studies making them difficult to compare. In neonatal sepsis research, consensus definitions, collaboration, and a common set of core outcomes have been stressed [15]. A predetermined "no sepsis" outcome was assessed in the present study serially by a senior pediatrician who was blinded to treatment allocation. The practice of this approach was helpful to ensure "standardisation" of outcome assessment and minimise observer-related bias. These marked differences seen at day 10 and 15 therefore indicate that there may be a treatment-response benefit to adding zinc, but not for every clinically important outcome.

The results of the present study are in agreement with previous studies that assessed the effect of zinc supplementation in neonates with sepsis. A systematic review and meta-analysis of four RCTs with a total of 986 patients showed that the supplementation of zinc significantly lowered mortality and raised serum zinc levels, but failed to significantly affect hospital days [16]. A further systematic review and meta analysis of nine RCTs involving 2553 infants demonstrated a significant decrease in treatment failure with therapeutic zinc supplementation. In that analysis, therapeutic zinc supplementation in neonates had no significant effect on hospital stay or neonatal mortality, however, they noted that larger studies are required [17]. A significant improvement in treatment response was also shown in the present study at days 10 and 15, but was not designed to demonstrate effects on mortality or long-term outcomes. However, there have been no entirely consistent findings from previous randomized evidence. In a double-blind, randomized controlled study of 614 neonates with probable sepsis, there were no statistically significant differences among groups with respect to mortality, hospital stay, or need for higher-line antibiotics [18]. Variations in outcome measures, definitions of sepsis, nutritional status, duration of zinc supplementation, zinc dose, disease severity and patient characteristics between the two studies may be contributing factors. The results of the present study should be viewed as suggestive for a possible benefit in resolving sepsis, but not as definitive that zinc improves the major neonatal sepsis outcomes.

The possible clinical benefit of zinc should be viewed as a supportive therapy for treatment of neonatal sepsis. The current treatment focuses on early detection, effective antimicrobial therapy, supportive care and close surveillance for complications [19]. The management of neonatal sepsis is also reviewed with an integrated approach to the treatment, including supportive care and individual neonatal care along with antimicrobial therapy [20]. In this context, zinc can offer an extra immunomodulatory effect of conventional treatment. But zinc should not be used to replace the use of antibiotics, infection control measures, nutrition, or other necessary aspects of neonatal care.

The present study offers a number of advantages: randomized allocation, equal group sizes, similar baseline data, blinded outcome assessment, serial follow-up data and assessment of treatment response at multiple clinically relevant points in time. An increasing absolute difference between treatment response at day 5 (7.8 percentage points) and day 10 (21.6 percentage points) was noted, as well as between day 5 and day 15 (29.4 percentage points). There are, however, a number of caveats to be taken into account. The study was monocentric and had a small sample size. The 15-day follow-up may not allow for long-term outcomes to be assessed, and non-probability consecutive sampling may restrict generalizability. This study was not powered specifically to look for any differences in mortality or length of hospital stay or neurodevelopment. Serum zinc was not measured as a baseline value and not all subjects had microbiological confirmation. The limitations must be taken into account when generalizing the results to other populations of neonates.

In summary, adjunctive zinc supplementation and regular antibiotic treatment was linked with a greater percentage of neonates reaching the pre-established state of no sepsis. No significant difference was seen on day 5 but significantly more neonates had no sepsis on day 10 and 15. The results are biologically plausible and supported by evidence from systematic review indicating therapeutic zinc does have an effect in lowering treatment failure, although overall evidence is still mixed [21]. The burden and complexity of neonatal bacterial sepsis remain significant in the contemporary era and the need for adequately powered studies to assess the effectiveness of better therapeutic options is continually underscored. Very large multicenter randomized controlled trials involving well-defined zinc supplementation doses, baseline zinc measurement, microbiological outcomes, treatment failure, mortality, hospital stay, and longer term follow-up are needed to determine the exact place of zinc supplementation as an adjunctive therapy for neonatal sepsis.

6. CONCLUSION

Adjuvant zinc supplementation with standard antibiotic treatment resulted in significantly more neonates reaching “no sepsis” on day 10 and 15 than did antibiotic treatment alone. The observed difference at day 5 was not significant but progressive improvement in treatment response was noted during the subsequent follow-up with 68.6% of the neonates in the zinc group having the predefined treatment response at day 15 compared to 39.2% in the control group. Based on the results, zinc could be considered as a potentially beneficial add-on therapeutic agent for the treatment of neonates with high probability of neonatal sepsis. But the existing literature is not uniform, as past randomized trials have shown inconsistent results of the effects on various clinical outcomes. The findings of the present study should thus be considered as supportive evidence of general zinc supplementation rather than conclusive. Prior to universal implementation of neonatal sepsis treatment protocols with adjuvant zinc, larger, multicenter, randomized controlled trials with standardized dose, microbiological evaluation, safety monitoring, and longer-term follow-up are recommended.

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