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ORIGINAL ARTICLE

Zinc Supplementation for Reducing Mortality in Patients with Neonatal Sepsis: A Systematic Review and Meta-Analysis of Randomized Controlled Trials

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ABSTRACT

Background: Neonatal sepsis remains a leading cause of neonatal mortality worldwide, disproportionately affecting low- and middle-income countries. Zinc, a micronutrient involved in immune regulation and host defense, has been proposed as an adjunct to antimicrobial therapy; however, evidence regarding its efficacy in reducing mortality and improving clinical outcomes in neonatal sepsis remains inconclusive.

Objectives: This study performed a systematic review and meta-analysis to evaluate existing evidence from randomized controlled trials (RCTs) on the effect of zinc supplementation on mortality, length of hospital stay (LOS), and levels of CRP and procalcitonin in neonatal sepsis.

Methods: CENTRAL, MEDLINE, and EMBASE were comprehensively searched. Eligible studies included RCTs of neonates with sepsis receiving adjunctive zinc supplementation. Risk of bias was assessed using the Cochrane RoB 2 tool. Fixed-effect meta-analysis was performed with sensitivity analyses to explore heterogeneity.

Results: Four RCTs (n=1,082) were included for analysis. The pooled estimate showed no significant reduction in mortality with zinc supplementation (OR 0.81; 95% CI [0.54,1.24]; I^2=49%). Sensitivity analysis excluding one lower-dose, shorter-duration study demonstrated a significant mortality reduction (OR 0.44; 95% CI [0.22,0.86]; I^2=0%), suggesting a possible dose–response relationship. Zinc supplementation was associated with a greater decline in CRP and procalcitonin in two trials but did not significantly reduce LOS. Most included studies were judged to have a high risk of bias, limiting certainty of evidence.

Conclusion: Adjunctive zinc at doses ≥1.4 mg/kg/day for at least 10 days may reduce mortality rate and accelerate resolution of inflammatory markers in neonatal sepsis. Definitive, adequately powered multicenter trials are needed before routine implementation can be recommended.

KEYWORDS: Neonatal Sepsis, Zinc, Neonatal Mortality

INTRODUCTION

Despite the advancements in neonatology, neonatal mortality remains a major public health issue. The World Health Organization (WHO) reports that there have been 2.3 million neonatal deaths in 2022, equating to over 6,300 newborn deaths daily. This report confirms that neonatal mortality accounts for 47% of all child fatalities under 5 years of age.[1]

In 2024, the Philippines registered a neonatal mortality rate (NMR) of 14.2 per 1,000 live births, the highest among Southeast Asia's biggest economies and just slightly below the global NMR of 17 deaths per 1,000 live births.[1] The most recent Global Burden of Disease (GBD) study reported that 3.88 million newborns suffered from sepsis, leading to 232,000 deaths, and

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establishing neonatal sepsis as one of the leading causes of neonatal mortality.[2,3] Neonatal infections in the Philippines accounted for 12.2% of the neonatal mortality rate, with sepsis contributing up to 7.7%.[2] Neonatal sepsis is a life-threatening condition targeting infants in their first 28 days of life, with its presentation ranging from non-specific symptoms to clinical deterioration.[3,4] The standard care in the management of neonatal sepsis involves the administration of antimicrobials mostly through synergistic antimicrobial therapy.[4-6] Other interventions, especially for severe sepsis, include double volume exchange transfusion and intravenous immunoglobulin.[6] However, these are costly and invasive, and likely to result in increased adverse effects.

Vulnerability of newborns to sepsis highlights their immune immaturity and neonatal immune tolerance.[7,8] The transitional neonatal immunity reflects a significantly higher threshold for an appropriate and protective antimicrobial response to microbes encountered during primary infections to spare the newly forming beneficial microbiota in the body, and to save as much energy as possible for growth and development.[7,8] Multiple studies have indicated that immune modulation through certain micronutrient administration has the potential to significantly improve protection against sepsis in the neonatal age group. Many of these studies demonstrated that zinc supplementation, when used alongside antimicrobials, can improve neonatal sepsis outcomes.

The seminal work of Prasad during the 1960s established zinc as an essential mineral in enhancing the immune system.[7] Research using animal models and human clinical trials demonstrated that zinc supplementation reduces organ damage and levels of many inflammatory cytokines, while zinc deficiency increases vulnerability to infectious diseases by weakening several mediators of host immunity, including the skin barrier, and both acquired cellular and humoral immunity.[7-11] Knoel et al.[9] observed that animal models with polymicrobial sepsis receiving zinc supplements had a lower mortality rate. Zinc's effect on immune cells highlights its critical involvement in the normal development and function of numerous crucial organs, cells, and immune effectors.[7-11] Recent developments in molecular and cellular biology have shed light on zinc's role in the synthesis of some interleukins and tumor necrosis factor.[7-11] Ali et al.[10] detailed that short-term zinc supplementation decreases the bacterial load and reduces the activity of NF-κB in vital organs, while Gammoh et al.[12] confirmed that during systemic infection, hepatic sequestration of zinc takes place to result in the production of IL-6, TNF-α and antimicrobial peptides. These processes, however, can lead to a marked reduction of the body's zinc levels. The persistent depletion of neonatal zinc stores during sepsis, along with the rapid physiological decline in zinc levels in neonates, especially those born prematurely, heightens the risk of sepsis-related mortality in this population.[10-11,18,20]

The WHO recommends a supplemental dose of 10 mg daily for infants under six months of age with acute diarrhea, but the current utilization of zinc supplementation in the neonatal age group is primarily to support growth and development among preterm and low-birth weight infants with doses ranging from 2 to 5 mg/kg/day.[12,13] Studies have suggested that oral zinc administration in these groups improved their weight gain, length, and head circumference compared to those who did not receive the intervention.[14,15] At present, no clinical guidelines have unequivocally endorsed oral zinc supplementation as an adjunctive treatment for patients with neonatal sepsis. There is growing evidence that zinc supplementation during sepsis can positively influence neonatal mortality, reduce hospital stay duration, and accelerate the decline in inflammatory markers.[7-11,14-15]

Neonatal sepsis is a life-threatening condition, and all possibly beneficial interventions should be explored to reduce mortality associated with it. A simple yet potentially effective intervention, such as zinc supplementation, could improve outcomes and may prove to be cost-effective, particularly in resource-limited settings. A systematic review of clinical trials on zinc supplementation for neonatal sepsis could strengthen the existing evidence base, recommend new clinical practices, and identify areas for future research. A meta-analysis, if appropriate, could further elevate the study's aim of informing policymakers, clinical guideline developers, and healthcare providers to potentially result in better policy and clinical decision changes. This study aimed to perform a systematic review and meta-analysis to identify and evaluate existing evidence from randomized controlled trials on the effect of zinc supplementation compared to placebo or no zinc supplementation on mortality, length of hospital stay (LOS), and levels of inflammatory markers [C-reactive protein (CRP), procalcitonin] in patients with neonatal sepsis. Specifically, this study sought to: (1) Determine the effect of adjunctive zinc supplementation compared to placebo or standard care alone on mortality among neonates with sepsis; (2)

Evaluate the effect of zinc supplementation on the levels of inflammatory markers, specifically C-reactive protein (CRP) and procalcitonin, among patients with neonatal sepsis compared to placebo or no zinc supplementation; (3) Investigate the effect of zinc dose and duration of supplementation on mortality, length of hospital stay, and level of inflammatory markers by examining pooled estimates and conducting a sensitivity or sub-group analyses; and (4) Provide a succinct synthesis of available evidence on the effect of zinc supplementation in the management of patients with neonatal sepsis.

MATERIALS AND METHODS

Study Design and Outcome Measures

We conducted a systematic review and meta-analysis with mortality as the primary outcome, while the secondary outcomes were LOS and levels of CRP and procalcitonin, in patients managed for neonatal sepsis who received zinc supplementation compared to those who did not.

Sampling Strategy and Selection Criteria

Major scientific databases like Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE via OVID (1946 to 2025 June 03), and EMBASE via OVID (1947 to 2025 June 03) were comprehensively searched from their inception up to June 03, 2025, to identify all published studies related to zinc supplementation in patients being treated for neonatal sepsis. There were no race and language restrictions during the search. Research written in non-English language was translated using Google Translate[16-17], and if required, by reaching out to the original authors for clarification. The following selection criteria were utilized: (1) Only randomized controlled trials of zinc supplementation compared to placebo or no zinc supplementation in neonates with sepsis were included; (2) The target population was restricted to neonates (<28 days of life) diagnosed with and being treated for sepsis, irrespective of their gestational age, birth weight, and severity of their illness; (3) The target population should have received zinc supplementation in any dose and duration versus placebo or no zinc supplementation, along with the standard of care; and (4) Studies should have identified at least some of the outcomes of interest.

These databases were searched using MeSH and free-text search terms for zinc, neonates, and sepsis, with database-prescribed limiters for neonates. Search terms and facets were combined by Boolean operators where appropriate. Once a list of prospective studies had been generated, careful elimination of duplicates was conducted manually. Two reviewers independently screened the titles and abstracts of each study. They collected, compared, and discussed to generate a list of studies eligible for full-text retrieval. Disagreements were settled by a third review author. They also systematically checked the reference lists of relevant papers to find any further studies that were not available in the databases. The selection criteria were applied to the chosen full-text studies until they arrived at a final list of papers suitable for data extraction.

Data Extraction and Risk of Bias Assessment

The Cochrane Collaboration's Risk of Bias Assessment Tool version 2 (RoB 2) for randomized controlled trials was used in assessing the risk of bias in included studies. This tool evaluates five domains of bias that are presently known to influence outcomes of randomized trials.[18-21] These five domains are: (1) Bias arising from the randomization process; (2) Bias due to deviations from the intended interventions; (3) Bias due to missing outcome data; (4) Bias in measurement of the outcome; and (5) Bias in selection of the reported result.[18-21] Each domain of bias employs the use of signaling questions to obtain information about the trial's design, its methods, and reporting, which are significant to an assessment of risk of bias. The answers to these questions were incorporated into algorithms that helped estimate the overall risk of bias for each study included.[18-21] Individual studies' risk-of-bias judgments were classified as having "low risk of bias", "some concerns", or "high risk of bias".[18-21] Two reviewers independently assessed for the risk of bias utilizing RoB 2 for randomized controlled trials. When information regarding any of the needed outcome variables was missing, attempts were made to contact the authors of the included studies.

Data were extracted using a specifically designed data abstraction form, and information collected were: (1) first author's last name, (2) sample size, (3) the year of publication, (4) intervention and control details, (5) outcomes of interest (mortality, LOS, level of procalcitonin or CRP), (6) other important parameters like the gestational age of participants, birth weight, severity of sepsis, dose and duration of zinc administered, and presence of any adverse events. Data extraction from the included studies was performed separately by two review authors using the data extraction form. The presence of disputes was resolved through discussions, or by consulting a third review author. Information gathered using the data extraction form was summarized in a tabulated literature matrix (Table 1) and all data extracted were entered into Review

Manager Web (RevMan Web) 2025 to streamline data synthesis.

Data Synthesis

Meta-analysis was conducted using RevMan Web 2025 utilizing the fixed effect model. The Mantel-Haenszel test was performed to estimate the group differences in mortality using the odds ratio (OR) with its corresponding 95% confidence interval. Data for continuous variables (LOS, inflammatory marker levels) were collected as means + standard deviation (SD) for each group to estimate the pooled effect size. If standard error (SE) was reported instead of SD, this was converted to SD by multiplying the given SE by the square root of the sample size.[18] Mean differences and their 95% confidence intervals were calculated using the inverse variance method. The I^2 statistic was used to examine heterogeneity among the studies. Interpretations of I^2 were based on the Cochrane Handbook, which states that I^2 between 0% to 40% might not be important; I^2 of 30% to 60% suggests moderate heterogeneity; I^2 of 50% to 90% may represent substantial heterogeneity; and an I^2 from 75% to 100% indicates considerable heterogeneity.[18] When moderate to considerable heterogeneity was apparent, it was assessed using sensitivity analysis to determine whether such a difference is a result of bias or due to methodological diversity between the included trials. Statistical significance is set at a p-value of <0.05. The reviewers intended to assess the presence of publication bias using funnel plots once the number of included studies reached 10 or more.

RESULTS

A total of 124 records were identified through database searches, with an additional 2 studies identified via reference screening (Figure 1). Following the deduplication process, 68 studies remained for further screening. A total of 59 studies were excluded after reviewing titles and abstracts, leaving 9 studies deemed eligible for full-text retrieval and thorough review. Among these, 5 were further excluded due to various reasons, resulting in 4 studies being included for both qualitative and quantitative synthesis (Figure 1). Among the 5 excluded studies, 2 were sub-studies derived from an already included trial, utilizing the same patient population (Banupriya et al., 2018 and Banupriya et al., 2020).[4,22] One study (Terrin et al., 2013) administered zinc supplements to non-septic neonates to evaluate its potential role in preventing neonatal sepsis and other morbidities.[23-24] Bhatnagar et al. (2012)[25] enrolled participants aged 7 to 120 days with probable serious bacterial infection, and Ali et al. (2020)[10] did not report any of the predefined outcomes of interest.

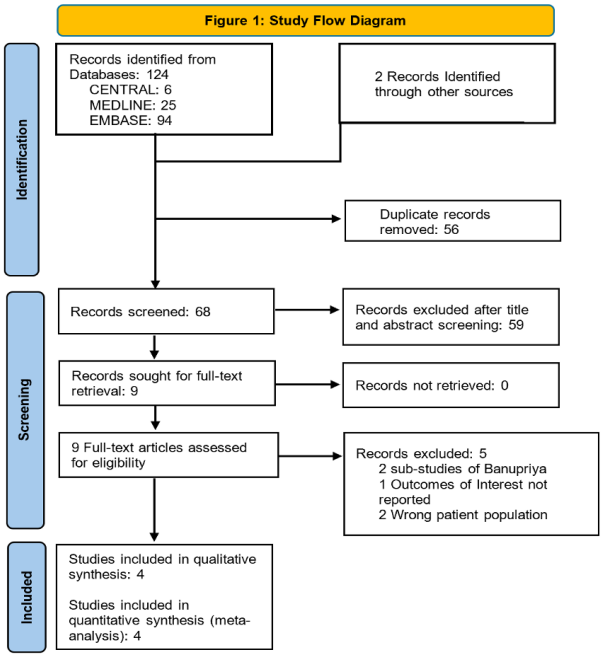

Table 1 summarizes the key characteristics of the 4 included studies. These studies were published between 2013 and 2020. Two studies were conducted in Egypt by the same research group (Elfarargy et al., 2016 and Elfarargy et al., 2020)[26,27] along with one study each from India (Banupriya et al., 2015)[29] and Nepal (Mehta et al., 2013)[28]. All enrolled participants were neonates with gestational age ≥ 32 weeks. Participants in the treatment group received zinc supplementation enterally at varying doses and durations, with Mehta (2013) administering the lowest dose at 1 mg/kg/day of elemental zinc and the shortest duration (mean=143 hours), whereas the rest of the studies provided zinc at 1.4 to 3 mg/kg/day and was given for at least 10 days. All studies used zinc supplementation as an adjunct to antibiotic therapy in the management of neonatal sepsis. The reported sample sizes ranged from 88 to 614. Mortality rate was reported in all included studies, but only the studies by Elfarargy provided values for CRP and procalcitonin. Length of hospital stay was reported by both Banupriya (2015) and Mehta (2013), but not in the studies by Elfarargy.

Table 1. Characteristics of included studies (n=4)

Author/Date	Country	Population	Objectives	Interventions	Outcomes
Banupriya (2015)	India	88 neonates ≥32 weeks and < 28 days with diagnosis of sepsis; 44 participants each for the intervention and control groups	To find the effect of zinc supplementation on the outcome of neonatal sepsis at one month of age.	Enteral zinc at 3 mg/kg/day BID for 10 days for both intervention and control arms along with antibiotics.	Serum zinc levels after 10 days, mortality and neurological findings at 1 month of age
Elfarargy (2016)	Egypt	200 neonates (treatment 36.3±1.98 weeks; control 36.5±2.2 weeks), 100 participants for each study arm, diagnosed with sepsis	To detect the effect of zinc as an adjuvant treatment in the management of neonatal sepsis.	Treatment group received zinc sulfate monohydrate given enterally at a dose of 3 mg/kg/day, BID for 15 days. Control group received placebo. Both study arms were given antibiotics based on a standard protocol.	Improvement in sepsis score, difference in mortality rate and hs-CRP levels after treatment
Elfarargy (2020)	Egypt	180 preterm neonates (34-36 weeks gestational age) with late-onset sepsis	To detect the role of zinc supplementation in preterm neonates with late-onset sepsis.	90 neonates belonged to the treatment group and received 1.4 mg/kg/day of elemental zinc orally for 10 days along with antibiotics. Control group only received antibiotics.	Improvement in sepsis score, mortality rate, and levels of CRP and procalcitonin
Mehta (2013)	Nepal	614 neonates ≥32 weeks with probable neonatal sepsis	To study the role of zinc in the treatment of neonatal sepsis.	307 neonates received 1 mg/kg/day of enteral zinc supplementation with a mean duration of 143 hours, control group (n=307) received placebo, both intervention is in conjunction with antibiotic therapy.	Decrease in mortality rate, duration in hospital stay and need for higher lines of antibiotic therapy

Risk of Bias Assessment

Figure 2 presents our risk-of-bias judgments for the included studies. The studies by Banupriya (2015) and Mehta (2013) were assessed as having "low risk of bias" in the randomization process because both demonstrated appropriate allocation sequence generation, particularly in their randomization techniques and allocation concealment methods. In contrast, the studies by Elfarargy lacked a detailed description of their randomization procedures. Only Mehta (2013) provided a thorough account of the blinding methods for outcome assessors and investigators. The absence of clear descriptions in the other studies introduced uncertainty regarding investigator blinding, leading to their classification as having "some concerns" for risk of bias due to deviations from the intended interventions. All studies were judged to have a "low risk of bias" in the domain for ROB due to missing outcome data. Three studies did not have any missing data and employed the Intention to-Treat (ITT) analysis. Mehta (2013) reported a minimal attrition rate, with well-justified reasons for the missing data. The gravity of the missing data in the study by Mehta (2013) was unlikely to have influenced the overall outcomes. The reviewers were not able to review the trial protocols of all included studies. Attempts to contact the study authors were made, but no responses were received. Banupriya (2015) registered their protocol with the clinical trials registry of India. As it is unclear whether the prespecified analysis plans were followed in all studies, each was judged to have "some concerns" regarding the risk of bias assessment in the measurement of outcomes and selection of the reported results. Mehta (2013) has an overall risk of bias assessment classified as "some concerns" while the rest of the studies fall under "high risk of bias". Owing to the small number (n=4) of included studies, publication bias was not assessed.

Effect of Zinc Supplementation on Mortality

This study compared the effects of zinc supplementation among neonates diagnosed with sepsis to a control group, with mortality as the primary outcome. As shown in Figure 3a, meta-analysis of the four studies comprising 1,082 participants demonstrated no statistically significant difference between the zinc supplementation group and the control group (OR: 0.81; 95% CI: 0.54, 1.24; p=0.34). The heterogeneity among the studies was moderate (I^2=49%; Chi^2=5.87, p=0.12), suggesting that variability among the included studies was present but not substantial. To investigate the source of this heterogeneity, a sensitivity analysis was made by excluding the study of Mehta (2013), which differed from the other studies in the dose and duration of zinc administered. Mehta (2013) provided the lowest dose of supplemental zinc at 1 mg/kg/day with a mean duration of 143 hours (6 days), while the other studies administered zinc at higher doses starting from 1.4 mg/kg/day and given for 10 days, with Elfarargy (2020) giving it for 15 days. Pooled estimate of effect (Figure 3b) of the remaining three trials (n=468) showed a statistically significant reduction in mortality (OR: 0.44; 95% CI: 0.22, 0.86; p=0.02), with no evidence of heterogeneity (I^2=0%; Chi^2=0.33, p=0.85).

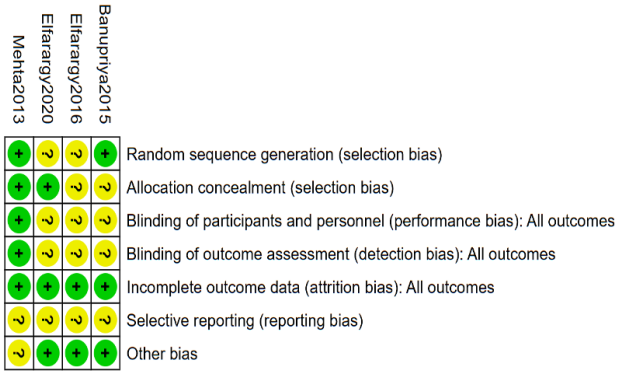

Figure 2. Risk of bias summary

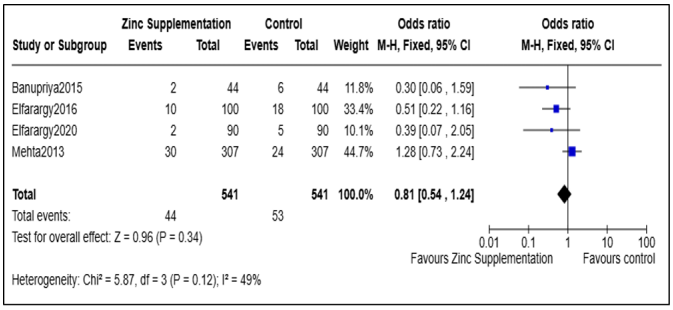

Figure 3a. Forest plot for the effect of zinc supplementation on mortality

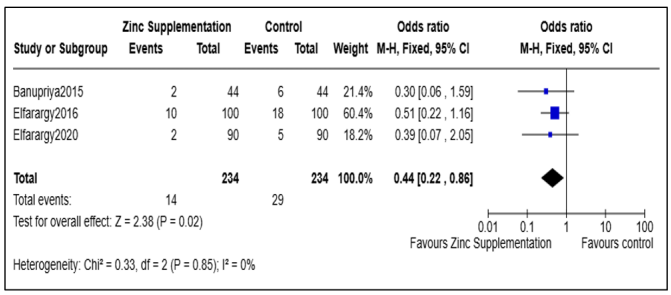

Figure 3b. Forest plot for the effect of zinc supplementation on mortality after sensitivity analysis

Table 2. Effect of zinc supplementation on secondary outcomes

Study ID	Zinc Group	Control Group	Mean Difference	P value
		CRP (mg/ml)		
Elfarargy (2016), mean (SD)	10.9 (±4.95); n=100	22.08 (±9.09); n=100	-11.18	0.044
Elfarargy (2020), mean (SD)	5.3 (±1.8); n=90	6.1 (±2); n=90	-0.8	0.008
		Procalcitonin (ng/ml)		
Elfarargy (2020), mean (SD)	0.39 (±0.13); n=90	0.61 (±0.22); n=90	-0.22	0.044
		Length of Hospital Stay		
Mehta (2013), mean (SD) in hours	142.85 (+69.41); n=307	147 (±73.13); n=307	-5.06	0.841
Banupriya (2015), median (range) in days	15 (10-25); n=44	15 (11-28); n=44	0.00	0.69

Two studies evaluated the effect of zinc supplementation on LOS in neonatal sepsis, both showing no statistically significant difference between the treatment and the control groups. Mehta (2013) reported a mean (±SD) LOS of 142.85 (±69.41) hours in the zinc-supplemented group and 147 (±73.13) hours in the control group (p=0.841). As seen in Table 2, the median LOS in the study by Banupriya (2015) was 15 days in both the zinc and the control groups (p=0.69). Given the differing methods of reporting LOS, with Mehta (2013) reporting it as mean (SD) and Banupriya (2015) using median (range), a meta-analysis is also not ideal. However, an exploratory pooled estimate comparing LOS in the zinc-supplemented group with the control group across the two studies can be obtained by converting the necessary outcome data in the Banupriya (2015) study into hours and estimating the standard deviation from the reported range. From these conservative estimates, a meta-analysis utilizing the random effects (Dersimonian-Laird) model was performed, demonstrating a statistically not significant pooled mean difference between zinc and control groups of -5.06 hours (95% CI: -16.24, 6.13; p=0.38) (Figure 4).

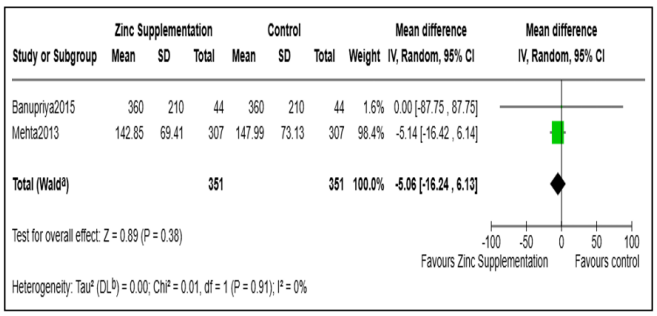

Figure 4. Forest plot on the effect of zinc supplementation on length of hospital stay (LOS) using an exploratory pooled estimate

DISCUSSION

This review included four single-center clinical trials conducted in the neonatal intensive care units from hospitals in low- and middle-income countries (LMICs). Three of the studies were judged to have a high overall risk of bias, while the trial by Mehta (2013) was rated as having some concerns. Evidence across these studies did not demonstrate a statistically significant effect of zinc supplementation on the reduction in the mortality rate in patients being treated for neonatal sepsis. The moderate heterogeneity prompted a sensitivity analysis utilizing the leave-one-out approach, resulting in the exclusion of the study by Mehta (2013), which provided the lowest dose and shortest duration of zinc administered among the included studies. Banupriya (2015) provided zinc supplements at 3 mg/kg/day, while Elfarargy (2016) and Elfarargy (2020) administered zinc at 3 and 1.4 mg/kg/day, respectively. All three remaining studies administered zinc for 10 days. After exclusion, the pooled estimate of the three studies revealed a significant reduction in mortality, with no evidence of heterogeneity, suggesting that a higher dosage of at least 1.4 mg/kg/day and a longer duration for at least 10 days may have influenced the overall effect estimate.

In the studies by Elfarargy, CRP levels declined in both the intervention and control groups following a 10-day treatment period; however, the decline was significant and more rapid in the zinc group. Similarly, Elfarargy (2020) reported that zinc supplementation led to significantly lower procalcitonin levels compared to antibiotic therapy alone. The observed significant reductions in both CRP and procalcitonin levels suggest that adjunctive zinc therapy may lead to a faster resolution of the systemic inflammatory response associated with neonatal sepsis. These findings are consistent with previous studies that support the anti-inflammatory or immunomodulatory function of zinc.

Across the two clinical trials that reported on the effect of zinc supplementation on LOS, there was no substantial evidence that zinc shortens the duration of hospitalization. Mehta (2013) found no difference in mean hours of hospitalization; Banupriya (2015) likewise reported no statistically significant difference when LOS is measured in days. The pooled estimate between these two trials suggests a very small reduction (-5 hours) in LOS with zinc, but the 95% CI crosses zero and the p-value was not significant. Given the approximations used (estimated mean/SD from median/range), this pooled estimate is exploratory and not strong evidence that zinc changes LOS.

Across all included studies, zinc supplementation was well tolerated and there were no reports of serious adverse events.

The predominance of studies with high risk of bias raises methodological concerns and may warrant downgrading the certainty of evidence if the GRADE approach is to be performed. Consequently, the findings of this review should be interpreted with caution, as the identified biases may have contributed to the observed variability and imprecision in the estimated effects of zinc supplementation.

Every effort was undertaken to minimize error in the data collection process. Attempts to contact study authors were made to obtain supplementary pertinent data for inclusion in the analysis, but no response was received. One major concern in the review process was the potential for reporting or publication bias despite the comprehensive search strategy, including searching reference lists of the included studies and relevant review articles. Because the meta-analysis contained fewer than ten studies, assessment of publication bias through examining symmetry in funnel plots was not performed. Evaluating the included studies' prespecified analysis plan cannot be reported because their trial protocols were inaccessible.

Two systematic reviews have evaluated the effect of zinc supplementation in neonates with sepsis. Tang et al. (2019)[30] included four clinical trials and found a significant reduction in sepsis-related neonatal mortality. However, three of the four clinical trials analyzed were interrelated studies that were published sequentially from 2013 to 2016 and have utilized the same patient population, thus seriously compromising the validity of their findings. Similarly, the review by Irfan et al. (2022)[31] was initially criticized for including three studies using data derived from the same patient cohort. The authors subsequently addressed this concern and made revisions in their analysis. The corrected version included nine randomized controlled trials involving participants ranging from newborns to young infants. Consistent with our finding, Irfan et al. (2022) have found no significant reduction in the mortality rate between the zinc and control groups. Despite the moderate heterogeneity in mortality outcomes, the authors did not conduct a sensitivity analysis. However, they performed a subgroup analysis stratifying the studies according to the duration of zinc supplementation, which revealed a significant reduction in mortality when zinc was administered for at least 10 days, with an even greater effect observed when zinc was given for 15 days. No other systematic reviews were found that address the impact of zinc supplementation on inflammatory marker levels and LOS.

CONCLUSION AND RECOMMENDATIONS

This systematic review and meta-analysis found that adjunctive zinc supplementation in patients with neonatal sepsis may reduce mortality rate and accelerate reduction of CRP and procalcitonin when administered at doses $\geq$ 1.4 mg/kg/day for at least 10 days. However, zinc supplementation did not have a statistically and clinically significant effect in shortening the length of hospital stay. The certainty of evidence is limited by the small number of available clinical trials and their clinical diversity and variability of risk of bias. Despite these findings, the current evidence remains insufficient to support its routine clinical use.

Zinc supplementation in neonates has the potential to impact important outcomes and warrants further research. Conducting well-designed, adequately powered multi-center randomized controlled trials to validate these findings, and to clarify the optimal dose and duration of administration in neonatal sepsis, should be included in future reviews. Trials should also incorporate standardized outcome measures, including gestational age, birth weight, nutritional status, and cost-effectiveness, to facilitate comparability and meta-analytic synthesis. Evidence generated from such studies could inform the development of evidence-based clinical guidelines and potentially establish zinc supplementation as a safe, cost-effective adjunct in the management of neonatal sepsis, especially in resource-limited settings.

Conflicts of Interest

None declared.

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