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Review Article OPEN ACCESS

Adjuvant Zinc Therapy in Young Infants with Sepsis: A Systematic Review

Raisa Enayet Badhan*[1], Md. Jahangir Alam[2]

Abstract

Introduction: *Two of the main risk factors for neonatal sepsis are prematurity and low birth weight. Previous researches demonstrated the advantages of zinc supplementation for small-for-gestational age delivery outcomes and during pregnancy. However, there is little data on the possible advantages of supplementing with zinc to cure or prevent serious infections in this age group. Aim of this review is to evaluate the effectiveness of zinc supplementation as a preventative and therapeutic measure in young infants with sepsis.* ***Materials and Methods:*** *PubMed, Elsevier Science Direct, Google Scholar, MEDLINE, Cochrane CENTRAL, and additional databases were searched for articles to be reviewed. Included studies were evaluated the effects of therapeutic and preventive zinc supplementation in young infants in relation to the incidence and results of suspected sepsis. Seven randomized controlled trials involving 2,081 infants were included.* ***Results:*** *Certain research indicates that zinc supplementation may have a protective effect on the neonatal mortality rate (NMR) of preterm newborns, but it has no influence on the incidence of sepsis. Therapeutic zinc was linked to a considerable decrease in treatment failure in young newborns. There was no discernible impact of therapeutic zinc supplementation on hospital stay or NMR in newborns.* ***Conclusion:*** *Supplementing with zinc has no significant effect on hospital stay or sepsis prevention, however it may lower mortality and treatment failure in early newborns. Larger sample numbers and additional research are required to determine the direction and extent of any impacts.*

Keywords: *Zinc, Neonatal sepsis, Young infant, Treatment, Efficacy, Mortality.*

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***1. Corresponding Author:**
Dr. Raisa Enayet Badhan
Medical Officer
National Institute of Burn and Plastic Surgery
Dhaka, Bangladesh.
Email: raisabadhan@gmail.com
Orcid: 0000-0002-2000-4995
Phone: +8801797507092

2. Dr. Md. Jahangir Alam
Medical Officer (OSD), DGHS
Department of Ophthalmology
Bangabandhu Sheikh Mujib Medical University
Shahbag, Dhaka, Bangladesh.
Email: drjahangir.alam2014@gmail.com
Orcid: 0009-0004-5557-2038

Introduction:

One of the main causes of morbidity and death in neonates and early infants is sepsis[1]. With an estimated 20 million illnesses and 2.9 million deaths in children under five, children accounted for over half of all sepsis cases globally[2]. In high-income nations, the incidence of neonatal sepsis is estimated to be 1–12 per 1,000 live births, while in low and middle income countries (LMICs), it can reach up to 38 per 1,000 live births[3]. Depending on when it first manifests, neonatal sepsis can be classified as either early-onset sepsis (EOS) or late-onset sepsis (LOS). While the infection in LOS is typically obtained from the community or in a hospital setting, EOS is typically acquired vertically from a contaminated mother. Neonatal sepsis is primarily associated with preterm birth and low birth weight[4]. Maternal intrapartum infection, numerous gestations, prolonged labor, premature rupture of the membrane, and meconium aspiration syndrome are risk factors for EOS[5]. A number of risk factors, including mechanical ventilation, hospitalization, extended parenteral feeding, intravascular catheterization, and underlying respiratory or cardiovascular disorders, are also associated with LOS[6]. Research indicates that initiating antibiotic therapy at an early age in infants suspected of sepsis can lower their risk of death and morbidity[3]. The most often prescribed antibiotic classes for neonatal sepsis are beta-lactams (e.g., penicillins, cephalosporins, monobactams, and carbapenems), aminoglycosides (e.g., gentamycin), and glycopeptides (e.g., vancomycin and teicoplanin)[7]. Approximately 85.0% of sepsis-related morbidity and mortality worldwide happened in LMICs[2], where there is an urgent need for interventions, particularly those that are affordable and easily accessible in low-resource settings. Zinc is an important vitamin having involvement in immunity, growth, and reproduction[8]. The World Health Organization (WHO) has designated zinc as a cost-effective

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intervention in the form of supplementation and fortification[9]. There is proof that zinc supports growth, immunity, brain function, and motor function. Zinc has anti-inflammatory and anti-oxidant properties that influence T-cell activity and the adaptive immune system[10]. The two most prevalent children infections in the world, pneumonia and diarrhea, can be effectively treated with zinc[11]. Targeting maternal nutrition is essential to ensuring that babies have an appropriate proportion of zinc. Low birth weight, fetal loss, fetal growth retardation, and preterm deliveries have all been related to lower maternal zinc status[12]. Reduced placental zinc transport and, thus, a decreased fetal zinc supply could result from reduced plasma zinc levels. The United Nations Children's Fund (UNICEF) advises all expectant mothers in underdeveloped nations to take numerous micronutrient supplements, including zinc[13]. Every episode of diarrhea in children should be treated with zinc supplementation for 10–14 days, in addition to oral rehydration and feeding, according to the World Health Organization[14]. However, because previous research on breastfed children under the age of six months failed to demonstrate any benefit, the significance of zinc in the treatment of diarrhea in young infants under the age of six months is unclear. Other consequences, like severe infections, haven't been thoroughly researched[15]. Increased serum zinc levels have been linked to better prognosis and immunity in cases of newborn sepsis[16]. To ascertain the effectiveness and safety of therapeutic and preventative zinc supplementation in lowering morbidity and mortality of clinical or blood culture-proven sepsis in newborns and early infants (the first four months after birth), we conducted a comprehensive study. There have been inconsistent conclusions on the benefits of zinc supplementation in neonates from controlled trials and systematic reviews on mortality and morbidity related to sepsis[17-21].

Materials and Methods:

Articles to be reviewed were chosen from PubMed, Elsevier Science Direct, Google Scholar, MEDLINE, Cochrane CENTRAL and other databases. Studies assessing preventive and therapeutic zinc supplementation in young infants in relation to incidence and outcomes of suspected sepsis were included. Seven randomized controlled trials involving 2,081 infants were included.

Objectives:

The following research goals will be covered by this review:

1. Compare the safety and efficacy of oral zinc supplementation for prevention and treatment against either no intervention or a placebo in cases of sepsis in newborns and early infants.

2. Identify the newborns and early baby subgroups that would benefit most from zinc supplementation.

Eligibility Criteria:

Randomized controlled trials (RCTs) were included. Non randomized and observational studies were excluded. The target population of the review was young infants (<4 months). There was no restriction applied for birth weight, gestational ages, and underlying comorbidities. This review focused on oral zinc supplementation in any form and dose in addition to standard care. Trials with additional micro-/macronutrient or antibiotics were considered if they were given equally in both intervention and placebo groups. Characteristics of individual studies included in the review article are shown in Table I.

Table I: Characteristics of individual studies included in the review article

Title	First author	Year	Source	Study population (cases/controls)	Conclusion
Zinc as Adjunct Therapy in Neonatal Sepsis	Ali M	2020	Med Today. 2020;32(2):112– 6. https://doi.org/10.3329/medtoday.v32i2.48825	144	Oral zinc as adjunct therapy shortens the clinical recovery time
Short Term Oral Zinc Supplementation among Babies with Neonatal Sepsis for Reducing Mortality and Improving Outcome - A Double-Blind Randomized Controlled Trial	Banupriya N	2018	Indian journal of pediatrics, 85(1), 5–9. https://doi.org/10.1007/s12098-017-2444-8	150	Short term zinc supplementation of newborns with sepsis reduces mortality.
Zinc as adjunct treatment in infants aged between 7 and 120 days with probable serious bacterial infection: a randomised, double-blind, placebo-controlled trial	Bhatnagar S	2012	Lancet (London, England), 379(9831), 2072–2078. https://doi.org/10.1016/S0140-736(12)60477-2	700	Zinc could be given as adjunct treatment to reduce the risk of treatment failure in infants aged 7-120 days with probable serious bacterial infection.
Zinc Supplementation in Preterm Neonates with Late-Onset Sepsis: Is It Beneficial?	El farargy MS	2022	American journal of perinatology, 39(10), 1097–1103. https://doi.org/10.1055/s-0040-1721659	180	Zn supplementation in preterm neonates with LOS is beneficial in improving the clinical and laboratory finding.
Zinc Supplementation in Preterm Neonates and Neurological Development, A Randomized Controlled Trial	Mathur NB	2015	Indian pediatrics, 52(11), 951–955. https://doi.org/10.1007/s13312-015-0751-6	100	Zinc supplementation till 3 month corrected age in preterm breastfed infants improves alertness and attention pattern; and decreases signs of hyperexcitability, and proportion with abnormal reflexes.
Oral zinc supplementation for reducing mortality in probable neonatal sepsis: a double blind randomized placebo controlled trial	Mehta K	2013	Indian pediatrics, 50(4), 390–393. https://doi.org/10.1007/s13312-013-0120-2	614	This study does not report decrease in mortality rates, duration of hospital stay and requirement of higher lines of antibiotic therapy following zinc supplementation in neonatal sepsis.
Zinc supplementation reduces morbidity and mortality in very-low-birth-weight preterm neonates: a hospital-based randomized, placebo-controlled trial in an industrialized country	Terrin G	2013	Am J Clin Nutr. 2013 Dec;98(6):1373-4. doi: 10.3945/ajcn.113.076489.	193	Oral zinc supplementation given at high doses reduces morbidities and mortality in preterm neonates.

Discussion:

The usefulness of zinc supplementation in early newborns is assessed in this review. There are 7 RCTs in this. According to RCTs, treating young infant sepsis with zinc supplementation at a dose of 3 mg/kg twice a day, in addition to antibiotics and supportive care, considerably lowers mortality. However, studies focusing just on neonatal sepsis (<1 month) did not discover this effect. Preventive zinc supplementation has also been linked to a decreased premature neonatal mortality rate. Comparing the effective dose across research should ideally take place inside the same investigation, comparing different doses.

Additionally, the studies revealed varying short-term zinc supplementation durations, highlighting the need for long-term intervention and follow-up research. The majority of research findings came from LMICs. Undernutrition and zinc deficiency continue to be serious public health issues in LMICs[22], where a number of factors including inadequate and inconsistent immunization, food insecurity, air pollution, overcrowding, low birth weight deliveries, and poor sanitation and hygiene increase the risk of infection. Developing large-scale intervention frameworks and figuring out the best ways to provide low-cost interventions to the underprivileged population in LMICs is crucial[23]. Supplementing and fortifying existing newborn and young child health and nutrition programs with zinc, a low-cost intervention with a favorable safety profile, is an excellent way to add this crucial minera[18]. Moreover, zinc insufficiency is particularly common in premature newborns. The death rate has improved in the two included studies on preventive zinc supplementation in premature neonates. Premature neonates need a sufficient intake of macronutrients and micronutrients for growth and rapidly growing organ systems since they missed a crucial stage of transplacental nutrition transfer during the third trimester of pregnancy. Because preterm infants have a lower ability to absorb zinc from the GI tract than full-term neonates do, they may benefit from a larger intake in order to increase growth and lower their risk of morbidities, which are common in preterm infants[24]. The majority of reviews that have been published have evaluated zinc's efficacy in treating or preventing common childhood illnesses including pneumonia and diarrhea, as well as those that affect older infants and preschoolers[25,26]. The effectiveness of zinc as a preventative and therapeutic agent for sepsis in the newborn and early infant age group is poorly supported by research. A more thorough examination of the included studies revealed significant subject overlap despite different study periods. Tang et al.'s previous review of four RCTs in neonates showed a significant reduction in the neonatal mortality rate and improvement in serum zinc levels in neonatal sepsis[17]. Moreover, the review presented mortality and patients who passed away as distinct outcomes with overlapping impact sizes. Smucker et al. conducted a recent study that narratively combined information from three RCTs[27]. The review revealed inconclusive results regarding the effectiveness of zinc supplementation as a therapy to reduce death in newborn sepsis. In comparison to placebo, newborns receiving preventative zinc supplementation had a similar incidence risk of bacterial sepsis, according to a newly published Cochrane analysis of two trials[21]. In order to give solid evidence in favor of zinc being prescribed as an adjuvant therapy to standard care for clinically severe sepsis in young newborns, RCTs with bigger sample sizes are required in the future. A significant trial evaluating the adjunct therapeutic benefit of zinc for lowering case-related mortality owing to severe bacterial infection in young infants (3–60 days old) was found in the literature search[28]. The trial is now taking place in India and Nepal. Further randomized controlled trials are required to ascertain whether supplementing pregnant women and/or young children with zinc might reduce the risk of sepsis and any associated mortality. Additional research evaluating the impact of zinc supplementation on brain development is required because zinc shortage raises the possibility of neurological disorders in childhood and adolescence[29]. Neurological results in newborns with sepsis significantly improved in one of the included trials[30]. Even though a one-month-old infant is too young to definitively identify any brain abnormalities, the results may have significance for further research.

Conclusion:

When given at a dosage of 3 mg/kg/day, therapeutic zinc supplementation during sepsis may considerably reduce treatment failure in young infants (less than 4 months) and perhaps lower the mortality rate in the same age group; however, caution must be exercised in interpreting this finding. Larger sample sizes are required for studies to offer solid proof in favor of zinc's advice for the treatment or prevention of clinically severe sepsis in young newborns.

Conflict of Interest: None.

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