2020

Is Oral Zinc Supplementation Effective In Reducing Mortality Rate In Neonatal Sepsis?

Abigail R. Smucker
Philadelphia College of Osteopathic Medicine

Is Oral Zinc Supplementation Effective In Reducing Mortality Rate In Neonatal Sepsis?

Abigail R. Smucker, PA-S

A SELECTIVE EVIDENCE BASED MEDICINE REVIEW

In Partial Fulfillment of the Requirements For

The Degree of Master of Science

In

Health Sciences – Physician Assistant

Department of Physician Assistant Studies
Philadelphia College of Osteopathic Medicine
Philadelphia, Pennsylvania

December 13, 2019

ABSTRACT

OBJECTIVE: The objective of this selective EBM review is to determine whether or not "Is oral zinc supplementation effective in reducing mortality rate in neonatal sepsis?"

STUDY DESIGN: Review of one randomized, double blind, controlled trial, one randomized controlled trial and one randomized, double blind, placebo-controlled trial published in English between 2013 and 2018.

DATA SOURCES: All three studies were gathered from peer-reviewed journals and found using PubMed.

OUTCOMES MEASURED: Patient mortality rate, defined as during hospitalization for treatment for Mehta el al. (*Indian Pediatr*. 2013;50(4):390-393. doi: S097475591200127 [pii]), within 1 month of birth for Newton et al. (*Indian J Pediatr*. 2016;83(4);289-293. doi:10.1007/s12098-015-1939-4 [doi]), and within 12 months of birth for Banupryia et al. (*Indian J Pediatr.* 2018;85(1):5-9. doi: 10.1007/s12098-017-2444-8 [doi]).

RESULTS: The RCT performed by Mehta et al. (*Indian Pediatr*. 2013;50(4):390-393. doi: S097475591200127 [pii]) showed no statistically significant reduction in the mortality rate among the septic neonates supplemented with oral zinc when compared to the placebo group (p=0.393). The mortality rate in the zinc group was 9.77% vs. 7.81% mortality rate in the placebo group. Newton et al. (*Indian J Pediatr*. 2016;83(4);289-293. doi:10.1007/s12098-015-1939-4 [doi]) similarly found no statistically significant reduction in mortality rate in those septic infants treated with zinc supplementation when compared to the no zinc group (p=0.27) . The mortality rate in the zinc group was 4.5% vs. 13.6% in the no zinc group. Conversely, Banupryia et al. (*Indian J Pediatr.* 2018;85(1):5-9. doi: 10.1007/s12098-017-2444-8 [doi]) found a statistically significant reduction in the mortality rate among septic neonates treated with oral zinc supplementation when compared to neonates who did not receive zinc (p=0.04). The mortality rate in the zinc group was 6.6% vs. 17.3% in the no zinc group.

CONCLUSIONS: The three RCTs evaluated in this review provided conflicting evidence on whether or not oral zinc supplementation is effective in reducing mortality rate in neonatal sepsis. Mehta et al. (*Indian Pediatr*. 2013;50(4):390-393. doi: S097475591200127 [pii]) and Newton et al. (*Indian J Pediatr*. 2016;83(4);289-293. doi:10.1007/s12098-015-1939-4 [doi]) demonstrated no statistically significant reduction in mortality rate whereas Banupryia et al. (*Indian J Pediatr.* 2018;85(1):5-9. doi: 10.1007/s12098-017-2444-8 [doi]) did acknowledge a statistically significant reduction in mortality rate. Due to inconclusive results and limitations noted in each study, further research is needed to better evaluate the effects of zinc supplementation in reducing mortality rate in neonatal sepsis.

KEY WORDS: Zinc supplementation, neonatal sepsis

INTRODUCTION

Neonatal sepsis is a systemic bacterial, viral, or fungal infection that affects infants ranging from birth to three months of age. Due to their immature immune system, newborns are at a higher risk for contracting infections. The infection can be passed from mother to baby or can be contracted from outside sources after delivery.[1] Once in contact with the causative agent, the infection travels through the newborn's blood stream causing a vast range of systemic symptoms. A newborn with sepsis may present with a fever, reduced sucking for feeding, diminished activity, lethargy, respiratory distress, hypoxia, seizures, vomiting and diarrhea.[1] Due to the debilitating nature of this disease healthcare personnel should have a low threshold for treating a newborn when one presents with early septic signs and symptoms.

Sepsis is a major cause of morbidity and mortality among the newborn population.[1] It is estimated that the incidence rate of neonatal sepsis in the United States is 0.77-1 per 1,000 live births.[2] The mortality rate ranges from 3-40% depending on the organism and whether the infection was early onset or late onset.[3] Specific neonatal populations, including preterm and low birth weight infants, have a higher incidence rate as well as mortality rate.[2] Among the survivors of the estimated 75,00 infants that contract sepsis each year, 47% will be hospitalized at least once more in their lifetime due to complications stemming from the disease.[4] Although an exact overall annual healthcare cost for neonatal sepsis has not been identified, the annual cost for neonatal sepsis caused by group B strep is estimated at $294 million.[5] Medical advancements in the field of neonatology continue, yet this deadly illness still prevails. Just as physician assistants specialize in a variety of areas of medicine, by specializing in neonatology they can help treat the youngest and most immunologically naïve patients.

Several pathogens are known to cause neonatal sepsis, with the leading pathogen being group B streptococcus. Other pathogens include, but are not limited to, *Escherichia coli*, *Streptococci virdans, Staphylococcus aureus,* and *Haemophilus influenzae.*[2] Whether transmission of the bacteria occurs vertically or horizontally, the gold standard treatment is IV antibiotics. Ampicillin with gentamicin is used for empiric treatment and vancomycin with an aminoglycoside is used for hospital acquired pathogens.[6] Once cultures are completed, antibiotic therapy can be tailored to the specific pathogen. In addition to the antibiotics, supportive treatment with IV fluids, oxygen and IV glucose is recommended.[6] Upon identification of a source, antibiotic treatment typically lasts 48 to 72 hours.[3] Considering group B strep is the leading cause of sepsis, medical efforts remain focused on prevention of vertical transmission from mother to baby through prophylactic treatment during labor.[3]

Zinc is a mineral that is essential in maintaining the strength and function of the body's immune system.[7] Deficiencies in this mineral impact the growth and function of T cells, B cells, cytokines, and phagocytes.[7] As mentioned earlier, newborns have an immature immune system and struggle to fight off even the most common bacteria. Previous studies have confirmed the benefits of zinc supplementation in increasing weight gain in low birth weight babies and decreasing infection rate of certain diseases such as malaria and infectious diarrhea.[7] Limited studies have attempted to evaluate the effects of zinc supplementation in neonatal sepsis.[7] This paper analyzes three randomized controlled trials to evaluate the effectiveness of zinc supplementation in reducing mortality rate of neonates with sepsis.

OBJECTIVE

The objective of this selective EBM review is to determine whether or not "Is oral zinc supplementation effective in reducing mortality rate in neonatal sepsis?"

METHODS

The key words used in the search of articles for this review included zinc supplementation and neonatal sepsis. All three articles selected were published in English between the 2013-2018. PubMed was used to research the articles which were selected based on their qualification to answer to my clinical question in terms of a patient-oriented outcome. Inclusion criteria consisted of studies that were RCTs published after 2008 and included the neonatal population. Exclusion criteria consisted of studies published in 2008 or earlier and those that were published in a foreign language. The statistics analyzed in this review included p-value and NNT.

One randomized, double blind, controlled trial, one randomized controlled trial and one randomized, double blind, placebo-controlled trial were utilized in this review. The focused population for the studies of this review included neonates diagnosed with sepsis. In the study performed by Mehta et al., the intervention group was given standard antibiotic therapy along with oral zinc monohydrate supplementation.[7] This group was compared to the control group which was given standard antibiotic therapy with a placebo.[7] In the studies performed by Newton et al. and Banupriya et al. neonates receiving the intervention of standard antibiotic therapy with oral zinc monohydrate supplementation were compared to the control group of those who received the standard antibiotic therapy alone.[8,9] The outcome measured in all three studies included reduction in mortality rate.

Table 1. Demographics & Characteristics of included studies

Study	Type	# Pts	Age	Inclusion Criteria	Exclusion Criteria	W/D	Interventions
Mehta[7] (2013)	Double blind placebo RCT	614	Neonates >32 weeks	Gestational age >32 weeks, parental consent, diagnosis of "probable sepsis" as defined by National Neonatology Forum of India	Parental refusal to consent, pts < 32 weeks gestational age, 5 min APGAR score <5, congenital malformations, and necrotizing enterocolitis	86	Placebo and standard antibiotic therapy vs. Zinc sulfate monohydrate 1mg/kg QD PO with standard antibiotic therapy until death or discharge
Newton[8] (2016)	RCT	88	Neonates >32 weeks and < 28 days old	Gestational age >32 weeks, < 28 days old, on enteral feeds (>50%), at least two screening tests positive for sepsis	Pts with congenital malformations, necrotizing enterocolitis, have undergone surgery or were treated earlier for sepsis, or who had an APGAR score <6 at 5 min	0	Standard antibiotic therapy vs. Zinc sulfate monohydrate 3mg/kg BID PO for 10 days with standard antibiotic therapy
Banupriya[9] (2018)	Double blind RCT	150	Neonates >32 weeks and < 28 days old	Gestational age >32 weeks, < 28 days old, on enteral feeds (>50%), at least two screening tests positive for sepsis	Pts with congenital malformations, necrotizing enterocolitis, have undergone surgery or were treated earlier for sepsis, or who had an APGAR score <6 at 5 min	15	Standard antibiotic therapy vs. Zinc sulfate monohydrate 3mg/kg BID PO for 10 days with standard antibiotic therapy

OUTCOMES MEASURED

Patient mortality rate was the outcome of focus for this EBM review. Each study defined mortality rate within a different time frame. The study performed by Mehta et al. defined mortality as death during hospitalization, Newton et al., defined mortality as death within one month of birth and Banupriya et al. defined mortality as death within 12 months of birth.[7,8,9]

RESULTS

Mehta et al. conducted a double blind, randomized, placebo-controlled trial that analyzed neonates with probable sepsis in a pediatric wing of a tertiary care hospital in Nepal from 2010 to 2011.[7] The neonates included in this study were greater than 32 weeks gestational age, had parental consent, and were given a diagnosis of "probable sepsis" as defined by the National Neonatology Forum of India.[7] Refer to Table 1 for the exclusion criteria. Of the neonates at the hospital, 1540 were eligible for the study. After applying exclusion criteria, the total was narrowed down to 700. These neonates were randomized evenly into the zinc group which received 1mg/kg of zinc sulfate monohydrate by mouth daily with standard antibiotics and the placebo group which received a placebo pill with standard antibiotic therapy.[7] Both groups of neonates were treated until they died or were discharged from the hospital. The neonates were evaluated on a daily basis to assess their stability. A total of 86 babies were withdrawn from the study leaving 614 to evaluated at the completion of the study. In the zinc group 9.77% (30/307 patients) died and in the placebo group 7.81% (24/307 patients) died (Table 2).[7] No statistically significant difference was observed as $p= 0.393$ and statistical significance was noted as $p<0.05$ (Table 2).[7] The RBI was -0.24, the ABI was -0.019 and the NNT was -52 (Table 3). No safety concerns or adverse side effects were discussed.

In a NICU of a hospital in India, Newton et al. evaluated 88 neonates between 2013-2014.[8] These babies were of greater than 32 weeks gestational age, less than 28 days old, on enteral feeds and tested positive on at least two screening tests for sepsis.[8] Refer to Table 1 for the exclusion criteria. Prior to reviewing exclusion factors 215 neonates were eligible for the study. After exclusion, 88 neonates were randomized into the intervention and control group. The 44 infants in the intervention group were given zinc sulfate monohydrate 3mg/kg by mouth twice daily for 10 days with the standard antibiotic therapy while the other 44 babies in the control group were given standard antibiotic therapy alone.[8] The neonates that had positive screening tests received 7 days of antibiotics whereas those with positive cultures received 10 days of antibiotics.[8] Zinc serum levels were taken in both groups prior to treatment and at the conclusion of treatment on day 10. The neonates were evaluated each day while in the hospital and were followed up with at one month of age.[8] No drop outs were accounted for at the conclusion of the study. Of those patients in the intervention group 4.5% (2/44 patients) died and of those in the control group 13.6% (6/ 44 patients) died (Table 2).[8] The p-value was 0.27 which showed no statistically significant difference between the two groups (Table 2).[8] However, the NNT was 11 which showed a large positive treatment effect implying clinical significance. The RBI was 0.67 and the ABI was 0.091 (Table 3). Additionally, no adverse effects were reported in this study.

Banupriya et al. assessed septic neonates of a gestational age greater than 32 weeks and less than 28 days old from 2013 to 2016 at the same hospital in India as a continuation of the study conducted by Newton et al.[9] The neonates included had to test positive on at least two septic screening tests and had to be on enteral feeds.[9] Refer to Table 1 for the exclusion criteria. A total of 203 neonates were eligible for the study, but that number was narrowed down to 150

due to exclusion factors. The patients were randomized and equally split into the intervention zinc group and control no zinc group. In this double blinded study, the intervention group received zinc sulfate monohydrate 3mg/kg by mouth twice daily for 10 days with standard antibiotic therapy while the control group received only the standard antibiotic therapy.[9] Once again, zinc serum levels were taken from the neonates in both groups prior to the intervention and upon completion of treatment on day 10. Throughout their hospital stay the babies were monitored and were followed up at 12 months of age.[9] At the completion of the study 6 drop outs were accounted for in the control group and 9 were lost to follow up in the intervention group.[9] A total of 17.3% (13/75 patients) neonates died in the no zinc group and 6.6% (5/75 patients) died in the zinc group (Table 2).[9] Between the two groups there was a statistically significant difference in mortality rate ($p<0.05$) with $p=0.04$ (Table 2).[9] The calculated RBI was 0.62, ABI was 0.107 and NNT was 10 as recorded in Table 3. No adverse events or safety concerns for zinc supplementation were noted.

Table 2. Patient Mortality and p-value by Study

Study	Zinc Group	No Zinc Group	P-value
Mehta et al.[7]	30 (9.77%)	24 (7.81%)	0.393
Newton et al.[8]	2 (4.5%)	6 (13.6%)	0.27
Banupriya et al.[9]	5 (6.6%)	13 (17.3%)	0.04

Table 3. Calculations for Treatment from Mehta et al., Newton et al., and Banupriya et al.

Study	CER	EER	RBI	ABI	NNT
Mehta et al.[7]	0.078	0.097	-0.24	-0.019	-52
Newton et al.[8]	0.136	0.045	0.67	0.091	11
Banupriya et al.[9]	0.173	0.066	0.62	0.107	10

DISCUSSION

It is well known that zinc deficiency leads to impaired immune functioning. While neonates in developing countries and those that are preterm are more at risk for being deficient, all neonates are immunocompromised at birth with their immature immune system.[9] The lack of immunity in combination with the continuing struggle to fight sepsis despite tailored antibiotic therapy leads to an increase of mortality in the world's youngest population.[9] While the goal of this systemic EBM review was to evaluate the effects of oral zinc supplementation on reducing mortality rate in neonatal sepsis, the three articles did not agree on a clear answer.

Mehta et al.'s RCT did not confirm statistical significance for zinc supplementation reducing mortality rate in neonatal sepsis.[7] The NNT was -52 and the zinc group had a higher mortality rate than that of the placebo group.[7] Similarly, Newton et al. did not establish statistical significance supporting the benefit of zinc supplementation on reducing mortality rate in neonatal sepsis.[8] However, the NNT was 11, supporting a large treatment effect and clinical significance.[8] Lastly, Banupriya et al.'s RCT established statistical significance in that zinc supplementation was effective in reducing mortality rate in neonatal sepsis.[9] The NNT was 10, supporting a large treatment effect and therefore clinical significance.[9]

Each study came to a different conclusion in regard to the effectiveness of zinc in reducing mortality rate in neonatal sepsis and each similarly noted their own limitations. Mehta et al. acknowledged the limitations in that the study took place at a single location, the neonates were not prescreened for an underlying zinc deficiency before they started the treatment, and that the treatment length was not standardized.[7] Newton et al. listed small sample size and marginal zinc dose as limitations in their study.[8] Lastly, Banupriya et al. specified the lack of a placebo group and the short 10 day treatment of zinc as limitations within the study.[9] Additionally, this study was a continuation of a prior study, and thus, not all of the neonates were recruited at the same time as the initial treatment group.[9]

Not only did the studies themselves pose limitations, but limitations arose when searching for the studies. The studies by Newton et al. and Banupriya et al. were performed at the same hospital in India, the latter being a continuation of the former.[8,9] This systemic review was limited to studies solely performed overseas. The two studies performed in India and the other in Nepal restricted the generalizability of the results gathered. Lastly, the defined time frame for mortality varied with each study, Mehta et al. defined mortality as death during hospitalization, Newton et al. defined mortality within 1 month of birth and Banupriya et al. defined mortality within 12 months of birth.[7,8,9]

CONCLUSION

Although cases can be made about the benefits zinc has on boosting the human immune system, the three RCTs in this EBM review have provided conflicting evidence on whether or not zinc supplementation is effective in reducing mortality rate in neonatal sepsis. Mehta et al. and Newton et al. failed to establish statistical significance.[7,8] In contrast, Banupriya et al. made a statistically significant argument in favor of the benefits of zinc enhancing first line antibiotic

treatment for neonatal sepsis.[9] The variability in clinical and statistical significance implies that further studies need to be performed to come to a definitive conclusion. Future studies are needed to enhance generalizability and validity of the use of zinc in reducing mortality among neonates with sepsis. These studies should account for infants that are breast vs. formula fed, considering breastfeeding has been known to enhance immunity in infants and the studies should have a universally defined time period for mortality. Furthermore, these studies should be expanded to developed countries such as the United States and higher doses of zinc could be studied to achieve a higher therapeutic level. Since mortality in the neonatal septic population still exists even in the most medically advanced countries, zinc supplementation to aid in the reduction of mortality rate should continue to be explored.

References:

1. Neonatal sepsis: MedlinePlus medical encyclopedia. Medline Plus Web site. https://medlineplus.gov/ency/article/007303.htm. Updated 2017. Accessed Oct 6, 2019.

2. Simonsen KA, Anderson-Berry AL, Delair SF, Davies HD. Early-onset neonatal sepsis. *Clin Microbiol Rev*. 2014;27(1):21–47. doi:10.1128/CMR.00031-13

3. Tesini BL. Neonatal sepsis - pediatrics. Merck Manuals Professional Edition Website. https://www.merckmanuals.com/professional/pediatrics/infections-in-neonates/neonatal-sepsis. Updated 2018. Accessed Oct 6, 2019.

4. Children. Sepsis Alliance Website. https://www.sepsis.org/sepsisand/children/. Updated July 2019. Accessed Oct 6, 2019.

5. Centers for Disease Control and Prevention. GBS | clinical information | group B strep | CDC. Centers for Disease Control and Prevention Website. https://www.cdc.gov/groupbstrep/clinicians/index.html. Updated 2019. Accessed Oct 6, 2019.

6. Edwards M. Management and outcome of sepsis in term and late preterm infants. UpToDate. https://www.uptodate.com/contents/management-and-outcome-of-sepsis-in-term-and-late-preterm-infants. Updated August 14, 2019. Accessed October 6, 2019.

7. Mehta K, Bhatta NK, Majhi S, Shrivastava MK, Singh RR. Oral zinc supplementation for reducing mortality in probable neonatal sepsis: A double blind randomized placebo controlled trial. *Indian Pediatr*. 2013;50(4):390-393. doi: S097475591200127 [pii].

8. Newton B, Bhat BV, Dhas BB, Mondal N, Gopalakrishna SM. Effect of zinc supplementation on early outcome of neonatal sepsis—A randomized controlled trial. *Indian J Pediatr*. 2016;83(4);289-293. doi:10.1007/s12098-015-1939-4 [doi].

9. Banupriya N, Bhat BV, Benet BD, Catherine C, Sridhar MG, Parija SC. Short term oral zinc supplementation among babies with neonatal sepsis for reducing mortality and improving outcome - A double-blind randomized controlled trial. *Indian J Pediatr.* 2018;85(1):5-9. doi: 10.1007/s12098-017-2444-8 [doi].