ORIGINAL ARTICLE

Role of Zinc Supplementation in Preterm Neonates with Sepsis

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ABSTRACT

Objective: Objective of the study was to assess the role of zinc in addition to antibiotics in reducing mortality & morbidity in preterm neonatal sepsis.

Study Design: Prospective randomized controlled trial.

Place and Duration of Study: Neonatal unit of Department of Pediatric Medicine, Jinnah hospital Lahore. The study duration was 10 months, from 1st January 2021 to 31st October 2021.

Materials and Methods: We enrolled 260preterm babies who had clinical findings of sepsis and positive blood investigations fulfilling the preset criteria. The intervention group was given zinc sulfate monohydrate at a dose 2mg/kg/day orally 2 times a day for 10 days with empirical antibiotics while the control group received empirical antibiotic treatment (Ampicillin & Amikacin) only without addition of zinc. Blood samples were withdrawn for laboratory investigations like complete blood count, CRP & blood culture & sensitivity from the two groups at days 0, 2, 5 & 10 of start of intervention. We compared both groups with the help of a predefined sepsis score including both clinical and laboratory data. Percentages were calculated to measure the outcomes in both groups to show the difference of CRP level and mortality. Demographic variables including weight in kilograms and age of gestation in weeks were mentioned in mean ± SD (standard deviation).

Results: Only 34% of blood cultures were organism positive, including Staphylococcus aureus, E.coli, Klebsiella Acinetobacter, Streptococcus, Pseudomonas and Candida. CRP levels before start of zinc therapy were comparable in both groups; while at day 5 and day 10 of zinc therapy, there was a relative decline in blood CRP level in intervention group. Mortality was 19% in the group with zinc addition as compared to the other group(25%) with no zinc supplementation.

Conclusion: Zinc supplementation along with antibiotics decreases morbidity (septic shock, seizures, organ dysfunction, metabolic acidosis, respiratory distress/apnea, feeding issues) and mortality in preterm babies with neonatal sepsis.

Key Words: *Infections, Low-Birth Weight, Newborns, Prematurity, Zinc.*

Introduction

Sepsis in newborns is defined as a systemic inflammatory response with clinical features of infection happening in the initial 4 weeks of life. Neonatal sepsis usually presents as fulminant infection without focus (septicemia). It may become localized to involve joint(arthritis) or meninges (meningitis), lungs (Pneumonia), urinary tract (UTI) gut (enteritis), and skin (cellulitis).[1] Sepsis of neonates is very dangerous and diverse condition. Pathogenic organisms and certain host factors i.e., age of gestation, maternal factors like anemia, infection, and environmental factors also worsen the sepsis of newborns.[2] Newborn infants are more prone to bacterial infection because of their weaker immunity; and preterm babies, therefore, are even more susceptible.[3]

Sepsis is a major cause of neonatal mortality in the world. According to World Health Organization neonatal sepsis adds a huge health burden in poor socioeconomic states.[4]

Preterm neonates have poor zinc stores in their body as compared to the full-term newborns because fetuses acquire around 60%of their total body zinc during the last trimester of pregnancy. Preterm infants are also deficient in zinc because of their poor intake, immature digestion and absorption and extra body losses as compared to term babies.[5]

Certain micronutrients like zinc play an important role in modifying immune reactions, therefore their

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deficiency can increase susceptibility to infection. Low zinc levels may disturb immunity by contributing to atrophy of lymphoid tissue, poor hypersensitivity reaction of skin, decreased activation of human B and T lymphocytic population and impaired chemotaxis of monocytes and nutrophills.[6]

In one study, neonates with sepsis were given zinc with routine antibiotic regimens. The results showed marked reduction in the levels of hematological markers of septicemia including inflammatory cytokines and serum calprotectin levels.[7] It is previously known from available data that zinc supplementation has been found to cause decreased chances of infections especially diarrhea, pneumonia, and skin diseases. Zinc as a supplementation therapy can also be used in neonatal sepsis.[8]Another study revealed that preterm neonates suffering from late onset sepsis showed improved clinical and laboratory findings when zinc was added to their regular treatment of sepsis.[9]

Advanced technology is being focused on specific immunometabolism of early human life and identifying the factors that might influence the susceptibility and risk of infection. In this context, certain metabolic agents such as zinc are currently being evaluated both as a prophylactic agent & as treatment for neonatal sepsis.[6]

Materials and Methods

It was a prospective clinical study. Written informed consent was taken from parents and guardians. We enrolled 260 preterm babies less than 37 weeks of gestation, with the diagnosis of sepsis taking predefined clinical and laboratory parameters. Diagnosis of sepsis was made according to these parameters shown in **Table-I.**

Any preterm baby fulfilling clinical and laboratory criteria with score> 4 was considered septic. Sepsis scoring was done upon admission & reassessed on day2,day5, and day10 of starting the treatment. Permission to conduct the study was obtained from the institutional Ethical Review Board (Letter attached).

All neonates with gross structural congenital anomalies, gastrointestinal bleeding, hypoxic ischemic encephalopathy, intracranial hemorrhage, respiratory distress syndrome & inborn errors of metabolism were excluded.

Table I: Clinical Criteria for Neonatal Sepsis

Clinical criteria for neonatal sepsis	Score>4 =positive sepsis
• General: pallor, petechiae, bruises or jaundice	1
• Cardiovascular system: tachycardia or bradycardia,	1
• Poor perfusion, or shock	1
• Variability in temperature (hypothermia or hyperthermia)	1
• Respiratory system: moaning, grunting, intercostals/subcostal retractions, apnea, or cyanosis.	1
• Central Nervous system:	1
• Hypotonia, hypertonia, lethargy, irritability or seizure, bulging/ tense anterior fontanelle.	1
• Gastrointestinal system: abdominal distension, hepatosplenomegaly	1
Laboratory Criteria for Neonatal Sepsis	
• White blood cells (WBC) count<5000/uL or>20,000/uL	1
• Absolute neutrophil count <1500 • Platelet (PLT) count<150,000/uL	1 1
• CRP >5mg/dl.	1
• Positive blood culture	1

Enrolled neonates were divided into 2 groups. Group 1 was named Intervention group (n=130) and group 2 as control group (n=130). Patients were enrolled in the Neonatal Intensive Care Unit of Jinnah hospital Lahore from January 2021 to October 2021. After written informed consent from parents/guardians, we started with detailed history of baby and mother, then a precise clinical examination was performed by residents and senior registrars and documented as daily vitals, anthropometry, and systemic assessment. Both groups had laboratory examinations in the form of Complete blood count (CBC) including (leukocyte and Platelet count),C reactive protein (CRP) and blood cultures before starting treatment. C-reactive protein (CRP) was measured quantitatively and a level >5 mg/ml was considered positive.

In group 1,neonates with sepsis were given zinc as 2 mg/kg /day twice daily of zinc sulfate monohydrate suspension per oral for 10 days in addition to

antibiotics as per the routine protocol, i.e., ampicillin, cefotaxime, and amikacin. In group 2, neonates with sepsis were not administered zinc but only received antibiotics. Zinc was given orally or through the orogastric or nasogastric tube by staff nurse on duty daily for the set time. Data was analyzed using the statistical software SPSS version 21. Results were obtained in the form of percentages and standard deviations.

Results

Total 260 preterm neonates were kept in this clinical trial.130 in group 1(intervention group) and 130 in group 2(control group).After data collection and analysis, we found no difference between the two groups in their gestational age (weeks),sex, weight in (kg), and mode of delivery.(Table II)

Table II: Comparison of Demographic Variables Among the 2 Groups (n= 260)

Variable	Control Group N (%)	Intervention Group N (%)
Sex:		
Male(n)	62 (47.7%)	59 (45.3%)
Female(n)	68 (53.3%)	71 (54.6%)
Birth weight(kg) mean ± SD	1.91 ± 0.74	1.87± 0.93
Mode of delivery:		
C-section(n)	48 (37%)	51 (39%)
NVD(n)	82 (63%)	79 (60.7%)
Gestational age Mean ± SD	33.5 ±2.43weeks	32.6 ±4.67 weeks

The initial CRP levels were comparable in both groups. Whereas, after administration of zinc therapy, there was quite a significant difference noted in the results of CRP levels on day 2, day 5 and day 10 of zinc therapy. A rapid decline of levels of CRP was noted in the Group 1 who received zinc sulfate with antibiotic regimen than the other group with antibiotics only.(**Table-III**)

Mortality was also compared in both groups, which was relatively higher in the babies who did not receive zinc supplements (25%) than the sample of babies with addition of zinc as intervention(19%). (**Table-III**).

Among all 260 blood samples drawn for culture and sensitivity, only 38% were organism positive, while 72% blood culture reports showed no growth. Most isolated organisms among positive culture reports were Staphylococcus aureus, E coli, Streptococci, Klebsiella, Acinetobacter, Pseudomonas and Candida.

Table III: CRP level & Mortality Rate in the two Groups

Variable		Control group Mean ± SD	Intervention group Mean ± SD
CRP *(mg/dl)*	Before	23±10.23	29.3±8.7
	At day 2	17.8±14.6	21.5±9.9
	At day 5	10.7±4.5	13.2±5.8
	At day 10	4.3±1.3	2.5±1.7
Mortality: *n (%)*		32 (25%)	23 (19%)

Discussion

Our study indicated that supplementing zinc (oral zinc sulfate monohydrate 2mg per kg per day) for 10 days markedly improved the rate of recovery from sepsis in most of the neonates recruited in the intervention group(n=130).

Among total 260 of babies, intervention was performed in 45%males and %54% female babies in comparison to 47.7% males and 53.3% females in control group.so there was no significant difference in sex distribution of two groups. Similarly, the mode of delivery in neonates in control and invention groups was comparable as SVD born babies were 63% and 60% in control and intervention groups respectively.

Mean CRP levels at the commencement of intervention were quite high in both groups. But the serial measurements of CRP in both groups at intervals imply significant decrease in the morbidity in terms of low CRP values and less mortality due to neonatal sepsis, i.e 25% and 19% in control vs intervention group respectively.

On day 1, mean CRP in control group was 23+-10.3 and in intervention group was 29.3+-8.7,which were found to fall at mean of 2.5+-1.7 in group I and 4.3+- 1.3 in group II at the 10th day of treatment with zinc supplementation. The rate of fall of CRP levels in infants with Zinc supplementation was 93% as compared to 82 % in the control group.

In other studies, supporting our findings, Chopani R et al, in 2021 used zinc sulfate in neonates with sepsis and found better outcomes of Neonatal sepsis in the form of weight gain, less need of total parenteral nutrition and better feed tolerance[18]. Our results were also in accordance with those of Banupriya et al. in an RCT 2018, who found a comparative low death rate and a higher mental quotient, among

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neonates supplemented with zinc compared to the babies without Zinc[7]. Premature babies have weak immune system, poor feeding abilities and hypoglycemia due to low glycogen store so have high risk of neonatal infections.[14] Laura G et al revealed that there is particular micronutrients found to be deficient and ultimately increasing the chances of infections in neonates. We can reduce the burden of neonatal sepsis and its treatment cost if these cheaper micronutrients can be replaced in newborns.[17]

In a trial by Ali SM et al, zinc was recommended as an adjunct therapy for septic neonates because it drastically decreased the time of recovery as the mean clinical recovery time in zinc group was 104.20 ± 16.61 hours and that of placebo group it was 111.46 ± 19.43 hours ,which was in favor of our results.[16]

In consistent with our findings, Heba GA et al, in a randomized controlled trial demonstrated a decrease in morbidity and mortality when extra doses of Zinc were administered to premature babies admitted in neonatal ICU.[21]

However, Kefle et al concluded that there was need to shift on higher order antibiotics and average length of hospital stay was also same even with addition of Zinc[19].Same was the conclusion by Mehta et al's RCT, which also confirmed no statistical significance for zinc supplementation in reducing death rate in septicemic neonates.[11]

According to Irfan O et al, A significant reduction in neonatal mortality rate with Zinc in neonatal sepsis was recoded as in our study. However, no significant effect was noted on length of hospital stay for septic infants.[20]

This huge variability in clinical, pathological, and statistical significance implies that further large-scale trials should be performed to reach a firm conclusion. There is a need to enhance the generalizability and validity of the recommendation for addition of zinc sulfate as adjuvant therapy in the management of neonatal sepsis.

Limitations:

In our study, the outcome was measured in terms of CRP only & other reliable acute phase reactants were not entertained. Compliance was poor because of the enteral route of zinc administration especially in cases with GERD, emesis after the dose was given, and gastrointestinal bleed. Neonates were not prescreened for an underlying zinc deficiency before the start of treatment. Other factors in deteriorating or improving sepsis in neonates were not entertained. Also, babies with early and late onset sepsis were not separately evaluated.

Conclusion

Oral zinc therapy as a supplement to antibiotics is beneficial in improving infection and decreasing mortality in preterm neonates with sepsis.

REFRENCES

1. El Frargy MS, Soliman NA. Zinc supplementation as an adjuvant treatment in neonatal sepsis. International Journal of Pediatrics. 2017;21(1):93-98.
2. Carbone F, Montecucco F, Sahebkar A. Current, and emerging treatments for neonatal sepsis. Expert Opinion on Pharmacotherapy. 2020 Mar 23;21(5):549-56. doi: 10.1080/14656566.2020.1721464.
3. Makkar M, Gupta C, Pathak R, Garg S, Mahajan NC. Performance evaluation of hematologic scoring system in early diagnosis of neonatal sepsis. Journal of clinical neonatology. 2013 Jan 1;2(1):[25-29] doi: 10.4103/2249-4847.109243.
4. Popescu CR, Cavanagh MM, Tembo B, Chiume M, Lufesi N, Goldfarb DM,et al. Neonatal sepsis in low-income countries: epidemiology, diagnosis, and prevention. Expert review of anti-infective therapy. 2020 May 3;18(5):443-52. doi: 10.1080/14787210.2020.1732818.
5. Terrin G, Berni Canani R, Passariello A, Messina F, Conti MG, Caoci S, Smaldore A, Bertino E, De Curtis M. Zinc supplementation reduces morbidity and mortality in very-low-birth-weight preterm neonates: a hospital-based randomized, placebo-controlled trial in an industrialized country. Am J Clin Nutr. 2013 Dec;98(6):1468-74. doi: 10.3945/ajcn.112.054478. Epub 2013 Sep 11. PMID: 24025633.
6. Conti MG, Angelidou A, Diray-Arce J, Smolen KK, Lasky-Su J, De Curtis M, Levy O. Immunometabolic approaches to prevent, detect, and treat neonatal sepsis. Pediatr Res. 2020 Jan;87(2):399-405. doi: 10.1038/s41390-019-0647-6. Epub 2019 Nov 5. PMID: 31689710.
7. Banupriya N, Vishnu Bhat B, Benet BD, Sridhar MG, Parija SC. Efficacy of zinc supplementation on serum calprotectin, inflammatory cytokines, and outcome in neonatal sepsis–a randomized controlled trial. The Journal of Maternal-Fetal & Neonatal Medicine. 2017 Jul 3;30(13):1627-31. doi: 10.1080/14767058.2016.1220524.
8. Taneja S, Bhandari N, Rongsen-Chandola T, Mahalanabis D, Fontaine O, Bhan MK, Study Group. Effect of zinc supplementation on morbidity and growth in hospital-born, low-birth-weight infants. The American journal of clinical nutrition. 2009 Aug 1;90(2):385-91. doi: 10.3945/ajcn.2009.27707.
9. Elfarargy MS, Al-Ashmawy G, Abu-Risha S, Khattab H. Zinc Supplementation in Preterm Neonates with Late-Onset

Sepsis: Is It Beneficial? Am J Perinatol. 2022 Jul;39(10):1097-1103. doi: 10.1055/s-0040-1721659. Epub 2020 Dec 7. PMID: 33285602.
10. Wynn JL, Polin RA. Progress in the management of neonatal sepsis: the importance of a consensus definition. Pediatric Research. 2018 Jan;83(1):13-5. doi: 10.1038/pr.2017.224.
11. 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 pediatrics. 2013 Apr;50:390-3. doi: 10.1007/s13312-013-0120-2.
12. Shane AL, Sánchez PJ, Stoll BJ. Neonatal sepsis. The lancet. 2017 Oct 14;390(10104):1770-80. doi: 10.1016/S0140-6736(17)31002-4.
13. Odabasi IO, Bulbul A. Neonatal Sepsis. Sisli Etfal Hastan Tip Bul. 2020 Jun 12;54(2):142-158. doi: 10.14744/SEMB.2020.00236. PMID: 32617051; PMCID: PMC7326682.
14. Staub E, Evers K, Askie LM. Enteral zinc supplementation for prevention of morbidity and mortality in preterm neonates. Cochrane Database Syst Rev. 2021 Mar 12;3(3):CD012797. doi: 10.1002/14651858.CD012797.pub2. PMID: 33710626; PMCID: PMC8092450.
15. Mathur NB, Agarwal DK. Zinc supplementation in preterm neonates and neurological development: a randomized controlled trial. Indian pediatrics. 2015 Nov;52:951-5. doi: 10.1007/s13312-015-0751-6.
16. Ali SM, Hoque M, Ali MM, Talukder MNU, Chowdhury T. Zinc as Adjunct Therapy in Neonatal Sepsis. Med. Today [Internet]. 2020 Aug. 29 [cited 2023 Aug. 27];32(2):112-6. Available from: https://www.banglajol.info/index.php/MEDTODAY/article/view/4882.
17. Laura G. Sherlock, Nancy F. Krebs; Small and Mighty: Micronutrients at the Intersection of Neonatal Immunity and Infection. *Neoreviews* March 2023; 24 (3): e158–e174. https://doi.org/10.1542/neo.24-3-e158.
18. Choopani, R., Asadpour, N., Hamidi, M., Khalili, M., Ebrahimi, N., Choopani, S. The Effects of Zinc Sulfate on Sepsis Outcomes in Neonates: A Blind Clinical Trial. *International Journal of Pediatrics*, 2021; 9(9): 14474-14480. doi: 10.22038/ijp.2021.54568.431.
19. Kafle SP, Rauniyar LP, Ahmad E, Koirala N, Rouniyar M. Oral Zinc supplementation in the treatment of sepsis in Nepalese children: A double-blind randomised placebo-controlled trial. J. Kathmandu Med. Coll. [Internet]. 2021 Sep. 30 [cited 2023 Aug. 26];10(2):84-91. Available from: https://jkmc.com.np/ojs3/index.php/journal/article/view/1082.
20. Irfan, O., Black, R. E., Lassi, Z. S., Bhutta, Z. A. (2022). Zinc supplementation and the prevention and treatment of sepsis in young infants: A systematic review and meta-analysis. *Neonatology, 119*(2), 164-175.
21. : Heba GA, Samar MS.Role of Oral Zinc Supplementation in Reduction of Neonatal Morbidity and Mortality in Zagazig University Hospitals. ZUMJ 2020;26(1);140-147.DOi: 10.21608/zumj.2019.16235.1454.

CONFLICT OF INTEREST

Authors declared no conflicts of Interest.

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Authors have declared no specific grant for this research from any funding agency in public, commercial or nonprofit sector.

DATA SHARING STATMENT

The data that support the findings of this study are available from the corresponding author upon request.