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Short Term Oral Zinc Supplementation among Babies with Neonatal Sepsis for Reducing Morbidities and Mortality in Neonatal Care Unit of Dr. B. C. Roy PIGS, Kolkata

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ABSTRACT
Neonatal sepsis is defined as systemic inflammatory response syndrome in the presence of or as a result of a suspected or confirmed infection in a new-born, per the 2005 international paediatrics sepsis consensus conference. This study aimed to reducing morbidities and mortality among neonatal sepsis patients with short term oral zinc supplementation. To evaluate the efficacy of short term zinc supplementation on the mortality rate and improving outcome of neonatal sepsis. To compare efficacy of zinc supplementation among case and control group of neonatal sepsis patients. The study was double-blinded randomized control study from June 2019 to June 2020. Place of study was Dr. B.C. Roy Pgips 111, Narkeldanga Main Road, P.S. Phoolbagan, Kolkata-54 total sample was 50. In with ZINC, the mean times to clinical recovery (Mean±S.D.) of patients were 4.5600±1.0832. In without ZIN, the mean times to clinical recovery (Mean±S.D.) of patients were 6.3913±0.9409. Difference of mean Time to clinical recovery with ZINC was statistically significant ($p<0.0001$). We concluded that new-borns with sepsis, oral zinc supplementation for a brief period of time seems to be a promising supplementary therapy for lowering morbidity and mortality. These results encourage more investigation into the best duration and dosage for zinc therapy as well as its incorporation into accepted sepsis care guidelines

INTRODUCTION

Neonatal sepsis is defined as systemic inflammatory response syndrome in the presence of or as a result of a suspected or confirmed infection in a newborn, per the 2005 international paediatrics sepsis consensus conference. The source of the infection could be rickettsial, fungal, viral, or bacterial[1]. Neonatal sepsis includes a range of systemic illnesses that affect the newborn, including osteomyelitis, meningitis, pneumonia, septicemia and arthritis. One major factor contributing to newborn mortality (deaths) in the first month of life is thought to be bacterial sepsis[2]. According to estimates from the World Health Organization, five million newborns die each year, with developing nations accounting for 98% of these deaths. Over the last 20 years, sepsis-related deaths in children have nearly doubled globally. Neonatal sepsis can be divided into two groups based on when the illness first appears: Early Onset Sepsis (EOS) (0-7 days) and Late-Onset Sepsis (LOS) (7-28 days). Clinical significance arises from this differential, since EOS disease is mostly caused by bacteria obtained prior to and during birth, while LOS disease is caused by bacteria acquired after to delivery (from nosocomial or community sources)[3]. A few articles make a distinction between three types of sepsis: Extremely early onset (within 24 hrs), early onset (24 hrs to seven days) and late onset (greater than seven days). Neonatal sepsis still has a high death and morbidity rate despite advancements in neonatal care. In Asia, the frequency of neonatal sepsis has been observed to range from 7.1 to 38 per 1000 live births. India and other developing nations in South-East Asia are in a similar scenario. Neonatals are more vulnerable to infection due to a variety of causes. These include reduced bone marrow neutrophil pool, developmental, quantitative and qualitative neutrophil abnormalities and deficits in immunoglobulins, both quantitative and qualitative[4]. Immune system dysregulation and insufficiency are caused by the trace element zinc, which is crucial for immune system function. Zinc can function as an intracellular signaling molecule in immune cells, according to recent research. It is well recognized that zinc is essential to the immune system. It is essential for the proper growth and operation of natural killer cells, neutrophils, macrophages and other cells that mediate innate immunity.

MATERIALS AND METHODS

Study design: Double-blinded randomized control study.

Period of study: June 2019 to June 2020

Sample size: 50

Place of study:

- Dr. B.C. roy Pgips 111, Narkeldanga Main Road,
- P.S. Phoolbagan, Kolkata-54

Inclusion criteria:

- Babies born with gestational age of more or equal to 32 weeks and post natal age < 28 days
- On enteral feeds on either by oro-gastric or oral >50 % of total feed
- At least two of the screening tests among (microESR, TLC, ANC, CRP, I/T and band cell count) should be positive
- Culture Positive for sepsis

Exclusion criteria:

- Babies with major congenital malformations
- Necrotising enterocolitis
- Who have undergone surgery
- Babies treated earlier for sepsis
- Those with Perinatal birth Asphyxia

Statistical analysis: For statistical analysis, data were initially entered into a Microsoft Excel spreadsheet and then analyzed using SPSS (version 27.0; SPSS Inc., Chicago, IL, USA) and GraphPad Prism (version 5). Numerical variables were summarized using means and standard deviations, while categorical variables were described with counts and percentages. Two-sample t-tests, which compare the means of independent or unpaired samples, were used to assess differences between groups. Paired t-tests, which account for the correlation between paired observations, offer greater power than unpaired tests. Chi-square tests (χ^2 tests) were employed to evaluate hypotheses where the sampling distribution of the test statistic follows a chi-squared distribution under the null hypothesis, Pearson's chi-squared test is often referred to simply as the chi-squared test. For comparisons of unpaired proportions, either the chi-square test or Fisher's exact test was used, depending on the context. To perform t-tests, the relevant formulae for test statistics, which either exactly follow or closely approximate a t-distribution under the null hypothesis, were applied, with specific degrees of freedom indicated for each test. p-values were determined from Student's t-distribution tables. A $p \leq 0.05$ was considered statistically significant, leading to the rejection of the null hypothesis in favour of the alternative hypothesis.

RESULTS AND ANALYSIS

In our study, 25 (50.0%) patients had ZINC. The value of z is 0. The value of p is 1. The result is not significant at $p<0.05$. In, with ZINC 7 (28.0%) patients had Pre term maturity and 18 (72.0%) patients had Term maturity. In, without ZINC 6 (24.0%) patients had

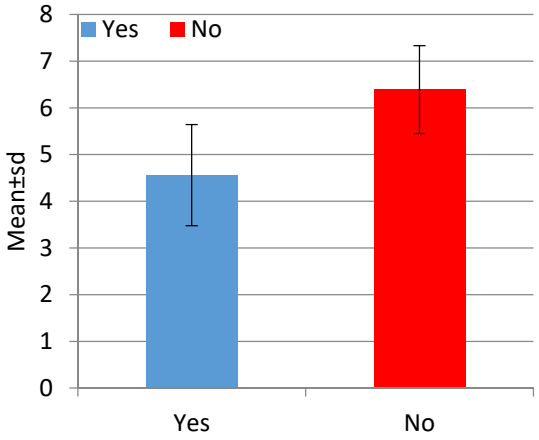

Fig. 1: Distribution of mean time to clinical recovery: ZINC

Table 1: Distribution of ZINC

ZINC	Frequency	Percentage
Yes	25	50.0
No	25	50.0
Total	50	100.0

Table 2: Association between maturity: ZINC

	ZINC		
Maturity	Yes	No	Total
Preterm	7.0	6.0	13.0
Row (%)	53.8	46.2	100.0
Col (%)	28.0	24.0	26.0
Term	18.0	19.0	37.0
Row (%)	48.6	51.4	100.0
Col (%)	72.0	76.0	74.0
Total	25.0	25.0	50.0
Row (%)	50.0	50.0	100.0
Col (%)	100.0	100.0	100.0

Chi-square value: 0.1040; p-value: 0.7471, Odds Ratio: 1.2315 (0.3470, 4.3709)

Table 3: Association between urine culture: ZINC

	ZINC		
Urine culture	Yes	No	Total
negative	21.0	22.0	43.0
Row (%)	48.8	51.2	100.0
Col (%)	84.0	88.0	86.0
positive	4.0	3.0	7.0
Row (%)	57.1	42.9	100.0
Col (%)	16.0	12.0	14.0
TOTAL	25.0	25.0	50.0
Row (%)	50.0	50.0	100.0
Col (%)	100.0	100.0	100.0

Chi-square value: 0.1661; p-value: 0.6835, Odds Ratio: 0.7159 (0.1428, 3.5887)

Pre term maturity and 19 (76.0%) patients had Term maturity. Association of maturity vs. ZINC was not statistically significant (p = 0.7471). In with ZINC, 4 (16.0%) patients were positive urine culture. In without ZINC, 3 (12.0%) patients were positive urine culture. Association of urine culture vs. ZINC was not statistically significant (p = 0.6835). In with ZINC, the mean times to clinical recovery (Mean±S.D.) of patients were 4.5600±1.0832. In without ZINC, the mean times to clinical recovery (Mean±S.D.) of patients were 6.3913±0.9409. Difference of mean Time to clinical recovery with ZINC was statistically significant (p<0.0001) (Table 1-3 and Fig. 1).

DISCUSSION

The purpose of this study is to determine whether short-term oral zinc supplementation can lower morbidities and mortality in the population of newborns with sepsis. 25 (50.0%) of the patients in our study received ZINC supplements (case), whereas 25 (50.0%) did not (control). The two groups' baseline characteristics (Table 1) were comparable. Twelve (48.0%) patients were male and thirteen (52.0%) patients were female at ZINC. The average age of the patients in ZINC was 11.9200±4.3101 (Mean±S.D.). ZINC did not show a statistically significant difference in mean age (p = 0.5858). The mean birth weight (gm) (mean± standard deviation) of the patients in ZINC was 2404.8000±288.4892. The mean birth weight (gm) did not differ statistically significantly from ZINC (p = 0.7778).The trial was a prospective, double-blind, age- and sex-matched case control group. Both groups received antibiotics in accordance with usual procedure, with the exception that one group (the zinc group) received zinc and the other group did not (the no zinc group). The current investigation showed that neonates with sepsis who were born with gestational age of more than or equal to 32 weeks and post-natal age of less than 28 days, on enteral feeds by oro-gastric or oral >50% of total feed and supplemented with short-term oral zinc for 10 days had significantly earlier exclusive oral feeding (Mean±S.D.) 5.1200±1.0132, p<0.0001 (VS. 6.8261±1.1929 in control group) and clinical recovery in comparison to those who had not received zinc (Mean±S.D.) (4.5600±1.0832 VS 0.6.3913±0.9409 p<0.0001). This could be as a result of zinc's notable ability to regulate the generation of inflammatory cytokines[5]. There were no statistically significant differences in the mortality relationship of death ZINC vs. no ZINC (04.0% vs. 0.0%, p = 0.1489) between the case and control groups. The Chi-square value was 2.0833. However, the weight at recovery did not differ much, nor did the requirement for stronger antibiotics, NICU, or MV alter the need for zinc supplements. Mehta did a study that was comparable. Reduced mortality with oral zinc supplementation in likely newborn sepsis: A double-blind, randomized, placebo-controlled study revealed a comparable result[6]. However, prior research on zinc supplementation in newborns has demonstrated a markedly lower death rate in small for gestational age (SGA) babies greater development in low birth weight (LBW) and very low birth weight (VLBW) infants[7-9]. This could be because there aren't enough data on zinc supplementation in newborns suffering from sepsis.In contrast, research on zinc supplementation in animal models of sepsis[10]. demonstrated greatly increased survival after sepsis at 72 hrs after induction Myeloperoxidase activity in lung tissue was significantly reduced (at 24 hrs) notably reduced bacterial load in the spleen and blood (after 24 hrs). Zinc as an adjuvant therapy in newborns with

sepsis has not, as far as we know, been documented before. It is commonly known that zinc deficiency poses a serious health risk to developing countries[11]. Immune system dysregulation and heightened vulnerability to infections result from zinc deficiency. Sepsis continues to be a leading cause of death and morbidity in critically ill patients despite the use of antibiotics. Research has indicated that administering zinc supplements proactively enhances survival rates in mice that are experiencing sepsis. Supplementing with dietary zinc lowers organ damage, inflammation and death in a relevant animal model of polymicrobial sepsis[12]. Since animal models can detect zinc shortage and restore zinc reserves in people at high risk for sepsis, they have important implications for human sepsis outcomes. Previous research has demonstrated that taking zinc supplements lowers the death rate from infectious infections. Additionally, during hospitalization, it lowers the death rate of Very Low Birth Weight (VLBW) premature newborns[13]. Like the earlier trial, the current investigation did not show a statistically significant decrease in the mortality rate among sepsis newborns in the neonatal period in the zinc group when compared to controls. Research has indicated that the immune response is significantly influenced by the trace element zinc. In neonatal sepsis, zinc supplementation for ten days at a dose of 3 mg kg^{-1} day^{-1} twice a day significantly improved early full oral feeding and the rate of recovery (ESNS), however, it had no influence on the patients' linear growth, requirement for NICU care, or need for mechanical ventilation. Since serum zinc levels were not measured at baseline in our investigation, it was not possible to interpret the data in relation to baseline zinc status. While the majority of research has linked zinc's health benefits to decreased infection rates, increased appetite, or zinc replenishment, the children in this study underwent routine monitoringa However, we think that the methodology and setting of this study are its strongest points. Additional research and subsequently meta-analyses are necessary to elucidate the function of zinc as an adjuvant in the management of sepsis in neonates.

CONCLUSION

We concluded that new-borns with sepsis, oral zinc supplementation for a brief period of time seems to be a promising supplementary therapy for lowering morbidity and mortality. These results encourage more investigation into the best duration and dosage for zinc therapy as well as its incorporation into accepted sepsis care guidelines.

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