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The Effects of Zinc Sulfate on Sepsis Outcomes in Neonates: A Blind Clinical Trial

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Abstract

Background: The present study aimed at assessing the effects of zinc sulfate supplementation on sepsis outcomes in neonates.

Methods: This randomized double-blind clinical trial was performed on neonates suffering neonatal sepsis. They were hospitalized in NICU ward at Hajar hospital in Shahrekord, Iran, in 2018. The patients were randomly assigned into two groups receiving a combined therapy of oral zinc sulfate (3mg/kg/day) and antibiotic for ten days (the intervention group, n=30) or routine anti-sepsis antibiotic therapy for the same time (the control group, n=30). The intervention and control groups were matched for baseline variables including gestational age, patients' age, time for beginning the first feeding and baseline anthropometric parameters. Height, weight, head circumference, feeding tolerance time, number of days of oxygenation, number of days hospitalized, NEC, duration of TPN reception, and time at feeding completion in the two groups were compared.

Results: In total, 37 males and 23 females participated in this study, 21.7% of whom were born by natural vaginal delivery and others by cesarean section. There was a significant difference between the intervention and control groups in terms of neonates' weight and height, the rate of receiving TPN, Apgar score and nutrition tolerance. The use of zinc sulfate resulted in a significant increase in body weight and height, requiring less TPN use, and also shorter time to achieve nutritional tolerance ($P<0.05$).

Conclusion: The use of oral zinc sulfate (3 mg/kg/day divided for 10 days) in neonates suffering from sepsis improves sepsis-related clinical outcomes, leading to improvements in linear growth and nutrition tolerance, along with shortening the time for TPN.

Key Words: Zinc sulfate supplement; Sepsis; Outcome.

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1- INTRODUCTION

Sepsis is responsible for more than six millions of deaths annually especially in children and thus it is now identified as the most common cause of neonatal mortality and morbidity (1, 2). Unfortunately, this event in commonly revealed in low income countries with an increasing trend and thus imposes a heavy burden on societies (3). Due to its urgent nature, managing neonatal sepsis needs to understand its definitive diagnostic criteria and to rely on the specific guidelines with the goal of early diagnosis and minutely management of sepsis, which lead to minimization of its complications. Recently, sepsis has been defined as a "life-threatening organ dysfunction caused by a dysregulated host-response to infection" (4). The main pathogenesis of sepsis refer to pathogens-related immune response comprised of pro-inflammatory mechanisms that ultimately damage healthy tissues and organs via triggering systemic inflammatory response and may lead to damage vital organs (5, 6). Thus, the fundaments of therapeutic regimens for treating and managing sepsis include anti-inflammatory regimens, specific antibiotic therapy, controlling vital signs, as well as regulating the host immune responses.

Zinc as an essential trace element in body has crucial responses as a co-factor for many enzymes and other proteins involving regulation of immune system's functional status (7). Zinc deficiency may lead to several abnormalities in body such as growth retardation, delayed wound healing, skin inflammations, severe infections, and even hormonal abnormalities (8-10). In other words, zinc deficiency may lead to complex immunological changes. Moreover, the central role of zinc in modulation of inflammatory cytokines and regulation of the functions of immune cells has been demonstrated. In this regard, zinc is directly involved in differentiation and maturation of immature T-cells and in fact zinc deficiency can result in alteration of T helper-1 to T helper-2 ratio (11-13). Therefore, using zinc sulfate supplements can regulate T cells development and thus can inhibit the processes related to autoimmune disorders (14, 15).

Due to the close link between sepsis and excessive immunological responses and also because of the central role of zinc in regulation of immune responses against pathogens, it is now hypothesized that using zinc supplements can regulate immune responses triggered by sepsis-related pathogens and thus can reduce the sepsis-related complications especially in children. In this regard, we aimed to assess the beneficial effects of zinc sulfate supplement on sepsis-related mortality and morbidity among children.

2- MATERIALS AND METHODS

2-1. Study design and population

This randomized double-blinded clinical trial was performed on neonates suffering from neonatal sepsis hospitalized in NICU at Hajar hospital in Shahrekord, Iran in 2018. The neonates who entered the study aged lower than 28 days, and suffered from neonatal sepsis without any evidence of other underlying abnormal conditions. We reached to a sample size of 60 people, using STATA software with a 5% error and a confidence level of 2% and according to a study that reported the length of hospital stay in two groups of children receiving zinc and not receiving zinc as 142.85±69 and 147.9±73 hours and antibiotic consumption as 13.35% and 12.5%, respectively (16).

Therefore, 30 cases in each group and a total of 60 cases were enrolled in the study. In this research, convenience sampling method was used, so that all neonates who referred to Hajar Hospital in Shahrekord during the study and had the desired characteristics were selected and

then the samples were randomly divided into two groups.

2-2. Measuring tools: Laboratory measurements

The neonatal sepsis was diagnosed based on both clinical manifestations (requiring oxygenation, nutritional intolerance, vomiting, malaise, and abdominal distension) and laboratory findings (positive blood culture). In total, 60 eligible neonates were included in the study.

2-3. Intervention

On admission, the baseline variables including demographics, anthropometric parameters (assessed daily), vital sign, chest X- ray, and laboratory indices (cell blood count, c - reactive protein, result of blood culture, urine culture, and CSF culture) were all collected and entered into the study checklist. The patients were then randomly (using the random number table) assigned into two groups receiving a combined therapy with oral zinc sulfate (3mg/kg/day) and antibiotic for ten days (the intervention group, n = 30) or routine anti-sepsis antibiotic therapy for the same time (the control group, n = 30). The two groups were matched for the types and protocols of antibiotics prescribed and the time needed for treatment.

After the treatment completion with respect to the study endpoints, the following parameters were assessed in both groups: the anthropometric parameters (weight, height, and head circumference), intolerance to nutrition, residual volume of milk in stomach after feeding, needing oxygenation, the length of stay in hospital and NICU ward, the number of days for receiving transparental nutrition (TPN), time to completing the nutrition (higher than 120 ml/kg), and the time to start the first oral feeding. The study endpoint was to assess the effect of oral zinc sulfate on mortality and morbidity of neonates who suffered from neonatal sepsis.

2.4-Ethical consideration

The study protocol was approved by the ethics committee of Shahrekord University of Medical Sciences (ID-code: IR.SKUMS.REC.1396.49) and registered in the Iranian Registry of Clinical Trials (IRCT20180915041040N2) and informed consent was obtained from all parents before beginning the study.

2-5. Inclusion and exclusion criteria

In this study, the neonates who were preterm or small for gestational age were also considered to be eligible for entering the study. The neonates with congenital malformations or genetic abnormalities, gestational ages less than 32 weeks, suffering asphyxia (defined by having resuscitations longer than 15 minutes at birth or 10^{th} minute Apgar scores less than 5) or NEC were all excluded from the study.

2-6. Data Analyses

The results were presented as mean±standard deviation (SD) for quantitative variables and were summarized by absolute frequencies and percentages for categorical variables. Normality of data was investigated using the Kolmogorov-Smirnoff test. Categorical variables were compared using Chi-square test or Fisher's exact test. Quantitative variables were also compared with t-test and Mann-Whitney U-test. Data analysis was done using the statistical software SPSS version 16.0 for windows (SPSS Inc., Chicago, IL). P values of 0.05 or less were considered statistically significant.

3- RESULTS

In total, 37 male and 23 female neonates were entered into the study. Twenty seven neonates (45.0%) were residents of rural areas. Ninety percent of neonates were singleton and others were

twin. Moreover, 21.7% were born by natural vaginal delivery and others by cesarean section. The mean age of neonates on admission was 5.70±8.17 days ranging from 1 to 29 days. The mean weight was 2.40±0.60 kg ranging from 1.2 to 3.7kg with the mean difference of 253.0±209.35 g. The heights ranged from 36 to 51cm with the mean difference of 0.77±0.39. The head circumferences ranged from 24.5 to 36cm with the mean difference of 0.77±0.39. The two intervention and control groups were matched for baseline variables including gestational age, patients' age, time for beginning first feeding and baseline anthropometric parameters (**Table 1**).

The mean day for receiving oxygen therapy was 7.51 ± 6.90 (range: 0-42) days. Number of days receiving TPN ranged from 0 to 31 days with the mean of 5.18 ±6.85 days. Also, the mean time to complete the oral nutrition was 110.53 ± 6.33 days ranging from 1 to 34 days. The first feeding on newborns occurred after 4.73 ± 4.25 days ranging from 1 to 26 days. The mean Apgar score was 7.40 ± 0.84 ranging from 4 to 9. Feeding tolerance has occurred on average after 4.2 ± 5.01 days. The mean gestational age in mothers was 33.76 ± 2.86 weeks. As shown in **Table 2**, there was a significant difference between the intervention and control groups in terms of neonates' weight and height, the rate of receiving TPN, Apgar score and nutrition tolerance. In this regard, the use of zinc sulfate resulted in a significant increase in body weight and height, requiring less TPN use, and also shorter time to achieve nutritional tolerance (P<0.05).

Table-1: Comparison of the baseline variables in intervention and control groups

variable	intervention group (n = 30)	control group (n = 30)	p value
patients' age, day	7.81 ± 5.03	8.60 ± 6.36	0.535
time for beginning first feeding, day	4.90 ± 3.93	5.53 ± 3.37	0.146
gestational age, week	34.14 ± 3.05	33.13 ± 2.55	0.336
weight on admission, kg	2.36 ± 0.58	2.35 ± 0.64	0.486
height on admission, cm	46.21 ± 3.89	45.86 ± 3.42	0.324
head circumference on admission, cm	31.69 ± 2.49	31.86 ± 1.96	0.886

Table-2: Comparison of the clinical outcomes in intervention and control groups

variable	Intervention group (n = 30)	control group (n = 30)	p value
length of hospital stay, day	17.10 ± 8.17	17.33 ± 6.70	0.900
weight on discharge, kg	2.79 ± 0.59	2.54 ± 0.62	<0.001
height on discharge, cm	47.18 ± 3.87	46.49 ± 3.41	<0.001
head circumference on discharge, cm	55.21 ± 2.93	79.32 ± 2.04	<0.001
change in weight, gram	309.23 ± 249.81	196.66 ± 142.15	<0.001
change in height, cm	0.93 ± 0.40	0.61 ± 0.32	<0.001
change in head circumference, cm	1.30 ± 0.67	1.09 ± 0.84	0.230
time for oxygen therapy, day	8.19 ± 6.83	8.20 ± 5.38	0.452
time for TPN use, day	6.74 ± 3.43	6.93 ± 6.61	0.047
time for completion oral nutrition, day	9.13 ± 6.26	11.93 ± 6.18	0.087
mean level of blood sugar, mg/dl	111.20 ± 25.88	84.00 ± 6.50	0.400
Apgar score	7.63 ± 0.55	7.16 ± 1.01	0.032
time for nutrition tolerance	4.47 ± 3.4	5.19 ± 6.2	0.029

4- DISCUSSION

In this study, we aimed to investigate whether using zinc sulfate supplements in neonates suffering from sepsis can effectively reduce adverse outcomes of sepsis. According to the findings, using zinc supplements could successfully prevent growth retardation (by improving body heightening and weighting), shorten time for receiving TPN and also improve oral nutritional tolerance. In other words, zinc supplements not only can modulate immune response against sepsis-related pathogens, but also it can compensate physical growth/development as well as helping oral nutrition to get started faster with digestive system readiness. The central effects of zinc on modulation of immune system were previously demonstrated by regulation maturation of T cells as well as regulation of inflammatory cytokines. However, the effects of zinc supplements on preparing the digestive system of the child have been less investigated. Regarding the effects of zinc on children growth and development, a meta-analysis of intervention studies in a variety of countries have demonstrated a positive association between zinc supplementation and linear growth in children (17). This meta-analysis by Van der Poll et al. showed that a dose of 10 mg zinc per day for 24 weeks could lead to a gain of 0.37 (±0.25) cm in height of children who received zinc supplements as compared to those who did not (6).

We suggest that due to the important effects of zinc supplement as an anti-inflammatory element, on preparing gastrointestinal system of children for oral nutrition as well as shortening time for TPN, it may lead to reducing inflammatory bed in the intestine. This claim can be confirmed through the evidence on treating effects of zinc supplements on inflammatory bowel diseases (18, 19).

In the present study, we demonstrated improvements in clinical outcomes among patients suffering sepsis and treated with anti-sepsis routine regimen. Although because of little sample size, we did not report death among our study subjects, some recent studies could show potential effects of zinc supplement on reducing mortality and morbidity in neonates. In our study, improvements in Apgar scores as well as in the linear growth of the patients may indicate for favorable outcomes following sepsis treatment. In a meta-analysis by Tang in 2017, zinc supplementation was able to significantly reduce mortality rate (20). In a study by Banupriya et al. in 2018, the mortality rate was significantly higher in no zinc compared to zinc group and also mental development quotient was significantly better among babies who received zinc supplementation (21). However, in another study by Newton et al. in 2016, outcome measures like days of hospital stay and mortality rate were not found to be significantly different between the groups receiving and no receiving zinc supplements (22). The pointed paradoxical effects may be due to the difference in drug dosages, the difference in medication protocol and also in the initial inclusion criteria for the study.

4-1. Study limitations

Limitations of our study included the unwillingness of the parents who were partially convinced by giving necessary explanations to them.

5- CONCLUSION

The use of oral zinc sulfate (3 mg/kg/day divided for 10 days) in neonates suffering from sepsis has positive effects on sepsis-related clinical outcomes, such as improving linear growth and nutrition tolerance, along with shortening the time for TPN.

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