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Original Article

Effects of oral zinc sulfate on hyperbilirubinemia in low-birth-weight neonates

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ABSTRACT

Background: Hyperbilirubinemia is one of the most common and persistent problems encountered in preterm newborns. This condition in preterm infant is more likely to be associated with neurological damage rather than terms. So far, no major studies have precisely assessed the effects of zinc sulfate on hyperbilirubinemia in low-birth-weight (LBW) neonates. Therefore, in this study, we aimed to evaluate these effects in LBW infants.

Methods: This randomized, double-blind, clinical trial (IRCT201401041162N22) was performed on 61 icteric LBW neonates, hospitalized in the neonatal intensive care unit (NICU) of Imam Reza Hospital in Mashhad, Iran from May 24, 2014 to May 24, 2015. The neonates were randomly divided into case and control groups, and the total serum bilirubin (TSB) level was measured at 0, 24, 48, 72, 96, and 120 h after treatment. The subjects received either 10 mg of zinc sulfate or placebo twice per day for five days (or by the end of treatment). The termination point of phototherapy was defined as a bilirubin level below 50% of the starting point. The collected data were analyzed, using SPSS version 20. Chi-square, t-test, and repeated measures ANOVA were carried out to compare the findings between the two groups.

Results: The mean TSB level was 14.87±2.65 and 14.73±3.22 mg/dl in the control and case groups. The mean decline in TSB level was only significant at 24 h after the treatment (2.71 and 2.13 mg/dl in the case and control groups, respectively; P=0.04), while being statistically insignificant on other days of the assessment. Also, similar findings were reported regarding the duration of treatment in the case and control groups (58.84±14.97 and 65.60±16.59 h in the case and control groups, respectively).

Conclusion: The present study showed that administration of oral zinc sulfate in icteric LBW infants could significantly reduce TSB level only at 24 h following the treatment.

Keywords: Hyperbilirubinemia, LBW, Neonate, Zinc Sulfate

Introduction

Increased serum bilirubin level resulting in clinical jaundice is one of the common problems during the neonatal period, occurring in the first week of life in 60% of term and 80% of preterm neonates (benign in many cases) (1). Jaundice is the most common cause of infant hospitalization in the neonatal period. As the serum bilirubin level may exceed the 95th percentile (high-risk zone) in 8-11% of newborns, precise evaluation and treatment are highly required (2, 3).

Bilirubin is the final product of heme catabolism, and the serum level is determined by the combination of bile production, hepatic conjugation, and enterohepatic circulation (4). In preterm neonates, hyperbilirubinemia is more common and persistent and is more likely to occur in patients with neurological damages rather than term neonates (5, 6).

The increased severity and duration of hyperbilirubinemia in preterm infants, along with the immaturity of the blood-brain barrier, have raised serious concerns regarding the greater risk of bilirubin encephalopathy for preterm infants (1, 7). Therefore, it is necessary to treat hyper-bilirubinemia, using three common methods of treatment, i.e., mechanical removal of bilirubin, photoisomerization, and bilirubin excretion in stool or urine which can be pharmacologically accelerated.

Deficient activity of uridine diphospho-glucuronosyltransferase-1A1 (UGT-1A1) can impair

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bilirubin conjugation and cause physiological jaundice. Over the first 10 days of life, uridine diphosphate glucuronyl transferase (UDPG-T) activity in full-term and premature neonates is usually low and less than 1% of adult values (8, 9). Overall, conjugated bilirubin is not absorbed in the intestine. On the other hand, bilirubin mono- and di-glucuronides are relatively unstable products, which are easily hydrolyzed to unconjugated bilirubin.

Circulation (comeback to circulating unconjugated bilirubin pool) and then arrive to liver for repeated conjugation.The reverted unconjugated bilirubin may be readily absorbed across the intestinal mucosa, circulation (comeback to circulating unconjugated bilirubin pool)and then arrive to liver for repeated conjugation. (10). Enteric mucosal β-glucuronidase enzyme at high concentrations plays an important role in the mechanism of enterohepatic circulation in both term and premature neonates (10). In fact, inhibition of enterohepatic circulation is one of the treatment methods used for the prevention of neonatal hyperbilirubinemia.

Various substances and strategies have been used to bind the bilirubin in the intestinal lumen in order to reduce its absorption and prevent enterohepatic circulation. Accordingly, some products, such as oral agar, have been used for this purpose, although inconsistent results have been reported. Zinc salt has been also investigated for its role in decreasing TSB level through inhibiting enterohepatic circulation (11, 12).

According to a study by Mendez-Sanchez, zinc salts, which flocculate at physiological pH, almost completely adsorb unconjugated bilirubin from unsaturated micellar bile salt solutions (11). Some animal studies have revealed the association between micronutrient deficiency and hyperbilirubinemia. Moreover, treatment with zinc has been found to be effective in reducing jaundice (13).

Methods

This randomized, double-blind, clinical trial (IRCT201401041162N22) was performed on 61 icteric low-birth-weight (LBW) newborns, hospitalized in the neonatal intensive care unit (NICU) of Imam Reza Hospital in Mashhad, Iran from May 24, 2014 to May 24, 2015. This research was approved by the Ethics Committee of Mashhad University of Medical Sciences. The study procedure was completely explained to the guardians of infants, and written informed consents were obtained before their participation.

Otherwise healthy breastfed neonates with jaundice and birth weight of less than 2500 g were selected among patients admitted to the hospital

NICU from January 2014 to April 2015. The exclusion criteria were as follows: 1) major congenital anomalies prohibiting feeding, 2) feeding intolerance, 3) gastrointestinal anomalies, 4) need for ventilator support, 5) hemolytic disease, 6) need for exchange transfusion, and 7) infections.

The laboratory assessments included complete blood count, red blood cell morphology, blood group assessment of the newborn and the mother, direct and indirect Coombs tests, reticulocyte count, and evaluation of erythrocyte glucose-6-phosphate dehydrogenase (G6PD) level. The results of clinical examinations, gestational age, birth weight, sex, serial TSB levels, direct bilirubin level, duration of phototherapy, and lenghth of hospital stay were recorded. The TSB level was measured, using a Unistat® bilirubinometer (Reichert-Jung, Germany).

An expert with a fellowship in neonatology, who was supervised by two academic personnel, evaluated the inclusion criteria and performed the procedures. The colorimetric method by Lathe and Ruthven was used for the measurement of direct bilirubin level (14). Zinc sulfate from simple 1% zinc sulfate syrup and placebo were prepared in bottles with a similar shape, volume, and taste (labeled with different codes). The involved physicians and laboratory staff were not aware of the administered agent for the neonates. The codes devoted to each infant were revealed as the study ended.

As all the subjects were healthy LBW newborns, phototherapy was initiated when TSB concentration reached the threshold value (TSB: 8-12 g/dl in newborns with a birth weight of 1500-2000 g and TSB: 11-14 g/dl in newborns with a birth weight of 2000-2499 g) (15). Phototherapy was discontinued as the bilirubin level decreased to 50% of the initial level (16). Each phototherapy unit contained six blue lamps. The energy output or irradiance of the phototherapy light was maintained at 8-12 μw/Cm2/nm. The irradiance level was checked at a specific time interval by Fluoro-Lite Meter 451 (Minolta Camera Co., Ltd.) and was maintained at 8-12 μW/Cm2/nm.

First, TSB levels were measured. If the neonate met the inclusion criteria, he/she received either 10 mg of zinc sulfate or placebo twice per day through enteral administration. The solutions were administered until the fifth day of the intervention or until hospital discharge. TSB and direct serum bilirubin levels were monitored before the intervention, at the onset of phototherapy, and at two, three, four, and five days after the intervention, depending on the treatment period. Duration of treatment was calculated from the onset to the end of phototherapy or five days after the onset of treatment (whichever occurred first).

The collected data were categorized and analyzed, using SPSS version 20. The normal distribution of the data was examined by Kolmogorov-Smirnov test. Independent sample t-test was also conducted to compare the quantitative data. Furthermore, to compare the qualitative data, Chi-square test was employed. In all the tests, the confidence level was set at 95%, and P-value less than 0.05 was considered statistically significant.

Results

In total, 44 out of 105 participants were excluded from the study due to gastrointestinal intolerance, parents' unwillingness to continue the treatment, infant death, symptoms of sepsis, and such as neonatal transport to other medical cente. The remaining 61 cases were then divided into case and control groups. The demographic characteristics of mothers and newborns were homogeneous in both groups. Table 1 illustrates the demographic information of the participants.

The subjects were homogenous in terms of the mode of delivery, intrauterine growth, and diseases during pregnancy. The results showed no significant difference between the two groups regarding the mode of delivery. In total, 41.9% and 58.1% of the subjects in the case group and 50.0% and 50.0% of the participants in the control group were born through cesarean section and natural vaginal delivery, respectively.

Table 1. Demographic characteristics of the participants

Variables	Case group (zinc sulfate)	Control group (placebo)	P-value
Age (days)	6.07±3.49	5.65±5.29	0.70
Weight (g)	2053±364.18	1962±315.45	0.30
Number of females (%)	19 (63.3)	21 (67.7)	0.71

Data are presented as mean±SD and n (%).

Table 2. The laboratory test results at the onset of treatment

Variables	Case group (zinc sulfate)	Control group (placebo)	P-value
Hemoglobin level (g/dl)	15.03±2.75	15.92±2.93	0.22
Reticulocyte count	1.80±1.41	1.51±.89	0.34
ABO setting, n (%)	7 (23.3)	7 (22.6)	0.94
Initial TSB level (mg/dl)	14.73±3.22	14.87±2.65	0.84

Data are presented as mean±SD and n (%).

Table 3. The mean decline in total serum bilirubin (TSB) level and treatment duration

Variables	Case group (zinc sulfate)	Control group (placebo)
Treatment duration (h)	58.84±14.97	65.60±16.59
Reduction in TSB level after 24 h (mg/dl)	2.71±0.90	2.13±1.26
Reduction in TSB level after 48 h (mg/dl)	5.59±1.73	4.94±2.16
Reduction in TSB level after 72 h (mg/dl)	6.65±1.64	6.70±2.60

The mean gestational age was 34.06±1.89 and 34.3±2.48 weeks in the case and control groups, respectively; however, the difference was not statistically significant. The mean birth weight of the infants was 1962.10±315.45 and 2053.00±364.18 g in the case and control groups, respectively, which indicated no significant difference between the two groups. Exclusive breastfeeding was the main feeding method in the two groups. Also, at the beginning of treatment, laboratory assessments did not exhibit any significant difference between the two groups in terms of hemoglobin level, reticulocyte count, ABO setting, G6PD level, Coomb's test results, and initial TSB level (Table 2).

Based on the findings, a significant decline was reported in TSB level and treatment duration in the first 24 h. Table 3 presents the detailed results of the analyses.

The assessment of patients continued for 120 h, as a few patients required treatment for more than 72 h (96 h for four patients and 120 h for one patient). However, given the low number of these patients, no major analyses were performed after 72 h.

Discussion

The present results showed the significant effect of oral zinc on the treatment of neonatal hyperbilirubinemia in the first 24 h of admin-istration. On the other hand, no significant reduction was reported in the case group in comparison with the control group after this period. As presented in Table 3, although the mean duration of phototherapy in the case group was lower than the control group (58.84 vs. 65.60 h), the difference was not statistically significant.

Numerous drugs, such as metalloporphyrins and d-penicillamine, have been known to affect bilirubin metabolism by the inhibition of heme oxygenase, agar, and charcoal through decreasing enterohepatic circulation (8). It seems that the action of zinc in hyperbilirubinemia depends on reducing the enterohepatic circulation (17). However, only a limited number of studies have specifically evaluated the efficacy of zinc in reducing hyperbilirubinemia among preterm or LBW neonates.

Among these limited studies, Mendez-Sanchez et al. showed the efficacy of zinc sulfate in decreasing hyperbilirubinemia only in adult patients with Gilbert's syndrome (11). They found a significant decline in serum bilirubin level, following the administration of 40 mg of zinc sulfate; however, it should be noted that this study was a small-scale research with only 20 patients. On the other hand, in

a previous study, oral zinc was shown to have no prophylactic effects on the development of jaundice or the decline in TSB level in VLBW newborns during treatment (18); however, in the present research, the therapeutic effect of zinc in LBW infants was confirmed.

Rana et al. (17) concluded that administration of oral zinc (10 mg) twice per day could not reduce the incidence of hyperbilirubinemia in term and late-preterm infants (>35 weeks) within 25 and 168 h after birth. They also showed that zinc administration was not associated with any decline in the number of neonates requiring phototherapy. However, the duration of phototherapy was lower in the group receiving oral zinc supplements, compared to the placebo group.

The results of a previous study by Maamori et al. showed that administration of zinc sulfate neither affected hyperbilirubinemia nor delayed the development of jaundice (19). However, a lower admission rate and reduced phototherapy duration were reported in the zinc group in comparison with the placebo group. In the mentioned study, transcutaneous bilirubin was assessed in infants above 35 weeks of age, while in the present research, TSB level was analyzed; this difference might be in fact the cause of discrepancy between the findings. Moreover, in the mentioned study, zinc was used for prophylaxis, whereas in the present research, the therapeutic effects of zinc were analyzed.

Furthermore, in a study on term neonates by Patton et al., oral administration of 5 mg of zinc twice per day did not cause a significant difference in the duration of hyperbilirubinemia (20). The cause of discrepancy between the mentioned study and the present research might be the gestational age of the participants and zinc dosage. It should be noted that in the present research, the dose of zinc (20 mg/day) was selected, based on several trials on a large number of children with diarrhea, measles, pneumonia, common cold, and malaria, all indicating the safety of this concentration (21-23).

The role of zinc in hyperbilirubinemia depends on its ability to reach the terminal ileum, where it precipitates unconjugated bilirubin to prevent enterohepatic circulation. However, the ineffectiveness of zinc in reducing bilirubin level in this study might be attributed to a number of factors such as delayed release of zinc to reach the active area, need for higher doses, or need for other zinc preparations. No significant adverse effects were found in the case group, and no mortality was reported in either of the groups throughout the study. Overall, zinc appeared to be a safe agent.

Conclusion

The present results showed that administration of oral zinc sulfate in icteric LBW infants could significantly reduce TSB level only within the first 24 h of treatment. Therefore, further studies are required to facilitate generalization of the present findings.

Acknowledgments

Conflicts of interest

None declared.

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