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The Therapeutic Effect of Zinc Sulfate on Neonatal Hyperbilirubinemia

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ABSTRACT

***Background*:** Approximately 60% of term neonates and 80% of preterm ones suffer from hyperbilirubinemia in their first week of life. This study sought to characterize the therapeutic effect of oral zinc sulfate on neonatal hyperbilirubinemia.

***Methods*:** In this randomized, double-blind, placebo-controlled clinical trial, 70 term neonates with total serum bilirubin (TSB) level ≥ 20 mg/dl were enrolled. Thirty-four cases were treated with phototherapy and zinc (10 mg/day, single dose) as case, while the remainder received phototherapy plus placebo. TSB level was measured at the onset of the intervention, as well as 12, 24 and 48 h after the intervention and compared with each other.

***Results*:** The mean TSB levels were significantly lower in the zinc group after 12, 24 and 48 h (P=0.038, 0.005, 0.001, respectively). The mean durations of phototherapy in the case and control groups were 2.03±0.174 and 2.33±0.478 days, respectively, being significantly less in the case group (P=0.002).

***Conclusion*:** This study revealed that oral zinc sulfate at a single dose of 10 mg/day diminished TSB level and duration of phototherapy.

Keywords: Hyperbilirubinemia, Neonate, Treatment, Zinc sulfate

Introduction

In the recent years, a substantial body of research has been carried out to predict neonates who are most likely to develop hyperbilirubinemia. Reliable prediction can reduce hospital stay for low-risk neonates and identify high-risk neonates facilitating their closer follow-up (1).

In general, 60% of term newborns and 80% of preterm ones present with hyperbilirubinemia in their first week of life (2, 3). The incidence of severe neonatal hyperbilirubinemia is the highest in Asians (2), accounting for one-thirds of neonatal admissions in Iran (3). Jaundice in such cases is mainly physiologic and diagnosed by ruling out other causes of jaundice such as hemolysis, infection, or metabolic diseases, whereas 5-10% require intervention (3, 4). The fundamental aim of detecting and treating severe neonatal jaundice is to prevent bilirubin encephalopathy and its chronic sequel (1, 5). Such complications underscore the importance of finding further treatments for this disease. As of yet, phototherapy and exchange transfusion were the treatment of choice in such cases; however, both of these approaches have several disadvantages (4).

Exchange transfusion poses the risk of graft versus host disease and a higher mortality rate (2). Phototherapy induces parental anxiety due to hospitalization and cost of care. Furthermore, it hinders mother-infant bonding. Drug therapy, on the other hand, is more practical, acceptable and cost-effective.

In several studies, the associations between microneutrients and jaundice have been proposed. Some of them, such as zinc sulfate, bind to bilirubin in the small intestine, reduce its absorption and therefore prevent enterohepatic circulation, but with inconsistent results (1, 6).

Zinc is one of the essential elements in

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neonatal growth, protein synthesis and regulation of inhibitory and stimulatory synapses of the brain. It has been shown to lower bilirubin level by inhibition of the normal enterohepatic cycling of unconjugated bilirubin (7-9). Therefore, the anticipated role of zinc supplementation in neonatal jaundice seems to be an attractive issue.

This randomized clinical trial was conducted on term neonates to characterize the therapeutic effect of oral zinc sulfate on neonatal jaundice.

Methods

This randomized, double-blind, placebo-controlled clinical trial was performed during July-December 2013. Seventy term neonates who were admitted to neonatal intensive care unit of Imam Reza Hospital of Mashhad, Iran, were selected for the study. The inclusion criteria comprised of gestational age ≥38 weeks, birth weight ≥2500 gr and total serum bilirubin level ≥20 mg/dl. All cases with hemolysis, glucose-6-phosphate dehydrogenase deficiency disease, sepsis, severe respiratory disease requiring mechanical ventilation, congenital anomalies and a total serum bilirubin (TSB) of exchange level on admission were excluded. Among the 70 enrolled neonates, four cases were excluded due to mechanical removal of bilirubin after exchange blood transfusion (1 case and 3 controls). Serum bilirubin level was measured using Unistar Bilirubinometer (Reichert-Jung, Germany). Direct bilirubin was determined by the colorimetric method proposed by Lathe and Ruthven.

Phototherapy initiation, duration and termination point were decided based on the American Academy of Pediatrics guidelines (AAP 2004) (10). Each phototherapy unit had four special blue lamps (Philips Co, Germany) and was adjusted to 25 cm above the infants' cots.

All the neonates received phototherapy during the study period. In the study group, besides phototherapy, 10 mg/day zinc sulfate was prescribed by the treating physician at a single dose in the form of syrup (based on Maamouri et al. study) (11).

The control group received placebo with a similar color, taste, volume and package to the zinc sulfate syrup for the same duration and at the same dosage. The zinc and placebo syrups were distributed by a single physician who was blinded to the group allocations and the study protocol. The pediatrician who visited the neonates was also blind to the type of intervention. The on-duty nurses were explained to repeat the dose after 5-10 min if the child vomited the drug.

Total and direct serum bilirubin levels were measured at the outset of the intervention, as well as 12, 24 and 48 h after receiving the intervention and in cases of extended hospitalization after 72 h.

A written informed consent was signed by the parents of each infant prior to the study. The parents were assured that they could withdraw their neonates from the study at any time. The study protocol was approved by the Ethics Committee of the Deputy of Research of Mashhad University of Medical Sciences (IRCT201306031162N19).

Statistical analysis

The minimum sample size was calculated based on Babaei et al. study (12). Data were analyzed using SPSS, version 11.5. Quantitative variables are presented as mean±standard deviation. The normal distribution of variables was proved by Kolmogorov-Smirnov test. We used independent samples t-test and Mann-Whitney U test for comparison of the variables with and without normal distribution, respectively. Pearson correlation coefficient and Chi-squared test were used for comparison of qualitative variables. P-value less than 0.05 was considered statistically significant.

Results

In the present study, 66 term newborns completed the study (n=33 for each group). There were no significant differences between the two groups regarding age, sex, date of jaundice onset, mother's parity, route of delivery, birth weight and weight at inclusion (Table 1).

Moreover, laboratory indices including reticulocyte count, hematocrit, as well as total and direct bilirubin were measured, showing no remarkable differences between the two groups (Table 1).

In the current study, at the first visit which was 12 h after receiving the medication, a significant difference was observed between the zinc and placebo groups regarding total serum bilirubin level (P=0.038). This difference was also present 24 and 48 h after initiating the medication (P=0.005 and 0.001, respectively). Direct serum bilirubin showed no significant differences between the two groups over time.

Figure 1 depicts the changes in total serum bilirubin level (mg/dl) over time compared to baseline in the two groups.

Changes in total and direct serum bilirubin

Table 1. Demographic characteristics of the case and control groups

	Zn	Placebo	P-value
Sex (%Female)	41.2	47.2	0.611
Age (day)	6.6±2.57	5.8±1.89	0.138
Date of jaundice onset (day)	3.3±1.35	3.0±0.95	0.300
Parity (Number)	1.4±0.65	1.6±0.75	0.326
Delivery route (%NVD)	75.0	52.0	0.095
Birth weight (gr)	3080.7±564.60	3155.2±458.17	0.592
Weight at inclusion (gr)	3159.6±489.37	3173.0±437.74	0.915
Hematocrit (%)	46.5±5.90	45.9±5.40	0.641
Reticulocyte count (%)	1.3±1.45	1.0±1.01	0.487
Total serum bilirubin (mg/dl)	22.5±2.31	21.5±1.61	0.052
Direct serum bilirubin (mg/dl)	0.62±0.218	0.67±0.224	0.718

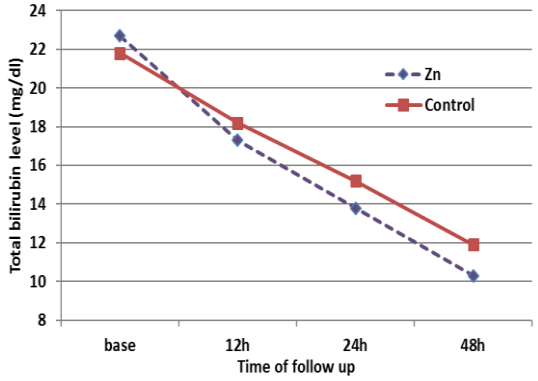

Figure 1. Changes in mean total serum bilirubin level over time in the study and control groups

in Table 2.

Moreover, one of the case and 11 of the control group subjects required treatment continuation up to 72 h. The other infants were all discharged after 48 h of treatment.

The mean durations of phototherapy in the case and control groups were 2.03±0.174 and 2.33±0.478 days, respectively, showing a significantly shorter duration in the zinc sulfate group based on Mann-Whitney test (P=0.002).

During the treatment period, no drug-related side effects were observed in either group.

Discussion

This study revealed that zinc sulfate supplementation at a dose of 10 mg/day along with phototherapy can significantly reduce TSB level. Moreover, we found a significant difference in the mean TSB levels after 12, 24 and 48 h of treatment between the zinc and placebo groups, suggesting that zinc sulfate may play a certain role in reducing neonatal hyperbilirubinemia.

Drug therapy is associated with high compliance and low cost of care. Clofibrate, phenobarbtal, bile salts, dipenycilamine, and zinc compounds were found to act through different mechanisms such as production inhibition, stimulation of hepatic clearance and enzymatic inhibition (3, 13-16). However, none of them has been proposed as a common therapeutic method so far.

Zinc salts were demonstrated to be promising both in-vitro and in-vivo (1). In other words, the action of zinc in hyperbilirubinemia depends on its ability to reach the distal intestine where it is once again absorbed into the blood, and therefore, reduces the enterohepatic circulation.

The first human study on this issue was carried out by Mendez-Sanchez et al. on 20 adult patients of Gilbert syndrome. They reported that zinc sulfate significantly decreased serum unconjugated bilirubin level (9).

In another study, Rana et al. (1) investigated the impact of oral zinc salt on the incidence of hyperbilirubinemia and need for phototherapy in term and late-preterm at-risk neonates between 25 and 168 h of age. They concluded that twice-daily

Table 2. Changes in total and direct serum bilirubin levels after the intervention

Plasma bilirubin level (mg/dl)	Zn (n=33) Mean (SD) range	Control (n=33) Mean (SD) range	P-value
Total serum bilirubin, baseline	22.5 (2.31) 20-26	21.5 (1.61) 20-26.5	0.052
Total serum bilirubin, after 12h	17.3 (1.62) 14.2-21.9	18.2 (1.33) 15.6-22.0	0.038
Total serum bilirubin, after 24h	13.8 (1.98) 7.1-17.4	15.2 (1.72) 12.3-18.0	0.005
Total serum bilirubin, after 48h	10.3 (2.09) 6.0-13.0	11.9 (1.74) 7.7-15.5	0.001
Total serum bilirubin, after 72h	8.6	11.4 (1.17) 9.8-12.6	0.045

administration of oral zinc at a dose of 10 mg does not reduce the incidence of hyperbilirubinemia in such cases during the first week of life (1).

Mosayebi et al. evaluated the serum zinc level alterations before and after phototherapy in hyperbilirubinemic newborns. They concluded that phototherapy increases serum zinc level by reducing bilirubin level, such that additional supplementation of this element can potentially lead to zinc toxicity (17).

Mafinejad et al. (2012) studied the prophylactic effects of zinc sulfate in neonatal hyperbilirubinemia. They showed that administration of zinc sulfate neither affected hyperbilirubinemia nor delayed jaundice manifestation. They observed that the duration of phototherapy and hospitalization were less in zinc group. Weight gain between the 3rd and 7th days of life was also more significant among the zinc sulfate group (11).

In Vitek et al. study, the oral administration of zinc salts efficiently decreased serum bilirubin level in hyperbilirubinemic rats, most probably due to the inhibition of enterohepatic circulation of bilirubin. They suggested that this approach might be useful for the treatment of severe unconjugated hyperbilirubinemia (8).

Nevertheless, Patton et al. studied the effect of oral zinc on 60 neonates with hyperbilirubinemia. The neonates received 5 mg oral zinc twice daily for five days. They reported that bilirubin level measurement on day 5 of treatment showed no significant difference between the two groups in terms of duration of hyperbilirubinemia (18).

The present study also showed that although zinc sulfate administration was not associated with any reduction in the proportion of neonates requiring phototherapy, it did curtail phototherapy duration compared to controls. A shorter duration by itself is highly beneficial as it can lead to earlier mother-infant bonding and impose lower costs on the medical system besides reducing possible side effects in the newborn.

Regarding several previous studies performed on children with diarrhea, measles, pneumonia, common cold and malaria, we decided to use oral zinc as a safe agent at a single dose of 10 mg/day (19-21). Accordingly, zinc sulfate syrup was well-tolerated by the newborns and no side effects were observed. It seems that zinc, as a micronutrient and a safe drug, can be beneficial in reducing bilirubin level in neonates through inhibition of enterohepatic circulation.

There were a few limitations in the current study. The study had a small sample size and although the dose of zinc was decided based on Recommended Dietary Allowance recommend-dations and the available literature, yet a different dosage may have resulted differently. In addition, starting the treatment sooner might have influenced our findings and limited the impact of other variables existing between birth and admission. Furthermore, we did not check the zinc serum level before and after the intervention.

Conclusion

Administering oral zinc sulfate at a single dose of 10 mg/day reduced the mean TSB level and duration of phototherapy. Zinc, as a micronutrient, may be recommended as a safe and effective medication in neonatal non-hemolytic jaundice besides phototherapy. Further studies with larger sample sizes, different dosages and formulations of zinc, and more precise laboratory studies are recommended to confirm our findings.

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Conflicts of interests

None

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