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Original Article

Efficacy of Oral Zinc Sulfate Intake in Prevention of Neonatal Jaundice

Gholamali Maamouri [1], Hassan Boskabadi [1], Shahin Mafinejad [2]*, Yasaman Bozorgnia [3], Ali Khakshur [2]

[1] Department of Pediatrics, Neonatal Research Center, Ghaem Hospital, Mashhad University of Medical Sciences, Mashhad, Iran
[2] Department of Pediatrics, North Khorasan University of Medical Sciences, Bojnurd, Iran
[3] Assistant professor of orthodontics, Department of Orthodontics, North Khorasan University of Medical Sciences, Bojnurd, Iran

ABSTRACT

Introduction: Jaundice is considered as a common clinical condition during infancy. Prevention of severe hyperbilirubinemia (jaundice) is safer and easier than current therapies, like phototherapy or blood exchange. In some animal studies, zinc was found effective in reducing jaundice. In this study we evaluated the effect of zinc sulfate on neonatal hyperbilirubinemia.

Materials and Methods: This randomized, double-blind clinical trial was performed on healthy term (35 weeks of age and more) neonates. Eligible newborns were randomly allocated to two groups: group A (receiving zinc sulfate, n=57) and group B (receiving placebo, n=74). They were screened for indirect bilirubin by BiliCheck at the end of the first, third and seventh day of age. We evaluated various characteristics such as weight, clinical signs, maternal and neonatal histories, and laboratory results.

Results: Mean bilirubin values of the 3rd and 7th day were determined as (12.9±3 vs. 12.6±2 mg/dl, p=0.473), and (12.4±3 vs. 12.4±4, p=0.989), respectively. The incidence of hyperbilirubinemia (Bil>15) among group A and group B was reported 26% and 22%, respectively. The rate of admission due to hyperbilirubinemia and phototherapy was significantly higher among the newborns in placebo group, (p=0.043). Weight gain between the 3rd and 7th day of infant's age was more significant in the zinc group, (p=0.039).

Conclusion: The current study showed that the administration of zinc sulfate neither affected hyperbilirubinemia, nor delayed the jaundice appearance; although fewer admission and phototherapy duration were reported in the zinc group in comparison with the placebo group. Weight gain between the 3rd and 7th day was more significant in the zinc group.

Keywords: Bilicheck, Hyperbilirubinemia, Newborn, Phototherapy, Zinc Sulfate.

Introduction

Jaundice is the most common reason for infants' admission during neonatal period. Serum bilirubin might rise above the 95th percentile within 8-11% of newborns; therefore evaluation and treatment would be needed (1, 2). Although a mild increase in serum bilirubin has some advantageous effects, potential central nervous system (CNS) toxicity may occur, due to the indirect bilirubin increase (3). Bilirubin is the end product of heme catabolism, and its serum level is determined by the combination of bile production, hepatic conjugation and enterohepatic circulation (4). Enterohepatic circulation may increase serum bilirubin through mechanisms mentioned below:

- decreasing calorie intake and defecation
- increasing lipid absorption
- decreasing urobilin production in the gut
- increasing glucoronidase activity within breast milk (5, 6)

Inhibition of enterohepatic circulation is one of the therapies being tested for the treatment of neonatal hyperbilirubinemia and Crigler-Najjar syndrome (7). Various substances have been used to bind the bilirubin in intestinal lumen to prevent its absorption and disrupt enterohepatic circulation. These substances are such as oral agar, orlistat, active charcoal, cholestyramine, calcium phosphate or glucoronidase inhibitor, like hydrolyzed casein; although the obtained results have been inconsistent (8).

* *Corresponding author:* Shahin Mafinejad, Assistant Professor, North Khorasan University of Medical Sciences, Mashhad, Iran; Tel: 09153101504; E-mail: shahinmaf@yahoo.com

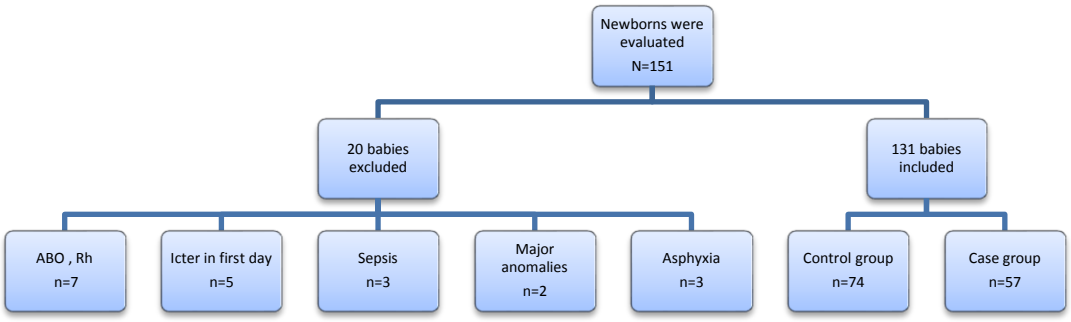


Figure 1. The flowchart of the study

The study by Mendez-Sanchez *et al* reported that the Zn salts that flocculate at physiological pH adsorb unconjugated bilirubin almost completely from unsaturated micellar bile salt solutions (9). Some animal studies showed the association between micronutrient deficiencies and hyperbilirubinemia, while treatment with zinc was found effective in reducing jaundice (10). The main aim of diagnosis and treatment of hyperbilirubinemia is to prevent kernicterous (10, 11).

We conducted this study to determine the effect of zinc sulfate on neonatal hyperbilirubinemia by inhibiting enterohepatic circulation mechanism.

Materials and Methods

This randomized, double-blind clinical trial on healthy term (35 weeks of age and more) neonates, who were born either through spontaneous vaginal delivery, or elective cesarean section (singletons or twins), was conducted at the Perinatology Ward of Ghaem Hospital, Mashhad.

Newborns aged 24±6 hr, were eligible to participate in this trial. We excluded newborns with Rh disease, ABO incompatibility, sepsis, major anomalies, low Apgar (<7 in min five), and clinical jaundice in the first 24 hr of life. The enrolled newborns were randomly categorized into two groups (the zinc group (A), and the placebo group (B)), and screened for transcutaneous bilirubin (TcB) by BiliCheck device (JH20-1A, made in Japan), at 24±6 hr of age. Afterwards, for a week, the newborns were administered zinc sulfate (10 mg within 2cc, daily) or the placebo, which was identical in color, taste and appearance to zinc sulfate, and was packaged in similar bottles by a pharmacist who was not involved in this study.

The code of intervention drug (zinc or placebo) was kept blind to the investigators, participants and statisticians until the results were thoroughly analyzed. The first dose of intervention drug was administered under direct supervision, and the mothers were instructed to administer the remaining doses. The Ethic Committee of Mashhad University of Medical Sciences (MUMS) approved this study, and all the mothers signed the informed consent.

Newborns were measured again for TcB on the 3rd and 7th day of life by BilliCheck. The neonate's weight, the clinical signs, feeding status (feeding intervals, breastfeeding, or formula), urination and defecation intervals were also controlled. We filled a questionnaire for each participant which included the medical information of the mother and the baby, such as the maternal history (age, parity, past medical history, blood type, Rh disease and history of previous babies with jaundice), labor status (route of delivery, PROM, oxytocin administration), and the neonatal history (birth weight, BG and Rh disease).

Hyperbilirubinemia was defined as TcB value was >75th percentile in the first day or >15 mg/dl in day 3 or 7. For these cases, we also measured the serum bilirubin by Diazo test, and the treatment and follow-up were planned based on the serum value results. Possible complications like vomiting, diarrhea and rash were inquired and reported among the newborns who had received zinc or placebo.

Data was recorded in SPSS 13.5 (SPSS Inc, Chicago, 13.5, USA) software with descriptive statistics (mean and standard deviation [mean ± SD]). Chi-square (x^{2}) test was performed for the analysis of qualitative variables, and t-student test and Mann-Whitney test were used for quantitative variables. Co-efficient confidence of this study was 0.95 and *P* less than 0.05 was considered significant.

Results

In this study, 151 newborns were evaluated, and 20 of them were excluded, based on the exclusion criteria (Figure 1). One hundred and

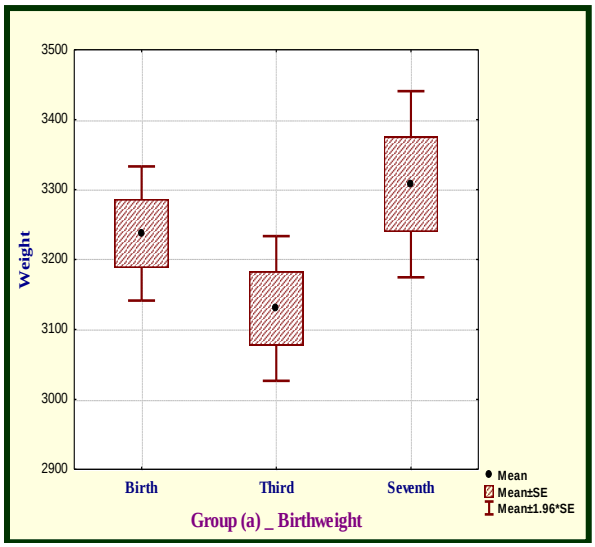
thirty one subjects were categorized into two groups. Fifty seven (44%) and 74 (56%) newborns were allocated in group A (zinc sulfate) and group B (placebo), respectively.

Table 1. Clinical characteristics of participant groups

Variable	Case (zinc sulfate)	Control (placebo)	*P*
Mean birth weight (gr)	3237	3128	0.091
Sex (male %)	63	51	0.177
Parity (multi vs. primi)	32/25	39/35	0.695
Mean mother age (y)	27.1	27.5	0.689
Vaginal delivery (%)	57.9	55.4	0.776
Previous baby with hyperbilirubinemia (%)	17.5	25	0.308
Oxytocin administration (%)	25	21	0.572
Exclusive breastfeeding (%)	88	91	0.663

Sex distribution between the two groups was relatively similar, with 56% of them being males and 44% being females. The mean age of mothers in the case and control groups was reported as 27.1 and 27.5 years, respectively. History of previous babies with hyperbilirubinemia was reported as 17.5 and 25 % among group A and B, respectively, (p=0.308). There was no significant difference between the two groups; neither for the route of delivery, nor the oxytocin administration, (p=0.776 and p=0.572, in order). In both groups, the vaginal delivery was preferred. Exclusive breastfeeding was the main way of feeding the newborns in both groups (Table 1).

The distribution of blood type (A, B, AB and O) among mothers of the two groups was not different, considering Z-test, (p=0.829). Student t-test did not indicate any significant difference between the two groups for variables such as birth weight and mean TcB, on day 3 and 7 (Figure 2 and 3). Hyperbilirubinemia (Bil>15) was determined 26 and 22% among babies within the case and control groups, respectively. Newborns



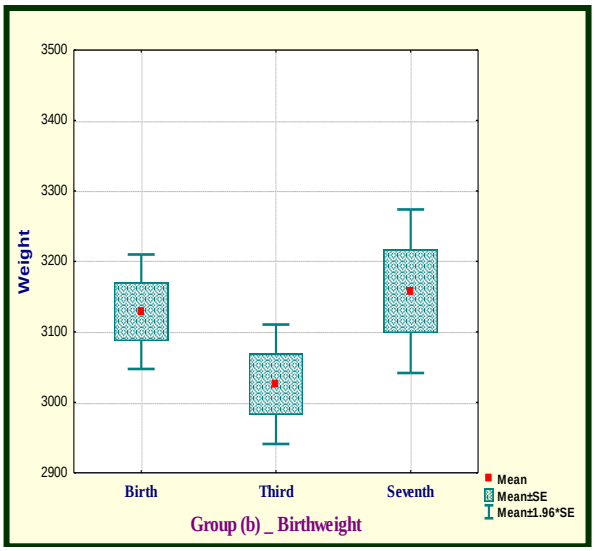
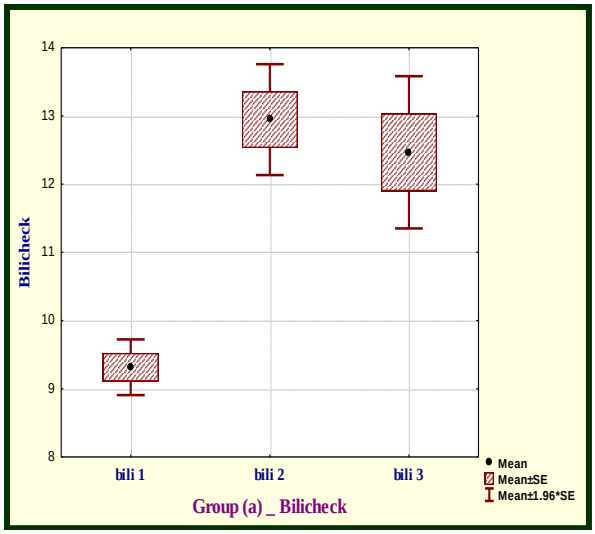


Figure 2. Weight difference on the 3rd and 7th day in both groups



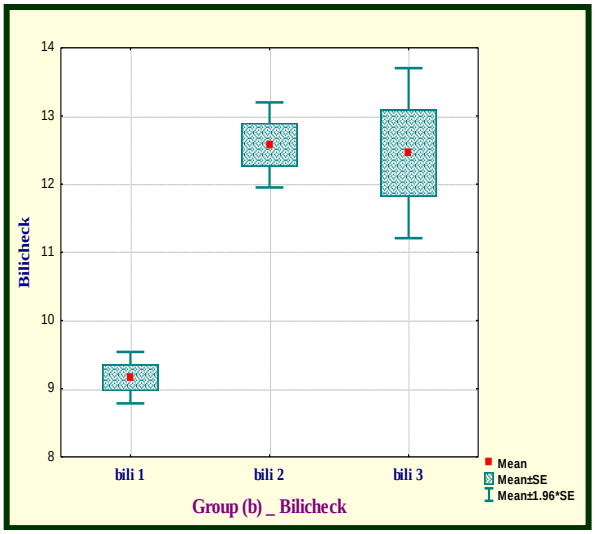


Figure 3. Mean bilirubin values by TcB in both groups

Table 2. Indication of phototherapy among babies in two groups

Phototherapy indication	A	B
Yes	4	11
No	43	35
Total	47	46

*X^2= 4.077, df =1, P-value = .043

in placebo group needed more admission and treatment with phototherapy, (p=0.043) (Table 2).

The mean phototherapy duration for group A and B was reported 18 and 36 hr, in order (Figure 4). Newborns in group A and B showed weight loss on the 3rd day in comparison with their birth weight (3.67% and 3.53%, respectively), although weight gain was observed on the 7th day, (2.22% and 1.3%, respectively, p=0.53.)

The weight difference between the 3rd and 7th day of life, among newborns in the zinc group (5.7%, p=0.039), was significantly higher than the placebo group (4.8%, p=0.069). The maximum (60 hr), and minimum (12 hr) duration of phototherapy was reported in the placebo and zinc group, respectively.

Discussion

The results demonstrated that the administration of zinc neither reduces hyperbilirubinemia, nor delays the jaundice appearance. The Only human study that showed the efficacy of zinc sulfate in decreasing hyperbilirubinemia is conducted by Mendez-Sanchez *et al* on adult patients of Gilbert syndrome (9). They showed a significant decrease in bilirubin serum levels in their subjects following the administration of 40 mg zinc sulfate; although, it was a small-scale study with only 20 patients.

Our study showed no significant difference in the incidence of hyperbilirubinemia (bil>15) among the two groups (26% vs. 22% in zinc and placebo groups, respectively, p=0.206). Our results were in agreement with Rana's study (17.9% vs. 19.1% in zinc and placebo groups, respectively) (12). The higher values of bilirubin in our investigation, in comparison with those of Rana's study, is attributed to the dissimilar methods of bilirubin measuring (TcB vs. Diazo test). It is possible that our study results are due to the low dosage of zinc administration, in comparison with 40-mg zinc, used by Mendez-Sanchez trial. Another possibility could be the absorption of small values of oral zinc salt in proximal intestine, leading to its unavailability in the distal intestine, where it should actually reach to prevent enterohepatic circulation of unconjugated bilirubin. There also could be a role of zinc preparation which is either non-absorbable or slowly absorbable. We could also use higher doses, or more frequent administration of oral zinc; although it requires further investigations.

According to the random categorization of enrolled newborns into case and control groups, neonatal characteristics, like sex (male gender is a minor risk factor for hyperbilirubinemia), birth weight and feeding status, were similar between two groups (Table 1).

Maternal risk factors for neonatal jaundice are as follows: mother's age (>25 years is a risk factor); parity (multiparity > primigravity); blood

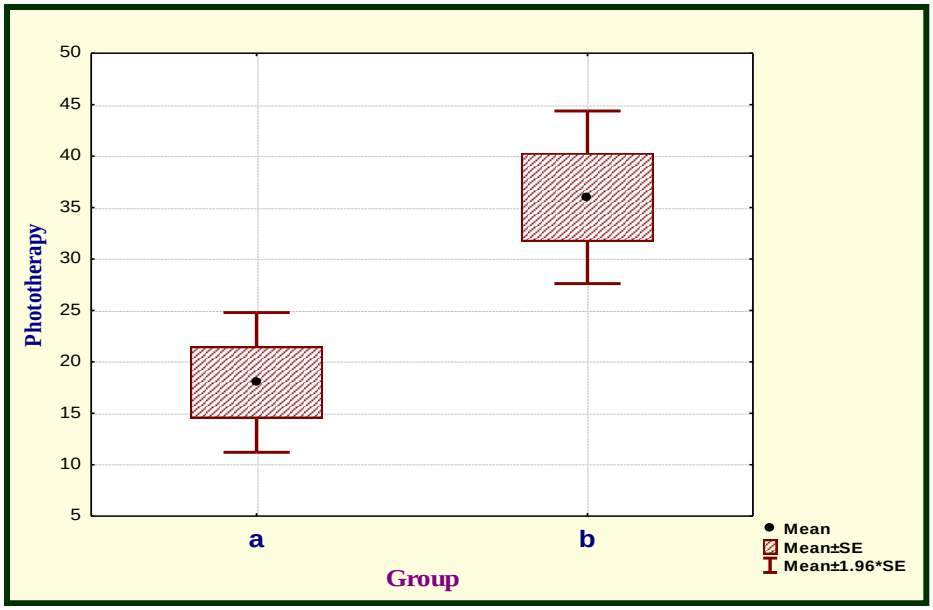


Figure 4. Mean duration of phototherapy in two groups

group; receiving Oxytosin for induction (a minor risk factor for infants' jaundice); smoking and addiction (negative effects on hyperbilirubinemia). All these factors were evaluated between the two groups, and there was no significant difference among the groups (13-15).

We assume there were few factors affecting our results, as nearly all subjects had similar conditions.

The current study showed significant differences in admission and phototherapy among the two groups, (p=0.043). The maximum bilirubin value was recorded 18 and 27 mg/dl, in case and control group, respectively. We also found significant variations in duration of phototherapy between the groups. Our results were in agreement with Rana's study. The reason for the decrease in admission and phototherapy in the zinc group could be the earlier onset of zinc administration, compared with Patton's study (16) (first day vs. after the second day).

In this trial, jaundice appeared among babies in both groups on the third day of life; therefore, zinc supplementation did not delay hyperbilirubinemia.

No adverse effects were reported in the zinc group, and all subjects were in good health throughout the study. Complications like vomiting, diarrhea and rashes among the newborns, who had received zinc, were similar to the placebo group.

We neither controlled the zinc serum levels before or after the intervention, nor did we check zinc and bilirubin levels in faces of our subjects, due to the limited laboratory facilities. We believe larger multi-center trials, preferably with different doses and formulations (absorbable vs. unabsorbable) of zinc supplements, would be necessary to confirm the efficacy of zinc supplements on the incidence of hyperbilirubinemia.

Conclusion

The current study in contrast with the previous human trial showed that the administration of zinc supplement (10 mg/daily zinc sulfate within the first week of life) neither reduces hyperbilirubinemia, nor delays the jaundice appearance. Weight gain between the 3rd and 7th day of age was more significant in the zinc group, and no adverse effects were reported in the zinc group. Less admission and phototherapy duration was reported in the zinc group, in comparison with the placebo group. Therefore, we recommend the administration of zinc sulfate to all the newborns with risk factors of developing

hyperbilirubinemia.

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