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Original Article

Effect of Oral Zinc Sulfate Therapy on the Management of Neonatal Non-Hemolytic Unconjugated Hyperbilirubinemia: A Randomized Control Trial

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ABSTRACT

Background: Zinc (Zn) salts have been tried for the prevention and treatment of neonatal jaundice as they are presumed to reduce serum bilirubin through the inhibition of enterohepatic circulation with controversial results. This study aimed to evaluate the effect of Zn sulfate on both bilirubin levels and the duration of phototherapy during the management of neonatal jaundice.

Methods: A double-blinded prospective study was conducted on 60 healthy neonates, ≥36 weeks gestation, with unconjugated non-hemolytic neonatal hyperbilirubinemia requiring phototherapy within the first week of life. They were divided into three groups of: A (n=20) receiving placebo, B (n=20) receiving low-dose oral Zn sulfate (10mg/day), and C (n=20) receiving high-dose oral Zn sulfate (20 mg/day), in combination with phototherapy for seven days. Serum bilirubin levels were measured on day 1 before starting the treatment and were reevaluated on days 3 and 7.

Results: Day 3 bilirubin was significantly lower in group C, compared to groups A and B (12.36±2.50 vs. 13.99±1.59 and 13.65±1.67 mg%; P<0.011 and P<0.043, respectively). Moreover, day-7 bilirubin demonstrated a significant decrease in group C than in group A (8.03±1.75 vs. 10.47±2.24 mg%, P<0.001). Total phototherapy duration was significantly shorter in group C, compared to groups A and B (26.05±11.42 vs. 37.70±18.27 and 36.90±12.47 h; P<0.032 and P<0.028, respectively).

Conclusion: The administration of oral Zn sulfate in a dose of 20 mg/day in combination with phototherapy could be helpful and safe in reducing both bilirubin level and phototherapy duration in jaundiced neonates.

Keywords: Hyperbilirubinemia, Neonatal Jaundice, Phototherapy, Zinc Sulfate

Introduction

Hyperbilirubinemia is a common clinical problem encountered during the neonatal period, especially in the first week of life (1). Pathologic hyperbilirubinemia is defined as a bilirubin value of more than 75th percentile on the first day or more than 15 mg/dl on days 3 or 7 of neonatal life (2). The main treatment of hyperbilirubinemia is the removal of bilirubin, photoisomerization, and bilirubin excretion in stool or urine with accelerating normal metabolic pathway for bilirubin excretion (3, 4). Phototherapy serves as the most common approach for the treatment of neonatal hyperbilirubinemia; however, it is limited by parental anxiety due to increased hospitalization of the infant, disrupted mother-infant bonding, and high cost of care (5, 6). Inhibition of enterohepatic circulation is one of the therapies being tried for the prevention of neonatal hyperbilirubinemia. Various substances have been used to bind the bilirubin in the intestinal lumen to resist its absorption and prevent enterohepatic circulation (3).

Zinc (Zn) salts have high compliance with a

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low cost they act by reaching the terminal ileum to precipitate with unconjugated bilirubin to enterohepatic circulation. Zn salts can be given orally in 2 doses: a low dose (≤ 10 mg/day) versus a high dose (11 to 20 mg/day). Giving a high dose is preferred since a part of the drug is absorbed in the proximal ileum (7). Zn salts are safe, and the basis for researchers to administrate Zn comes from several trials treating a large number of children and neonates with diarrhea, measles, pneumonia, common cold, and malaria that have shown oral Zn safety (8). Moreover, Ali et al. revealed that Egyptian term neonates with hyperbilirubinemia seemed to have lower serum Zn levels than other well-term neonates (9).

Our primary outcome was to evaluate and compare dose-related effects of oral Zn sulfate administration on both serum bilirubin level and duration of phototherapy during the treatment of neonatal indirect hyperbilirubinemia; therefore, this may shorten the stay of neonates in the neonatal intensive care unit (NICU).

Methods

This double-blinded prospective interventional study was carried out from December 2017 to September 2018 in the NICUs of Ain Shams University Hospitals, Cairo, Egypt. The study was approved by the ethical committee of the faculty of medicine, Ain Shams University (FMASU 10/2019), and informed written consent was obtained from the parents/caregivers.

The inclusion criteria were neonates with gestational age ≥ 36 weeks with unconjugated non-hemolytic neonatal hyperbilirubinemia requiring phototherapy within the first week of life. On the other hand, neonates with sepsis, seizures, hydrops fetalis exchange transfusion within 24 hours, hypoxic-ischemic ence-phalopathy, major congenital anomalies, and evidence of hemolytic causes of jaundice (e.g., ABO and RH incompatibility, glucose 6-phosphate dehydrogenase) were excluded from the study.

In total, 80 neonates were assessed for eligibility; however, 20 cases were excluded from the study for not fulfilling the inclusion criteria (n=15) and parents' unwillingness (n=5). Accordingly, 60 neonates were enrolled in the study and randomly divided into three groups of 20 cases each according to the study intervention therapy and the oral Zn solution dose. Neonates received oral therapy by syringe twice daily (9 am and 9 pm) before feeding for an hour from day 1 of admission till day 7.

Group A

Neonates received a physically matched solution of distilled water as a placebo.

Group B

Neonates received oral Zn sulfate solution in low dose (10 mg/day) given as 5 mg twice daily.

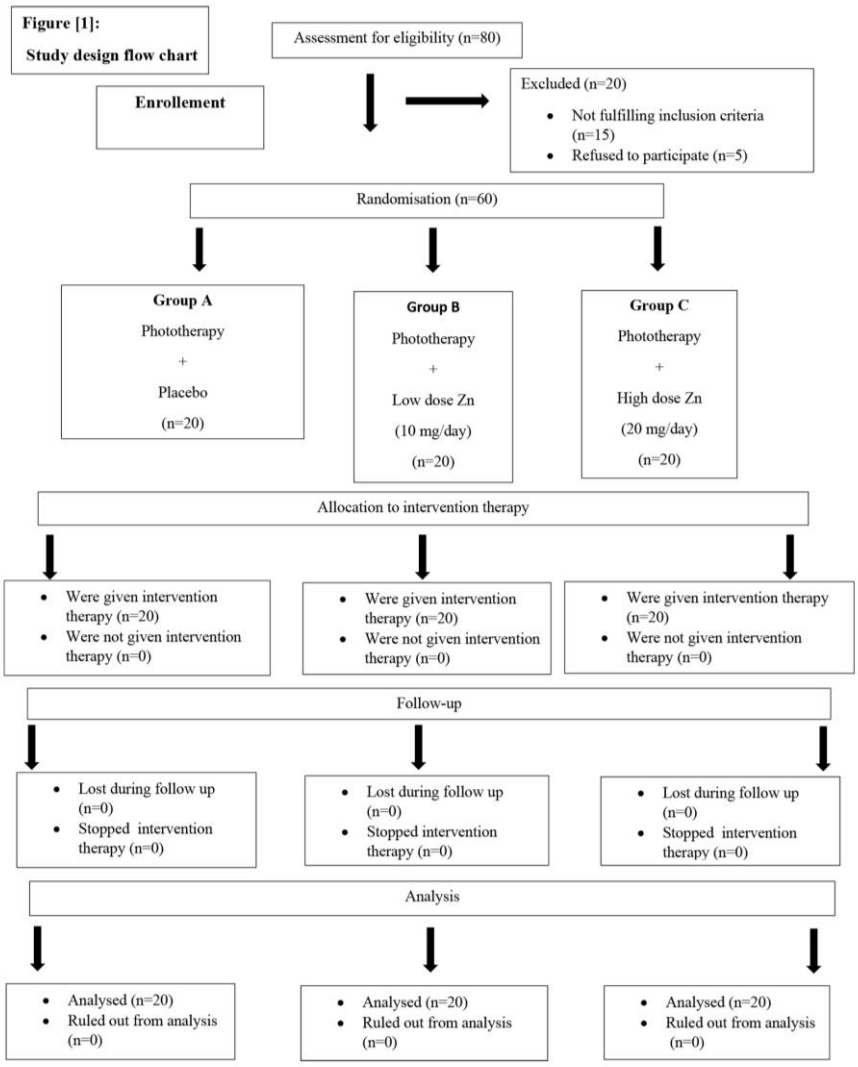
Group C

Neonates received oral Zn sulfate solution in high dose (20 mg/day) given as 10 mg twice daily.

The study design flowchart was presented in Figure (1).

Zn sulfate solution used was Zn origin (10mg/5ml) each 100 ml contains 0.8793 g Zn sulfate hepta-hydrated, equivalent to 0.2 g Zn, produced by the Egyptian group for pharmaceutical industries, origin international pharma. All enrolled neonates were subjected to detailed perinatal history; thorough clinical examination and anthropometric measurements. Laboratory investigations included complete blood count (CBC) with reticulocyte counts, total serum bilirubin (TSB), direct serum bilirubin (DSB), and serum albumin on admission. TSB was repeated on days 3 and 7. For doing CBC, two ml of fresh venous blood were collected in a tube containing EDTA as an anticoagulant and was performed using Sysmex XT-1800i (Sysmex, Kobe, Japan). Other blood sample tests were withdrawn and collected with metal-free all-plastic syringes and stainless steel needles into metal-free plastic tubes. After the blood had clotted, serum was separated immediately by centrifugation at 800 g for 20 min, aspirated into metal-free plastic storage vials, and kept frozen at -25°C until analysis. Blood specimens were collected by peripheral venipuncture on the first day of admission and follow-up of total and direct serum bilirubin on the third and seventh days.

All neonates were managed according to the protocol of NICU besides routine neonatal care. Babies admitted to NICU were bathed, placed in incubators, attached to monitor, and started oral feeding. All neonates were on phototherapy whether single, double, triple, or tunnel using conventional or led (Lullaby Tm and Fanem Bilitron Sky 5006 since 2006) phototherapy. Precautions of phototherapy included covering the eyes and genitalia; moreover, the adequacy of hydration was monitored by urine output monitoring, and nutrition was controlled by weight gain assessment. Temperature, clinical improvement in jaundice, and potential signs of bilirubin encephalopathy were also monitored in this study.



Eligible neonates fulfilling the inclusion criteria were randomly assigned to the groups, using a computer random number generator program (Stattrek.com/statistics/random-number-generator), where a random list of numbers for participant allocation was produced, and participant randomization assignment remained concealed in sealed envelopes. The study was double-blinded. It means that the parents/caregivers of enrolled neonates, NICU clinicians, and staff responsible for assessments remained blind from randomization. Standard operating procedures assured that all other operational personnel, including nurses and lab technicians, as well as those who performed lab analysis and blood sample collections were blinded to group assignment. Zn sulfate in two different doses and placebo syrups were kept in the ward in bottles of similar color and shape labeled A, B, and C and were administered by nurses upon the prescription by one of the researchers. A checklist about neonate information, including the type of drug used, bilirubin levels, and phototherapy duration, was filled out by one researcher and only s/he was aware of the treatment course and the results.

Sample Size

An exploratory randomized control study would be conducted on at least 60 neonates (20/per group) to evaluate the efficacy of Zn sulfate in the reduction of the duration of phototherapy during the treatment of neonatal indirect hyperbilirubinemia.

Statistical Methods

The obtained data were analyzed using IBM© SPSS© Statistics (version 23, IBM© Corp., Armonk, NY). Normally distributed numerical data were presented as mean±SD; moreover, categorical data

were presented as numbers and percentages. Comparisons of normally distributed numerical data between groups were conducted using the unpaired t-test or one-way analysis of variance (ANOVA) for multiple groups. Paired numerical data were compared using the paired-sample t-test. Categorical data were compared using Fisher's exact test (for nominal data) or the chi-squared test for trend (for ordinal data). A two-sided p-value <0.05 was considered statistically significant.

Results

Neonates in the three studied groups were comparable regarding gender, gestational age, age on admission, mode of delivery, type of feeding, and anthropometric measurements (P>0.05, respectively) as shown in Table (1). There were no significant differences among the three groups regarding any of the hemoglobin concentrations, reticulocyte counts, serum albumin, and direct serum bilirubin levels (P>0.05, respectively, Table 1).

There was also no significant difference between the placebo group and each of the low- or high-dose Zn groups in terms of the occurrence of symptoms that are possibly related to Zn administration (P>0.05, respectively) as shown in Table (2).

Table 1. Demographic and laboratory characteristics of the studied groups on admission

		Group A N=20	Group B N=20	Group C N=20	Test value	P-value
Gender No (%)	Female	13 (65.0%)	11 (55.0%)	12 (60.0%)	0.417*	0.812
	Male	7 (35.0%)	9 (45.0%)	8 (40.0%)		
Gestational Age (weeks)	Mean±SD	36.85 ± 1.23	36.80 ± 1.20	36.95 ± 1.23	0.079•	0.925
	Range	36 – 40	36 – 40	36 – 40		
Age at admission (hours)	Mean±SD	81.60 ± 10.20	80.70 ± 7.89	80.25 ± 9.48	0.111•	0.895
	Range	69 – 108	69 – 100	69 – 100		
Mode of delivery	C.S	11 (55.0%)	9 (45.0%)	12 (60.0%)	0.938*	0.626
	N.V.D	9 (45.0%)	11 (55.0%)	8 (40.0%)		
Type of feeding	Artificial Fed	3 (15.0%)	4 (20.0%)	4 (20.0%)	0.610*	0.962
	Breast Fed	15 (75.0%)	14 (70.0%)	13 (65.0%)		
	Mixed	2 (10.0%)	2 (10.0%)	3 (15.0%)		
Haemglobin (gm/dl)	Mean±SD	15.98 ± 1.74	15.88 ± 1.87	15.85 ± 1.84	0.028	0.972
	Range	13.5 – 19	13.2 – 19	13.4 – 19.1		
Retics (%)	Mean±SD	1.78 ± 0.58	1.77 ± 0.53	1.63 ± 0.52	0.495	0.612
	Range	1 – 3	0.8 – 3	1 – 3		
Albumin (gm/dl)	Mean±SD	3.61 ± 0.33	3.56 ± 0.41	3.60 ± 0.39	0.090•	0.914
	Range	3 – 4	3 – 4.1	3 – 4.2		
Direct S. bilirubin (mg%)	Mean±SD	1.29 ± 0.43	1.05 ± 0.43	1.13 ± 0.40	1.669	0.198
	Range	0.2 – 1.8	0.3 – 1.8	0.3 – 1.8		
Weight (kg)	Mean±SD	3.22 ± 0.44	3.12 ± 0.56	3.14 ± 0.53	0.182•	0.834
	Range	2.5 – 3.95	2.45 – 4.2	2.45 – 4.1		
Length (cm)	Mean±SD	51.08 ± 2.51	50.43 ± 2.39	50.55 ± 2.31	0.411•	0.665
	Range	46.5 – 56	46.5 – 55	46 – 55.5		
Occipitofrontal circumference	Mean±SD	35.06 ± 0.20	35.06 ± 0.32	35.03 ± 0.36	0.057	0.945
	Range	34.7 – 35.5	34.5 – 36	34.5 – 35.8		

*: Chi-square test; •: One Way ANOVA test
Cs: Cesarean section, N.V.D: Normal vaginal delivery
Group A: Control group (placebo group)
Group B: Zinc sulfate low dose group
Group C: Zinc sulfate high dose group

Table 2. Clinical manifestations suggestive of zinc side effects (rash, vomiting, diarrhea, and abdominal distention) in the studied groups

		Group A		Group B		Group C		Test value*	P-value
		No.	%	No.	%	No.	%		
Rash	No	17	85.0%	16	80.0%	17	85.0%	0.240	0.887
	Yes	3	15.0%	4	20.0%	3	15.0%		
Vomiting	No	18	90.0%	15	75.0%	16	80.0%	2.571	0.632
	Once	2	10.0%	3	15.0%	2	10.0%		
	Twice	0	0.0%	2	10.0%	2	10.0%		
Diarrhea	No	18	90.0%	16	80.0%	17	85.0%	0.784	0.676
	<3	2	10.0%	4	20.0%	3	15.0%		
Abdominal distention	No	15	75.0%	17	85.0%	14	70.0%	1.304	0.521
	Mild	5	25.0%	3	15.0%	6	30.0%		

*: Chi-square test; •: One Way ANOVA test
Group A: Control group (placebo group)
Group B: Zinc sulfate low dose group
Group C: Zinc sulfate high dose group

Table3. Total serum bilirubin levels on admission, day 3, and day 7 in three groups

		Group A No=20	Group B No=20	Group C No=20	Test value•	P-value
Bilirubin Level TSB (baseline) mg%	Mean±SD	18.98 ± 1.12	18.37 ± 1.50	18.12 ± 1.57	1.984	0.147
	Range	16.9 – 21.1	16.1 – 21	16.1 – 21.8		
Bilirubin Level TSB 3	Mean±SD	13.99 ± 1.59	13.65 ± 1.67	12.36± 2.50	3.176	0.049
	Range	11.6 – 18.2	10 – 16.2	9.2 – 18.2		
Bilirubin Level TSB 7	Mean±SD	10.47 ± 2.24	9.16 ± 2.74	8.03 ± 1.75	5.757	0.005
	Range	4.5 – 14.2	4.6 – 12	4.8 – 11.4		

*: Chi-square test; •: One Way ANOVA test
Group A: control group (placebo group)
Group B: zinc sulfate low dose group
Group C: zinc sulfate high dose group
TSB : total serum bilirubin

Moreover, initial (Day 1) mean±SD levels of indirect serum bilirubin were 18.98±1.12 mg% (in the placebo group), 18.37±1.50 mg% (in the low-dose Zn group), and 18.12±1.57 mg% (in the high-dose Zn group), with no significant difference among the three groups (P=0.147). Day 3 mean±SD indirect serum bilirubin levels were 13.99±1.59 mg%, 13.65±1.67 mg%, and 12.36±2.50mg% in the placebo, low-dose, and high-dose groups, respectively, being significantly lower in the high-dose group with P=0.049. Furthermore, day 7 mean±SD of indirect serum bilirubin levels were 10.47±2.24 mg% (in the placebo group), 9.16±2.74 mg% (in the low-dose group), and 8.03±1.75 mg% (in the high-dose group) being significantly lower in the high-dose group (P=0.005; Table 3).

No significant difference was also observed among the three groups in neither the number of phototherapy devices applied nor their types (either fluorescent or lead) (P=0.934 and P=0.446, respectively). However, the phototherapy duration needed was significantly lower in the high-dose group (26.00±11.21 h), compared to the placebo and low-dose groups (37.70±18.27 and 37.7±18.14 h, respectively, P=0.045; Figure 2).

Discussion

The current study has evaluated the efficacy and safety of both low- (10 mg/day) and high-dose (20 mg/day) Zn sulfate therapy in the treatment of neonatal unconjugated non-hemolytic hyperbilirubinemia, where Zn was given on admission day for seven days, and bilirubin level was measured on admission day and followed up on days 3 and 7. Most of the earlier studies have come across the efficacy of low-dose Zn sulfate (10 mg daily), compared to placebo (10, 17). However, Mohammadzadeh et al. studied the effect of high dose Zn sulfate (20mg\day) on lowering the hyperbilirubinemia incidence in preterm low birth weight neonates; accordingly, Zn therapy was started prior to developing jaundice (3). Similarly, Rana et al. studied the Zn therapy influence on lowering hyperbilirubinemia incidence among risky neonates with subsequent effects on TSB during their treatment (10). To our knowledge, no study had been performed before comparing both low and high doses of Zn sulfate with placebo before.

Our enrolled neonatal demographic criteria were comparable in the three groups similar to previous studies (3, 10, 20). The type and number of used phototherapy devices were also well matched in these groups. Concerning the Zn adverse effects, there were no significant Zn adverse effects among our three groups, followed by no seizures, sepsis, and mortality. These results are consistent with the findings of a study conducted by Kumar et al. (13) and a systematic review by Li yang et al. published between 2011 and 2015. The sample sizes in this study ranged from 30 to 148 with a total of 645 cases. There were no significant Zn adverse effects, including vomiting, diarrhea, rash, abdominal distension, seizures, sepsis, and mortality in any group throughout the study period. In general, zinc appeared to be a safe drug (2).

Similarly, Agrawal et al. and Eldesoky et al. revealed no significant adverse effects of Zn therapy (18,19). Even in premature Iranian neonates with a gestational age of 31-36 weeks, no adverse effects were reported by Faal et al. in a study on the effect of Zn sulfate on decreasing TSB with phototherapy. In this study, the Zn and the control groups were given 1 cc/Kg Zn sulfate syrup (containing 5 mg/5 cc Zn sulfate) and sucrose as a placebo (1 cc/kg), respectively (20).

Our laboratory results on admission day were all comparable among the three groups. Additionally, Zn therapy succeeded in decreasing TSB significantly in our high-dose group on day 3, compared to both low-dose and placebo groups, and on day 7, compared to the placebo group only,

with a subsequent significant reduction in the phototherapy duration, compared to both low-dose and placebo groups.

Correspondingly, Hashemian et al. proved that the administration of oral Zn sulfate in neonatal jaundice might reduce the duration of phototherapy and TSB in neonates (14). Moreover, Agrawal et al. found that low-dose oral Zn therapy (10 mg/day) in risky near-term and full-term neonates decreased both the incidence of indirect hyperbilirubinemia and TSB levels (18). In contrast to Rana et al. who used low-dose Zn, Mohammadzadeh and Ramezani tried high-dose Zn, and they both confirmed no impact of oral Zn therapy on decreasing the incidence of hyperbilirubinemia (3, 10).

However, Rana et al. showed that the low-dose Zn succeeded in decreasing the phototherapy duration (10). Additionally, Eldesoky et al. detected a significant lowering of TSB after 12 h, 24 h, and upon discharge by using low-dose Zn (10mg/day) together with decreasing the phototherapy duration during the treatment of full-term Egyptian neonates with indirect hyperbilirubinemia (19). Furthermore, Faalet al. confirmed that oral Zn sulfate significantly decreased bilirubin levels within 48 h of treatment of preterm neonates with indirect hyperbilirubinemia (20).

On the other hand, both Maamouri et al. and Ahmadpour-kacho et al. found no impact of low-dose Zn on TSB, yet it succeeded in reducing the duration of phototherapy (12, 15). However, Kumar et al. (2014) observed no significant effect of low-dose Zn (10 mg\day) on both TSB and the phototherapy duration, where the duration of phototherapy was 21.3 h less in the Zn group, compared to the placebo but the difference did not reach statistical significance (13).

In addition, Li yang et al. in their systematic review detected that oral Zn sulfate had no role in either reducing TSB on days 3 and 7 or reducing the incidence of indirect hyperbilirubinemia and phototherapy need; however, it significantly reduced the duration of phototherapy (2). On the contrary, Beiranvand et al. showed that a low-dose Zn (10 mg\day) did not alter either the duration of phototherapy or bilirubin level, compared to the placebo (16). In addition, Khoshhevisasl et al. revealed no significant reduction in either TSB or the duration of hospitalization in neonates given low-dose Zn sulfate, compared to the control group.

Regarding the strengths of this study, a placebo group was compared with low- and high-dose Zn groups; moreover, to the best of our knowledge, no current published studies investigated both doses together. Additionally, as shown from our earlier studies, Zn might be recommended as a safe effective medication in neonatal indirect hyperbilirubinemia treatment beside phototherapy. The scientific explanation for our results may be related to the Zn sulfate physiological effects on the body. Zn sulfate consumption has been associated with an increase in bowel motion number, and this excretion probably leads to a decrease in the enterohepatic cycle, thereby, reducing the levels of serum bilirubin (21).

In addition to Zn sulfate effects on bilirubin metabolism regulation, studies revealed that infants with hyperbilirubinemia had lower serum Zn levels. Beskabadi et al. showed that the mean serum Zn levels in healthy and hyperbilirubinemia newborns were 245.17± 1024.74 µmol/L and 241.17±1024.74 µmol/L, respectively. Accordingly, they concluded that higher levels of serum Zn could protect against hyperbilirubinemia (22).

Conclusion

In conclusion, the results of this study revealed that while the administration of an oral low-dose of 10 mg/day of Zn sulfate solution in neonates was ineffective, a high-dose of 20 mg/day oral Zn sulfate solution supplement in neonates for at least 3 days seemed safe, with no serious adverse effects and efficient to reduce serum bilirubin levels and the duration of phototherapy required for the treatment of neonatal unconjugated hyperbilirubinemia.

Limitation of the study

Our admitted neonates in the NICU with eligible criteria were of limited number; therefore, further studies might be needed on larger sample sizes. Moreover, no preterm neonates were investigated in this study. Another limitation of this study was the lack of serum Zn level measurement which could be monitored in further studies. Furthermore, the role of Zn salts was assessed neither in the prophylaxis of neonatal jaundice nor in the treatment of other conditions as hemolytic causes of neonatal hyperbilirubinemia.

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Conflicts of interest

The authors declared that they have no conflicts of interest in publishing this study.

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