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Impact of Combined Oral Zinc Sulfate and Phototherapy on Serum Bilirubin Levels in the Term Neonates with Jaundice

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ABSTRACT

Background: Jaundice is a physiological phenomenon and common disorder in the neonatal period. Jaundice occurs in the first month of life in 60% of term and 80% of preterm neonates, leading to hospitalization. The present study aimed to determine the effect of oral zinc sulfate on serum bilirubin levels in the neonates undergoing phototherapy.

Methods: This randomized clinical trial was conducted on 90 normal term neonates aged more than 24 hours with the total serum bilirubin of 14-19 mg/dc, who were admitted to the neonatal ward of Shahid Madani Hospital in Khorramabad, Iran for uncomplicated jaundice. Based on the inclusion criteria, these infants were divided into two groups of experimental (n=45) and control (n=45) via block random allocation. Infants in the control group only received phototherapy, and the experimental group received oral sulfate zinc (5 mg b.i.d.) in addition to phototherapy. Total serum bilirubin levels were measured upon admission and 24 and 48 hours after admission.

Results: No significant differences were observed between the experimental and control groups in terms of age, gender, birth weight, hemoglobin level, reticulocyte percentage, and total serum bilirubin at the beginning of the study (P>0.05). Comparison of the bilirubin levels using repeated measures ANOVA at different times indicated significant differences in the neonatal serum values and blood cell counts between the study groups (time effect) (F=598.078; P<0.001). However, no significant difference was observed difference in the bilirubin levels between the experimental and control groups (group effect) (F=0.103; P=0.749). Additionally, the interactive time-group effect was not statistically significant.

Conclusion: Although oral zinc salts inhibit the enterohepatic circulation of bilirubin, they might not be effective in the treatment of physiological jaundice in neonates. Due to the lack of human studies on the effect of oral zinc salts, further investigation is recommended.

Keywords: Hyperbilirubinemia, Jaundice, Term neonates, Zinc sulfate

Introduction

Neonatal jaundice is a physiological phenomenon and the most common cause of hospitalization in neonates within the first months of life. Jaundice affects 60% of term and 80% of preterm infants (1). The highest incidence rate of severe neonatal hyperbilirubinemia is reported in Asia. Neonatal hyperbilirubinemia accounts for one-third of infantile admissions in Iran (2). In such cases, jaundice is mainly physiological and diagnosed by ruling out the other causes of icterus, such as hemolysis, infections or metabolic diseases. According to reports, jaundice is severe enough to require intervention in 5-10% of the cases (3).

Bilirubin is the final product of heme

catabolism, and the serum level is affected by a combination of factors, such as bile production, hepatic conjugation, and enterohepatic circulation. Although mild hyperbilirubinemia could be an antioxidant and a benign phenomenon (4), increased indirect bilirubin is considered to be a dangerous metabolic waste product, which could be destructive to the brain and requires timely detection and treatment (5).

The standard treatment for neonatal jaundice involves phototherapy and blood transfusions depending on the bilirubin levels. Both these approaches necessitate the hospitalization of infants, which leads to separation anxiety, disrupted mother-infant relationship, high costs of care, and risk of infection in the infants (6). Some researchers even believe that phototherapy involves potential risks, such as DNA changes (7). Among the other reported complications of phototherapy are dehydration, patent ductus arteriosus, and lack of mother-infant interactions (8).

Despite the widespread use of phototherapy, there are treatments that maximize its impact and reduce the duration of phototherapy and its complications. Considering that increased enterohepatic circulation is one of the main causes of neonatal jaundice, factors that may lead to the faster elimination of meconium from the infant's intestines or binding to the bilirubin present in the gut and averting its absorption could prevent increased serum bilirubin levels. Inhibition of the enterohepatic circulation is a preventive treatment method for neonatal hyperbilirubinemia (9).

Various materials have been used for bilirubin binding in the intestine in order to resist the absorption; such example is the use of oral agar and laxatives. Additionally, oral zinc salts at normal body pH have been shown to curb the total serum bilirubin as they deposit unconjugated bilirubin (10). In a study by Mendez-Sanchez et al., zinc salts at normal body pH could separate unconjugated bilirubin from unsaturated bile salts in the intestines of mice, binding to it and preventing its reabsorption (11).

In this regard, Babaee et al. conducted a double-blind clinical trial entitled the "Effect of Oral Zinc Sulfate on the Treatment of Jaundice in Healthy Term Infants". In the mentioned research, zinc sulfate (5 mg) was administered daily to the experimental group, and the control group received routine neonatal care. The results showed a reduction in skin bilirubin in the infants receiving zinc sulfate compared to the control group (12).

On the other hand, in a study by Maamouri et al., the serum bilirubin levels of the infants had no significant difference on the third and 7th day of the intervention with zinc sulfate compared to the placebo group. However, the duration of phototherapy was significantly higher in the control group (13). Previous studies investigating the effect of zinc sulfate on pediatric diseases (e.g., diarrhea, middle ear infections, and colds) have confirmed the safety of the drugs, and no severe side-effects have been reported (14, 15). Use of effective drugs with few side-effects could reduce the duration of phototherapy in the neonates with jaundice and prevent the associated complications.

Considering the high rate of physiological jaundice in infants in Iran and responsibility of nurses in neonatal care to ameliorate jaundice, the present study aimed to determine the effect of zinc sulfate combined with phototherapy on the reduction of serum bilirubin levels in the term infants with jaundice.

Methods
Study Population
This randomized clinical trial aimed to investigate the effects of oral zinc sulfate on serum bilirubin levels in the term neonates with jaundice, who were admitted to Shahid Madani Hospital in Khorramabad, Iran during 2013-2014.

Inclusion criteria of the study were as follows: 1) term neonates (37-41 weeks); 2) birth weight of >2,500 grams; 3) age of >24 hours; 4) serum bilirubin levels of 14-19 mg/100cc; 5) hematocrit level of <65% and 6) no abnormalities and disease symptoms (e.g., infections, metabolic and hemolytic disorders, glucose-6-phosphate dehydrogenase deficiency, incompatible ABO, positive Coombs test). Exclusion criteria were the presence of respiratory disorders during hospitalization and conditions requiring the administration of antibiotics or other drugs.

Neonates were selected via convenience sampling in accordance with the inclusion criteria. Afterwards, they were randomly assigned to two groups of experimental and control based on the hospital bed number (patients with even-numbered or odd-numbered beds were assigned to different groups). The infants in the control group received routine care and constant phototherapy in a supine position. The infants in the experimental group received zinc

sulfate syrup (5 mg) twice per day in addition to constant phototherapy. With an error probability of the first type ($\alpha=0.05$) and 80% test power (16), the sample size was determined to be 90 infants.

In total, 90 infants were enrolled in the study and equally divided into the experimental group (zinc sulfate and phototherapy) and control group (phototherapy only). Data collection was performed in two stages. The first stage consisted of obtaining the demographic characteristics of the neonates, including weight, gestational age, gender, breastfeeding or formula feeding, and maternal characteristics (mode of delivery, gravidity, and history of jaundice in other children). In the second stage, a form was completed to record the test results before and after the admission. The form was prepared using research resources, and its content validity was confirmed based on the comments of 10 faculty members of the School of Nursing and Midwifery at Lorestan University of Medical Sciences.

The newborns were examined thoroughly by a neonatologist before phototherapy. In the next step, pre-admission routine tests were performed on the infants to determine the blood type of the mother and infant, reticulocyte percentage, total and direct bilirubin levels, Coombs test, enzyme glucose-6-phosphate dehydrogenase, hemoglobin, and hematocrit. Serum bilirubin levels of the neonates were also measured upon admission and 24 and 48 hours after admission. If the bilirubin level was less than 14, phototherapy would be discontinued, and the infant would be discharged. We used six-lamp phototherapy devices for all the neonates (Philips, 20 watts,

with the same lifetime), which were placed at a distance of 20 centimeters from the surface of the body. Duration of phototherapy was recorded for each infant.

Prior to the research, arrangements were made with the related authorities, and informed consent was obtained from the mothers of the neonates. Moreover, the mothers were assured that participation in the research was voluntary, and they could withdraw from the study at any given time. The study protocol was approved by the Ethics Committee of Lorestan University of Medical Sciences.

Statistical Analysis

Data analysis was performed in SPSS version 18 using descriptive statistics (frequency, mean, and standard deviation), inferential statistical, independent t-test, Chi-square, and repeated measures analysis of variance (ANOVA).

Result

No significant differences were observed between the experimental and control group in terms of gender, blood type, gestational age, gravidity, birth weight, weight during hospitalization, hemoglobin level, reticulocyte percentage, maternal pregnancy compli-cations, and history of jaundice in other children ($P>0.05$) (Table 1).

According to the information in Table 2 and Figure 1, based on the results of repeated measures ANOVA comparing neonatal bilirubin levels in the two groups at different times, (due to the given the lack of compound

Table 1. Comparison of Demographic Characteristics of Newborns and Mothers before Intervention

	Mean±SD		Experimental Group (Zinc Sulfate and Phototherapy)	Control Group (Phototherapy Only)	P-value
Quantitative Variables	Birth Weight (g)		3080.22±473.27	3116.88±406.86	0.694
	Mean Weight of Infant upon Admission (g)		2964±465.44	3052±379.21	0.328
	Mean Hemoglobin Level of Infant		16.11±2.2	16.33±2	0.621
	Gestational Age (week)		37.85±1.17	38.14±1.21	0.251
Qualitative Variables	Gender of Infant (%)	Female	26 (57.8)	22 (48.9)	0.398
		Male	19 (42.2)	23 (51.1)	
	Blood Type of Infant (%)	A	19 (42.2)	16 (35.6)	0.67
		B	6 (13.3)	10 (22.2)	
		AB	2 (4.4)	1 (2.2)	
		O	18 (40)	18 (40)	
	Gravidity (%)	1	23 (51.1)	19 (42.2)	0.694
		2	14 (31.1)	17 (37.8)	
		≥3	8 (17.8)	9 (20)	
	Maternal Problems during Pregnancy (%)	Yes	11 (24.4)	7 (16.6)	0.292
		No	34 (75.6)	38 (84.4)	
	History of Jaundice in Other Children (%)	Yes	35 (77.8)	39 (86.7)	0.270
		No	10 (22.2)	6 (13.3)	

Table 2. Comparison of Mean Serum Bilirubin Levels in Newborns on Different Days of Hospitalization in Experimental and Control Groups

Index	Group	
	Experimental Group (Zinc Sulfate and Phototherapy)	Control Group (Phototherapy Only)
Bilirubin at Admission	15.08±1.51	14.96±1.26
Bilirubin at 24 Hours after Phototherapy	12.78±1.35	12.55±1.31
Bilirubin at 48 Hours after Phototherapy	10.45±1.09	10.58±1.36
Time Effect	F=598.78 P=0.001	
Group Effect	F=0.103 P=0.749	
Interactive Time-Group Effect	F=0.950 P=0.389	
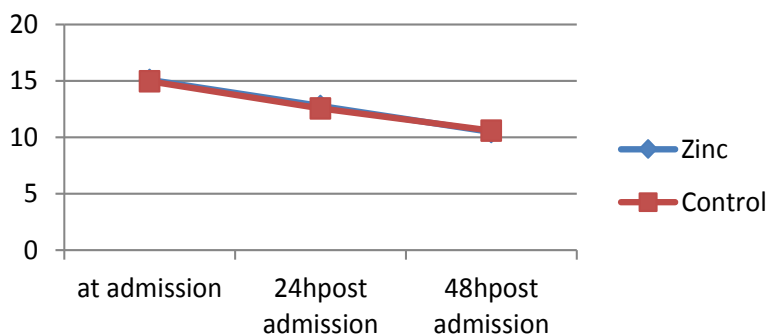
Figure 1. Comparison of Serum Bilirubin Levels of Neonates Receiving Zinc Sulfate and Control Group during Hospitalization

symmetry), and based on the results of Mauchly's test of sphericity (P < 0.001), for data analysis were used of Greenhouse-Geisser corrections.

Based on the results of the corrections, there were statistically significant differences in the neonatal blood values and counts over time between the experimental and control groups (time effect) (F=598.078; P<0.001). However, no significant difference was observed between the groups regarding the bilirubin levels (group effect) (F=0.103; P=0.749). Additionally, the interactive time-group effect (difference in the serum bilirubin levels) over time (F=389; P=0.099).

Mean duration of phototherapy within the first 48 hours of birth was 35.91±7 hours in the experimental group and 37.11±5 hours in the control group, and the difference was not considered statistically significant (P=0.882).

Discussion

According to the results of the present study, administration of oral zinc sulfate (5 mg) twice per day could not reduce physiological jaundice in term neonates. Random selection of the subjects resulted in the homogeneity of the infants, so that the effects of the confounding factors for neonatal jaundice were minimized. In another study with the homogeneity of the maternal, neonatal, and obstetric variables, Rana et al. claimed that the administration of zinc sulfate (10 mg) twice per day could not decrease the incidence of neonatal jaundice in term neonates (10).

A double-blind clinical trial by Patton et al. aimed to determine the effects of zinc sulfate on the prevention of neonatal jaundice in term newborns. In the mentioned study, the newborns were divided into two groups (receiving zinc sulfate or placebo) based on the inclusion and exclusion criteria. No statistically significant difference was observed in the bilirubin levels on day five of birth and at discharge between the two groups (17).

A study by Mohammadzadeh et al. (2014) was conducted to determine the preventive effects of zinc sulfate on the incidence of hyperbili-rubinemia in low-birth-weight, premature infants. The infants in the experimental group were administered with oral zinc sulfate (20 mg) twice per day, and the control group received placebo. No statistically significant difference was observed between the two groups in terms of the reduction of bilirubin levels and duration of phototherapy (1). The results of the aforementioned studies are consistent with the findings of the current research.

The findings of a study by Babaee et al.

indicated that the preventive and early administration of zinc sulfate syrup (5 mg) per day within the first 24 hours after birth to healthy, term newborns could reduce the skin bilirubin levels compared to the control group (12). In this regard, the results obtained by Mafinezhad et al. showed that the daily administration of oral zinc sulfate (10 mg) since the first day of birth for seven days could reduce serum bilirubin levels in preterm infants. Furthermore, the need for phototherapy and duration of phototherapy (hour) decreased significantly in the zinc sulfate group compared to the placebo group (18).

According to the findings of Mendez-Sanchez, at physiological pH, zinc salts could separate almost all unconjugated bilirubin from unsaturated bile salts in the intestines of hamsters and bind with it, thereby preventing its reabsorption. It has also been observed that oral zinc can suppress the secretion of biliary bilirubin in hamsters (11). Previous studies have denoted that oral zinc combines with unconjugated bilirubin in the small intestine and prevents its reabsorption into the bloodstream. Following that, bilirubin is excreted in the feces, and the amount of unconjugated bilirubin decreases in the blood. Based on this theory, we expected that oral zinc would ameliorate neonatal jaundice (17). However, the difference was not considered significant in the present study, as well as most of the previous studies in this regard.

One of the most important findings in the animal experiments is that zinc reduces bilirubin levels. After two weeks of treatment with zinc sulfate or zinc methacrylate, serum bilirubin levels of animal models have been reported to decline (9). Therefore, zinc sulfate may have beneficial effects on reducing bilirubin levels *in-vitro* and *in-vivo*. It is notable that the effectiveness of zinc in the reduction of jaundice depends on its ability to reach the final section of the intestine, where it binds to unconjugated bilirubin and prevents its reabsorption (1). It is likely that in the human body, the absorption of zinc salts occurs in the first section of the intestine, preventing the enterohepatic cycle of unconjugated bilirubin. Frequent administration of oral zinc or zinc salts at higher doses may be required in this respect. Lack of a significant difference in the present study could be attributed to the small sample size. Studies have rarely reported such potential side-effects of zinc salts as vomiting, diarrhea, and rashes. In the current research, these side-effects occurred equally in the experimental and control groups; therefore, zinc sulfate could be considered a safe drug (19).

One of the limitations of the present study was the small sample size. Additionally, due to the shortage in laboratory facilities, the zinc and bilirubin levels in the stool of the infants and serum zinc levels of the newborns were not measured before and after the intervention. It is recommended that further investigation be conducted on larger sample sizes to determine the other influential factors in the severity of jaundice, including bilirubin levels, serum zinc levels, drug dosage, and use of various compounds containing absorbable and non-absorbable zinc in different groups of newborns. Moreover, similar investigations could involve the measurement of fecal bilirubin levels and adequate follow-ups.

Conclusion

Although oral zinc salts inhibit the enterohepatic cycle and reduce bilirubin levels, they might not be effective in the treatment of physiological jaundice in neonates. Therefore, further complementary studies are recommended.

Acknowledgments

Conflicts of interests

None declared.

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