

## The Effect of Oral Zinc Sulfate on Serum Bilirubine Level in Term Neonates with Jaundice

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### Abstract

#### Background

The most commonly used treatment for neonatal hyperbilirubinemia (NH) are phototherapy and exchange transfusion. Among the drug therapy for NH less has been paid to the effect of zinc administration on serum bilirubin level (SBL). This study was carried out to determine the on the effect of oral zinc sulfate on the SBL in term neonates with hyperbilirubinemia.

#### Materials and Methods

In this randomized clinical trial, we studied term neonate with jaundice hospitalized in Amirkola Children's Hospital, Babol-Iran for phototherapy .Eligible neonates were randomly divided into two; intervention (n=30) and control (n=30) groups. Both groups received standard conventional phototherapy but the intervention group received 5 mg per day oral zinc sulfate until discharge. The outcome variables were SBL and the duration of phototherapy.

#### Results

Out of the 105 studied neonates, 50 cases were in the intervention group and 55 patients were in the control group. The mean SBL before intervention in the intervention and control groups, was  $17.4 \pm 2.1$  and  $17.1 \pm 2.2$  mg/dl, respectively ( $P > 0.05$ ) but after the intervention, it decreased to  $8.8 \pm 0.77$  and  $8.7 \pm 0.99$  in intervention and control groups respectively ( $P > 0.05$ ).

The mean differences in the decrease in SBL between the two groups were 8.8 and 8.3 in intervention and control groups respectively ( $P > 0.05$ ). But the mean duration of phototherapy in the intervention group and the control group was 4.1 days and 3.6 days respectively ( $P < 0.05$ ).

#### Conclusion

Administration of oral zinc in neonatal hyperbilirubinemia under the phototherapy could decrease the duration of phototherapy. Further studies are needed to recommend it as an adjunctive therapy to phototherapy.

**Key Words:** Bilirubin, Jaundice, Newborn, Phototherapy, Zinc.

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## 1- INTRODUCTION

There are several treatment modalities for neonatal hyperbilirubinemia. Phototherapy is the most common method. If the bilirubin level reaches to toxic levels for newborns based on birth weight, gestational age, and additional risk factors, exchange transfusion is then required (1, 2). In recent years, the tendency has risen for using medications to treat jaundice (3-5). There are few medications with proven safety for treating jaundice. Intravenous immunoglobulin is one of these drugs. In neonates with blood group incompatibilities it is indicated when bilirubin rises to 2-3 mg/dl near to the exchange transfusion level despite phototherapy (6, 7).

Phenobarbital is another medication used in treating hyperbilirubinemia due to Crigler–Najjar type-II (autosomal dominant) disease (8, 9); however, it is not recommended routinely for the treatment of neonatal jaundice (10). Oral administration of clofibrate reduces the serum bilirubin level by increasing the activity of glucuronyl transferase enzymes, so enhances bilirubin excretion (11). Studies have shown that concurrent use of oral clofibrate with phototherapy causes a faster reduction of serum bilirubin (12, 13). Preliminary studies on rats showed that oral administration of zinc salt for newborn rats increased the intestinal excretion of bilirubin and decreased serum bilirubin (14). Similar results were observed on human samples (15, 16).

Most of the human-related studies were conducted to prevent the hyperbilirubinemia. There are few studies on the treatment of hyperbilirubinemia (17). In some studies, serum bilirubin did not decrease (18, 19). Therefore, this research was carried out to determine the effect of oral administration of zinc salt on neonatal jaundice undergoing phototherapy in the term neonates.

## 2- MATERIALS AND METHODS

### 2-1. Study design and population

This is a double-blind randomized clinical trial on neonates older than 72 hours age with good general conditions who visited at Amirkola Children's Hospital (ACH) of Babol city, Mazandaran province, North of Iran, only because of indirect hyperbilirubinemia. They were hospitalized and underwent phototherapy based on the guideline of ACH for the treatment of neonatal hyperbilirubinemia (**Table.1**) during the June, 2016 till February 2017. A sample of 60 subjects was selected in each group. This allocated sample size can detect the effect size of 0.5 in difference the levels of bilirubin between groups with 95% confidence interval and 80% power.

### 2-2. Inclusion and exclusion criteria

Inclusion Criteria were neonates (older than 72 hours) with general good conditions who visited at Amirkola Children's Hospital only because of indirect hyperbilirubinemia entered the study. Exclusion criteria were as the following: Premature infant, intrauterine growth restricted (IUGR) infants, zinc sulfate intake by the mother and infant, infants with a history of taking phenobarbital by their mother and other drugs including Cotoneaster, Manna and Sisymbriumirio.

### 2-3. Methods

All the neonates who met the inclusion criteria were selected using census sampling. Then, they were assigned in two groups using computerized random-number table (experimental and control group). Both groups were matched for confounding factors including age, gender, weight, age at birth, maternal age, and causes of jaundice. Routine tests to work-up a neonatal indirect hyperbilirubinemia including total and direct bilirubin measurement, maternal and fetal blood

group, direct coombs test, glucose-6-phosphate dehydrogenase deficiency, thyroxine (T4), thyroid-stimulating hormone (TSH), peripheral blood smear, and reticulocyte count were performed for all participants.

#### 2-4. Intervention

Both groups were hospitalized and underwent conventional phototherapy by phototherapy devices (David Co, China) with the same quality, based on the guideline of ACH for the treatment of neonatal hyperbilirubinemia. As every hospital could have a local guideline for the treatment of neonatal hyperbilirubinemia, this guideline was developed here and examined for several years (20) (**Table.1**).

In the intervention group, 5mg zinc sulfate in the form of oral solution contains 5mg Zn in 5 milliliters (manufactured by Razak Co, Iran) was prescribed twice a day until the discharge from hospital. In the control group, however, phototherapy was used only. The phototherapy was stopped and they were discharged from the hospital when the serum bilirubin level (SBL) decreased to less than 10 mg/dl. The primary outcome was SBL, and the secondary outcomes were the time needed for phototherapy, length of stay, serum zinc level, drug side effects, and the need for exchange transfusion.

#### 2-5. Laboratory measurements and measuring tools

The SBL was measured in both groups during the hospitalization and discharge, but SBL at the time of admission and at the time of discharge used for comparison between the two groups. SBL was measured using spectrophotometry with biochemistry kits made in Iran at the Amirkola Children's Hospital laboratory. Serum zinc level was measured using the enzymatic method by Hitachi, 912 in the laboratory at Amirkola Children's Hospital.

#### 2.6-Ethical consideration

Informed consents were taken from the parents and the protocol was submitted in the Ethics Committee of Babol University of Medical Sciences (MUBABOL, HRI.REC. 1395. 27) and it was registered at [www.irct.ir](http://www.irct.ir) under the number IRCT2016072629077N1.

#### 2-7. Statistical analyses

The data were analyzed using SPSS version 20.0 software. The description of data was presented as mean (standard deviation) for experimental and control groups. The Chi-square test was used to compare the distribution of baseline categorical data between groups. The paired t-test was performed to show the changes of bilirubin levels before and after intervention and the independent t-test was applied for comparison of bilirubin levels and duration of phototherapy between experimental and control groups. The P-values less than 0.05 were considered significant.

**Table-1:** Guideline for the treatment of neonatal hyperbilirubinemia in term neonates after the age of 72 hours at Amirkola Children's Hospital, Babol, Northern Iran (total serum bilirubin level -mg/dl)

Phototherapy	Exchange Transfusion		Phototherapy Stop and Discharge
	Without Risk Factor*	With Risk Factor	
≥15	≥25	≥ 20	≤10

Note: These criteria are applicable after 72 hours from the birth.  
\* Risk factors include asphyxia, intraventricular hemorrhage, hemolysis, hypoxia, sepsis, hypoalbuminemia, G6PDdeficiency, incompatible blood groups, and hypothermia.

### 3-RESULTS

A total of 125 neonates entered into the study. Fifteen neonates were excluded during the study due to incomplete blood sampling and cell lyses. Five were also excluded due to early discharge of neonate by their parents. Therefore, 105 neonates (50 in experimental and 55 in the control) were analyzed. In both groups, 49 (46.7%) were female (23 in experimental and 26 in the control), and 56 (53.3%) were male (27 in experimental and 29 in the control). The mean weight in the experimental group was  $3.2 \pm 0.42$  kg, while it was  $3.1 \pm 0.40$  kg in the control group ( $P=0.32$ ).

The mean age to start phototherapy was  $5.8 \pm 3.3$  days in the experimental group and  $5.4 \pm 1.6$  days in the control group ( $P=0.36$ ). No significant differences were found between the two groups for baseline data such as birth weight, gender, and cause of jaundice. (**Table.2**) shows the demographic data and causes of jaundice in experimental and control groups. Mean SBL was  $8.8 \pm 0.7$  and  $8.7 \pm 0.9$  in experimental and control groups after intervention, respectively. The mean SBL reduction was  $8.56 \pm 2.18$  and  $8.38 \pm 2.19$  in experimental and control groups,

respectively ( $P=0.5$ ), showing no significant difference. But mean phototherapy length was  $3.6 \pm 1.5$  days in the experimental and  $4.1 \pm 1.8$  days in the control group, showing a significant difference ( $P=0.01$ ). **Table.3** shows the difference between mean SBL in experimental and control groups before and after intervention. After intervention, SBL declined by almost  $8.56 \pm 2.18$  mg/dl. This was a significant decline compared to the amount before the intervention ( $P<0.001$ ), but it was  $8.38 \pm 2.19$  mg/dl in the control group, showing a significant decline either ( $P=0.04$ ).

On the other hand, in both group SBL decreased significantly in comparison to the before phototherapy, but the mean differences between the two groups was not significant. Findings of **Table.3** show that both SBL and zinc serum level declined in both groups. Comparing the difference in both groups, as shown in **Table.4**, indicated that neither SBL nor its reduction were significant between the two groups; however, the time for phototherapy had got a significant difference between two groups.

**Table-2:** Demographic data and causes of jaundice in experiment and control groups

Variables		Two Groups		Total number (%)	P-value
		Experiment Group n (%)	Control Group n (%)		
Gender	Male	27 (54)	29 (52.7)	56 (53.3)	0.89
	Female	23 (46)	26 (47.3)	49 (46.7)	
Weight		$3.2 \pm 0.42$	$3.1 \pm 0.40$	0.32	
Type of Delivery	NVD	13 (26)	13 (23.6)	26 (24.8)	0.73
	CS	36 (72)	42 (76.4)	78 (74.3)	
Cause of Jaundice	Unknown	36 (72)	35 (63.6)	71 (67.6)	0.95
	G6PD	3 (6)	5 (9.1)	8 (7.6)	
	ABO	8 (16)	12 (21.8)	20 (19)	
	RH	1 (2)	1 (1.8)	2 (1.9)	
	ABO, RH	1 (2)	1 (1.8)	2 (1.9)	
	ABO, G6PD	1 (2)	1 (1.8)	2 (1.9)	

NVD: Normal Vaginal Delivery; CS: cesarean section; G6PD: Glucose 6-Phosphate Dehydrogenase Deficiency; ABO: ABO incompatibility.

**Table-3:** Mean Differences in serum bilirubin and zinc levels before and after intervention in experiment and control groups

Statistics	Experiment group (Mean ± SD)	Control group (Mean ± SD)
Mean SBL before Intervention (mg/dl)	17.4±2.1	17.1±2.2
Mean SBL after Intervention (mg/dl)	8.87±0.77	8.75±0.99
Mean Difference	-8.56±2.18	-8.38±2.19
P-value	<0.001	0.046
Mean Zinc Level before Intervention (µg/dl)	140±43	136±48
Mean Zinc Level after Intervention (µg/dl)	130.06±51.44	123.22±40.36
Mean Difference (CI 95%)	-10.48±36.13	-12.94±38.08
P-value	<0.001	0.015

SBL: Serum bilirubin level; SD: Standard deviation; CI: confidence interval.

**Table-4:** Mean serum bilirubin and zinc levels in experiment and control groups before and after intervention

Statistics	Experiment group (Mean ± SD)	Control group (Mean ± SD)	P-value
Mean SBL before Intervention (mg/dl)	17.4±2.1	17.1±2.2	0.49
Mean SBL after Intervention (mg/dl)	8.87±0.77	8.75±0.99	0.5
Mean Zinc Level before Intervention (µg/dl)	140±43	136±48	0.62
Mean Zinc Level after Intervention (µg/dl)	130.06±51.44	123.22±40.36	0.63
Mean Length of Phototherapy (days)	3.6±1.5	4.1±1.8	0.017

SBL: Serum bilirubin level; SD: Standard deviation

#### 4- DISCUSSION

Although the results of this study showed that oral administration of zinc sulfate in the neonatal jaundice treatment, had no significant effect on SBL at the end of the treatment; but, it accelerated the time to decline SBL and reduced the number of hospitalization days. The study by Rana et al. in New Delhi, India showed that early administration of zinc sulfate had not decreased the incidence of neonatal jaundice; however, it decreased the length of stay for phototherapy (17). In our study, mean length of stay showed statistically significant difference in two groups. The study by MafiNejad et al. in Bentolhoda Hospital of Bojnourd, Iran on 66 neonates with a birth weight less than

1,800 grams showed that administration of 10 mg daily oral zinc sulfate to all neonates who developed hyperbilirubinemia in the first week after could reduce the SBL in premature neonates. The need for hospitalization and phototherapy also declined (21). Low level of maternal serum zinc level facilitates the preterm delivery. Therefore, serum zinc level is lower among the preterm and low-weight infants than full-term neonates (22). Our study was conducted among full-term neonates. On the other hand, 5 mg oral administration of zinc twice a day until discharge did not increase the serum zinc level in both groups. Therefore, no difference was found on bilirubin level (23). The study by NabaviZadeh et al. in

78 full-term neonates on the age 2-7 days with non-complicated hyperbilirubinemia, who were hospitalized in Imam Sajjad Hospital of Yasuj, Iran, showed that although oral zinc salts can reduce bilirubin levels through the inhibition of intestinal-hepatic circulation of bilirubin, but they are not effective in treating neonatal physiologic jaundice (24). In the study by Mamouri et al. in Mashhad, Iran (2013) on 151 neonates (35 weeks and over), administration of 10 mg oral zinc sulfate was shown that zinc administration had no significant difference with placebo in SBL reduction. However, the need for phototherapy was less for neonates in the experiment group (18). This finding is consistent with our study; however, in our study, no significant in SBL reduction was found between the two groups. In our study, the need for phototherapy decreased, indicating the gradual effect of zinc supplementation in reducing SBL.

The hypothesis of the effect of zinc sulfate on reducing SBL were first raised by Méndez-Sánchez N et al. in 2001 (25), and 2002 (19), on hamsters and then on the patients with Gilbert's syndrome, respectively. This gastrointestinal research group published their study in Mexico City. They concluded that zinc sulfate salt inhibits the intestinal-hepatic cycle of bilirubin re-absorption and can be effective in reducing the serum level by indirect bilirubin excretion (19, 25). Our results are consistent with those of Indrio et al. in neonatal ward of the University Bari, Italy. Their study was entitled "Do neonates with jaundice still benefit from zinc sulfate?" This research group concluded that zinc sulfate was effective in rats after two week and long-term follow-up might be needed to see the real results. On the other hand, despite rats, neonatal intestine may not be able to absorb zinc. Therefore, it is essential to be cautious in expressing that oral zinc administration is effective in neonatal jaundice treatment. However, it

might be more effective in treating other types of jaundice such as Gilbert's and Crigler–Najjar syndromes (26). Meta-analysis can help find out whether or not oral zinc administration is effective in treating and preventing neonatal jaundice. The recent meta-analysis by Mishra et al. (2015) on 17 published studies, only the study, which was done by Rana et al got the criteria to enter to the meta-analysis. He showed that there was not sufficient evidence on the effectiveness of zinc in reducing the serum bilirubin level (15).

Another review by Sharma et al. showed that only 6 studies had the inclusion criteria and were qualified for the review. One of these studies was on low birth weight infants and the rest were on neonates over 35 weeks. The review emphasized that the current evidence cannot support the role of zinc in preventing neonatal hyperbilirubinemia. Of 6 studies, one showed that the SBL and the need for phototherapy declined. The rest showed no positive effect in this regard. None reported the effects on length of phototherapy, the incidence of phototherapy, phototherapy starting age, and adverse complications (27). In our study, the SBL reduction after intervention at the end of the study had no significant difference in the experimental and control groups; however, the length of stay was shorter in the experimental group than the control group. This can be justified by the fact that zinc administration is likely to reduce and gradually excrete bilirubin.

#### **4-1. Limitations of the study**

Not a significant difference in SBL in two groups is associated with this fact that we compared SBL at the beginning and at the end of the study in both groups. If we could compare SBL more frequently during the phototherapy, for example every day, and draw the trend, the difference might be significant. This is considered one of the limitations. So we suggest measuring SBL more frequently in

the future study. Zinc administration dose's was another limitation. Lack of significant increase in serum zinc level of the experimental group can be explained by zinc doses or the effect of phototherapy on serum zinc level. The increasing zinc dose may show its effect on the SBL. On the other hand, serum zinc levels declined in both groups after the completion of phototherapy. This supports the hypothesis of serum zinc reduction by phototherapy. In our study, serum zinc level declined in both groups; however, so far, no study was found to determine the effect of phototherapy on the serum zinc level.

## 5- CONCLUSION

Although oral administration of zinc sulfate, used for treating neonatal jaundice during the first week, was not effective in reducing SBL, but it accelerated the time to reduce the number of hospitalization days. On the other hand it shortened the time to reach to the discharge bilirubin level. More clinical trials with larger sample size and more frequent SBL measurements seem to be needed.

## 6- CONFLICT OF INTEREST

The authors have nothing to declare.

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