Original Paper

Effect of Zinc on Hyperbilirubinemia of Newborns, a Randomized Double Blinded Clinical Trial

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ABSTRACT: Background: Jaundice is one of the most common causes of hospitalization in newborn infants. Zinc may have a possible role as a cofactor of enzymes in the metabolism of bilirubin and can prevent red blood cell destruction as an antioxidant agent. The present study aims to investigate the effect of zinc in the treatment of neonatal hyperbilirubinemia. Material&Methods: In this double-blind, randomized clinical trial, 112 healthy newborns with idiopathic neonatal hyperbilirubinemia were divided into two groups receiving zinc and placebo. The case and control group received 10mg of zinc and placebo daily. The total bilirubin levels in the second, third, fourth and fifth day and duration of hospitalization and phototherapy were compared. Results: The mean total bilirubin value in the second to fifth days in the zinc group were 11.95 ± 2.35, 9.49 ± 1.79, 8.54 ± 1.63 and 8.64 ± 0.96 respectively, and in the placebo group were 12.95 ± 2.73, 9.88 ± 2.35, 9.5 ± 2.9 and 10.16 ± 0.86 respectively and there was no significant difference between two groups. The duration of phototherapy and hospitalization in the zinc and placebo groups did not show any significant difference. Conclusion: We did not find a significant reduction in serum bilirubin levels nor the duration of hospitalization in neonates receiving zinc sulfate compared to control group.

KEYWORDS: Hyperbilirubinemia, Icter, Jaundice, Neonate, Zinc.

Introduction

Hyperbilirubinemia, mostly observed during the first week of life [1], is one of the most common causes of hospitalization in newborns [2].

When the newborn`s total serum bilirubin is increased more than 95% of percentile, it is necessary to be evaluated and must be treated [2,3].

Neonatal jaundice occurs in 60% of term and 80% of premature newborns [2,3].

Hyperbilirubinemia and its central nervous system complications are more common in premature newborns compared to term newborn infants [2].

Bilirubin is a result of heme metabolism [4] and besides its production, hepatic conjugation and enterohepatic cycle can influence its serum levels [2].

Increased enterohepatic cycle due to constipation, decreasing calorie intake and urobilin production in intestine, increasing lipid absorption and glucuronidase activity can increase serum bilirubin level [5].

Some oral agents like Orlistat, have been used to decrease the enterohepatic cycle by attaching unconjugated bilirubin in intestine and inhibiting its absorption [6,7].

An experimental study has proved that zinc salts can completely absorb unconjugated bilirubin from biliary salts in hamsters [8].

In addition, it has been shown that oral zinc salts inhibit enterohepatic circulation of bilirubin in rats and decrease the bilirubin levels [9].

Studies on patients with Gilbert syndrome showed that administration of oral zinc decreases the serum bilirubin level [10] but there are inconsistent data about preventive and therapeutic effects of zinc on hyperbilirubinemia in newborn infants [2,5,11-16].

In this study we decided to evaluate the effect of zinc sulfate on neonatal hyperbilirubinemia by a double-blinded clinical trial in our patients in Mousavi Hospital in Zanjan, Iran.

Material and Methods

This study is a double blinded clinical trial which was conducted in the Mousavi Hospital of Zanjan, northwest, Iran.

The study was approved by the ethics committee of the Zanjan university of medical sciences (Ethic code: ZUMS. REC.1396.30) and registered on the IRCT (IRCT2017061515835N5).

Study population included term newborns with idiopathic neonatal hyperbilirubinemia and sampling was done from December 2017 to August 2018 by the method of block randomization.

Inclusion criteria were term newborns with idiopathic neonatal hyperbilirubinemia receiving phototherapy, total serum bilirubin 15 to 20mg/dl and age of 3 to 7 days, without any obvious cause of neonatal hyperbilirubinemia and not receiving any other drugs.

Exclusion criteria were: recent weight loss, infection, hemolytic disease, oral intolerance, congenital diseases, gastrointestinal anomalies, need for ventilator, and parents' dissatisfaction for participation in the study.

After obtaining a written informed consent from parents, blood count and peripheral blood smear, blood group and Rh type of mother and infant, direct and indirect coombs, reticulocyte count and G6PD levels were measured.

For each patient, a demographic questionnaire containing length of hospital stay, duration of phototherapy, maternal age, type of delivery, birth weight, gestational age, gender was filled and the clinical examinations, direct bilirubin and the amount of total serum bilirubin at the first to fifth day of study, drug side effects and patient compliance were recorded.

Total bilirubin was measured by the Unistat®bilirubinometer (Reichert-Jung, Germany) and direct bilirubin was measured by Colorimetric Method by Lathe and Ruthven.

Patients were randomized in one of two groups receiving placebo or zinc.

The duration of the intervention was until the fifth day or hospital discharge.

In the intervention group, patients received 5mg of zinc sulfate syrup (product of Donyaye-Behdasht Company) twice daily.

The placebo that was produced by the faculty of pharmacy in Zanjan University of Medical Sciences, completely similar to the original drug, was given at the same amount to controls.

The medication was given by the nurse of the department.

Neither the nurse, nor the patient's mothers were aware of nature of the administered drug. Phototherapy was discontinued when the total serum bilirubin level reached 50% of first day serum bilirubin.

Duration of treatment was calculated from the onset of phototherapy until its end.

The phototherapy devices were the same in intervention and control groups and calibrated for each patient.

The primary outcome of our study was the duration of hospitalization and the amount of total serum bilirubin in days 1-5.

Data, further reported as average±SD, were analyzed by SPSS version 16.0 software and qualitative variables were analyzed by Chi-square test and Spearman correlation test, and quantitative variables analyzed by t-test and Repeated Measure methods.

P value was calculated in each group and the level of significance was less than 0.05.

Results

In this double blinded clinical trial, a total of 112 neonates, 50 (44.6%) girls and 62 (55.4%) boys were equally divided into intervention and placebo groups.

The most common blood group in mothers was O (51.8%) and 86.6% of mothers were Rh positive.

The most common blood groups in neonates were O (39.3%) and A (39.3%) and 91.1% of them were Rh positive.

The mean ages of mothers in the case and control groups were 28.9±6.98 and 28±5.38 respectively.

Mean gestational ages in intervention group was 38.8±1.03 while in the placebo group it was 38.8±0.98.

The mean age of newborns in both groups was 5±1.24 days.

Fifty seven (50.9%) neonates were first born child and 58 (51.8%) were born by vaginal delivery.

The mean birth weight in case and controls were 3223.8±424.90 and 3165.5±339.71 grams respectively.

There were no significant differences between the intervention and control group regarding the gender, type of delivery, maternal and neonatal ages, birth weight and gestational ages.

In the intervention group, 31 (55.4%) were treated with phototherapy with 4 lamps and 25 (44.6%) were treated with phototherapy with 8 lamps.

In control group 27 (48.2%) received phototherapy with Four lamps and 29 neonates (51.8%) have been treated with phototherapy with 8 lamps.

Chi-square test showed that there was no significant difference between the zinc receiving group and placebo in the phototherapy type (P Value=0.449).

Table 1 and Table 2 show the summery of demographic, type of Phototherapy and type of delivery in placebo and Intervention groups.

The mean length of hospital stay in intervention group was 3.5±0.69 days which did not differ significantly with control group (3.5±0.79).

The mean bilirubin levels in both groups are compared in Table 3.

Table 1. Demographic characteristics of the case and control groups.

Variables	Placebo group		Intervention group		P value
	Mean	SD	Mean	SD	
Mother's Age (years)	28	5/38	28/9	6/98	0/459
Length of hospital stay (Days)	3/5	0/79	3/5	0/69	1/000
Infant's Age (days)	5	1/24	1/24	5	1/000
Gestational age (week)	38/8	0/98	38/8	1/03	0/777
Infant's Birth weight (gram)	3165/5	339/71	3223/8	424/90	0/424

Table 2. Characteristics of the subjects.

Variables	Placebo group N (%)		Intervention group N (%)		P value
Delivery type	NVD 31 (55/4%)	C/S 25 (44/6%)	NVD 27 (48/2%)	C/S 29 (51/8%)	0.449
Infant's Gender	M 34 (60/7%)	F 22 (39/3%)	M 28(50%)	F 28(50%)	0.254
Type of Phototherapy	4 lamps 27 (48/2%)	8 lamps 29 (51/8%)	4 lamps 31 (55/4%)	8 lamps 25 (44/6%)	0.449

Table3. The mean serum total bilirubin levels in two groups.

| Bilirubin level (mg/dl)	Placebo group		Intervention group		P value
	Mean	SD	Mean	SD	
1st day	17.40	3.24	16.98	3.33	0.505
2nd day	12.59	2.73	11.95	2.35	0.183
3rd day	9.88	2.35	9.4	1.79	0.074
4th day	9.5	2.09	8.54	1.63	0.073
5th day	10.16	0.86	8.64	0.96	0.056

Considering that the P. value of total bilirubin on the third, fourth and fifth days are close to the significant level but still not significant, the Repeated Measure analysis was performed.

The result of this analysis shows that there is a significant reduction in the amount of bilirubin over time in both case and control groups (Within group P. value<0.001) and it was shown that between groups P. value was also significant (Between group P. value=0.006).

Meanwhile, the amount of bilirubin decreased over time, but this trend had a statistically significant difference between the two groups and a further decrease in the intervention group was observed.

Total bilirubin levels during the first to fifth days of hospitalization in both zinc recipients and placebo recipients are shown in Figure 1.
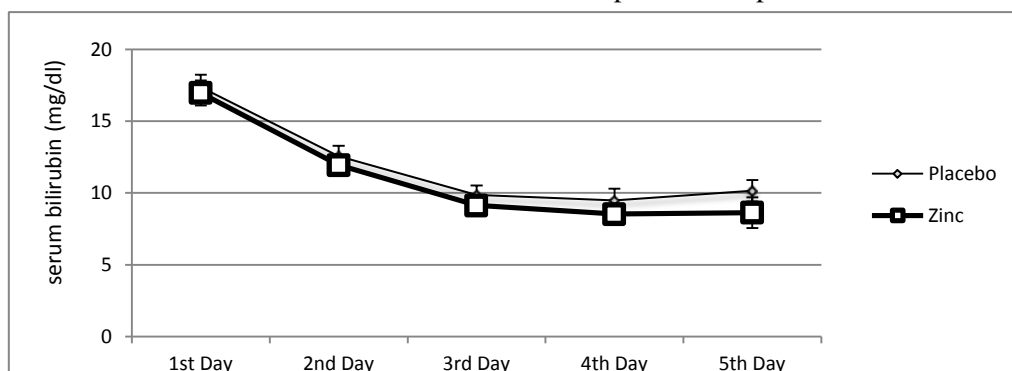
Figure 1. Total bilirubin values during the first to fifth days.
Error bars represent standard deviation of the means.

Discussion

Animal studies have shown that zinc may have a possible role as a cofactor of enzymes in metabolism of bilirubin, can prevent red blood cell destruction as an antioxidant agent, and its oral administration in rats, decreases serum bilirubin level by inhibition of the enterohepatic cycle of bilirubin and decreasing its secretion.

In this interventional study, a total of 112 neonates (the case and control groups) with idiopathic neonatal hyperbilirubinemia were evaluated for the effect of zinc administration and compared with placebo.

There was no significant difference between the intervention and the control group in terms of the number of hospitalization days and the duration of phototherapy, and the total serum bilirubin levels.

Although serum bilirubin decrease were very close to the significance level.

In Kumar's clinical trial in India on 80 icteric newborn infants with gestational ages of 35 to 41 weeks similar results were found [11].

Nabavizadeh's clinical trial in Yasuj, Iran, on 78 neonates 2 to 7 days old with uncomplicated jaundice didn't show significant relationship between total bilirubin levels in two groups which is similar ot our findings [4].

The study of Maamouri showed that prophylactic administration of zinc did not show a significant reduction in the incidence of hyperbilirubinemia [5].

The same results were shown in Mafinejad's study in 2015 in Bojnourd, Iran, in a clinical trial performed on 66 infants weighing less than 1800 grams with jaundice [12].

Our results are also similar to the double-blinded clinical trial of Mohammad Zadeh in Mashhad, Iran.

They didn't find a significant reduction in duration of phototherapy and in serum total bilirubin levels of 61 low birth weight icteric neonates enrolled in the study.

But declared that zinc sulfate decreased total serum bilirubin level only at the first 24 h which is in contrast to our results [2].

The Patton 's study in 2010 on 60 healthy term neonates who were born spontaneously or by elective caesarean section in Hasan Sadikin Hospital, Indonesia, showed no significant difference in hyperbilirubinemia duration between zinc receiving group compared to placebo which is similar to our findings [13].

Although in the study of Rana in India in 2011 as a double-blind randomized clinical trial

on 294 neonates with uncomplicated hyperbilirubinemia, the mean serum total bilirubin levels did not differ between two groups, but the duration of phototherapy in the intervention group was shorter [14].

Also in Ahmadpour's trial in Iran (Babol city) in 2017 on 60 term neonates with non-complicating neonatal jaundice, the serum bilirubin level did not differ between cases and controls, but a significant reduction in duration of phototherapy in cases (3.6±1.5 days) was shown compared to controls (4.1±1.8days) [15].

The study of Hashemian in 2017 in Iran (Mashhad city) on 70 healthy term neonates with total serum bilirubin more than 20mg/dl who were admitted to NICIU, had shown a significant reduction in total serum bilirubin level and duration of phototherapy [16].

The diversity in the sample size, study design and different zinc dosages may explain the different results in various studies.

It should be considered that oral supplementation of any type, may not have a therapeutic effect in neonates because gastrointestinal tract may not effectively absorb the zinc salts especially in preterm infants, and icteric neonates may have altered intestinal permeability [17].

Therefore, we may expect a better zinc absorption and a more effective reduction in serum bilirubin level as the duration of therapy exceeds.

This fact could be shown in our results with a more reduction of serum bilirubin level in third, fourth and fifth days that are very close to the level of significance.

Conclusions

We did not find a significant reduction in serum bilirubin levels in neonates receiving zinc sulfate.

Based on Repeated Measure analysis, it seems that with more sample size, the effect of zinc can be shown.

Acknowledgments

Conflict of interests
None to declare.

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