

# THERAPEUTIC EFFECTS OF ZINC SULPHATE IN REDUCTION OF NEONATAL HYPERBILIRUBINEMIA: AN EXPERIMENTAL STUDY

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## ABSTRACT

**Objective:** Neonatal hyperbilirubinemia is a common condition affecting 60% of the term and 80% of the preterm neonates. Bilirubin can be neurotoxic, when its concentration rises more than 20mg/dl which occurs in 2% of infants. The most prevalent therapeutic method for managing infantile icterus and preventing its complications is phototherapy and exchange transfusions at higher bilirubin levels.

**Material and Methods:** A quasi experimental study was conducted on 60 neonates with hyperbilirubinemia. They were randomly divided into two groups. Group A (n=30) received zinc sulphate 5mg twice daily for 5 days, in addition to phototherapy. Group B (n=30) received phototherapy. Total serum bilirubin was calculated at 0, 24 and 72 hours for both groups.

**Results:** No significant difference was found in total serum bilirubin at 0, 24 and 72 hours in both groups (p=0.46, 0.39 and 0.20 respectively)

**Conclusion:** Oral zinc sulphate is not effective in the treatment of hyperbilirubinemia in neonates.

**Key Words:** Jaundice, Hyperbilirubinemia, Zinc sulphate, Phototherapy, Physiological Jaundice, Neonate

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## INTRODUCTION

Neonatal hyperbilirubinemia is a common condition affecting 60% of term and 80% of preterm neonates. It is clinically visible as jaundice when serum bilirubin is >5mg/dl. There are mainly two types of jaundice; physiological and pathological. The former is more common and is the diagnosis of exclusion. Neonates are prone to develop physiological jaundice because of several reasons. These include greater RBC load at birth and greater bilirubin turnover, less development of hepatic enzymes, suboptimal feeding causing dehydration and increased enterohepatic circulation, presence of beta glucuronidase in breast milk which causes conversion of conjugated bilirubin to unconjugated bilirubin and less establishment of colonic gut flora [1]. The physiological jaundice usually resolves within 7-10 days of life however, around 5-10% neonates need intervention and treatment [2].

Bilirubin is neurotoxic, when its concentration rises >20mg/dl which occurs in 2% of neonates, it starts accumulating in the brain causing neurological damage and kernicterus, if early therapeutic action is not taken. The most prevalent therapeutic method for

managing neonatal icterus and preventing its complications is phototherapy, which has been applied for decades as safe method. Exchange transfusions are required for the higher levels of bilirubin [3]. Previous studies have suggested medications such as phenobarbital, clofibrate, IVIG, active charcoal are used along with phototherapy for decreasing bilirubin levels [4]. Most of the time neonates are discharged within 48 hours of life unless there are some complications. A 5% to 10% admitted in neonatology unit for hyperbilirubinemia and treated with phototherapy for longer duration. Recently increase in early hospital discharge have led to a rise in rate of hyperbilirubinemia and kernicterus and hence increase in hospital costs due to hospital readmissions.

The role of zinc supplementation is well established in many conditions such as in acute and chronic diarrhea. However, its role in hyperbilirubinemia is still under consideration. It is postulated that zinc interferes with the absorption of bilirubin from the gut and therefore decreases enterohepatic circulation [5]. While a lot of work has been done to see the efficacy of zinc in reducing hyperbilirubinemia, very few studies gave promising results. The aim of this study is to examine the efficacy of oral zinc sulphate in reducing hyperbilirubinemia in neonates.

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## MATERIAL AND METHODS

An experimental study was conducted in the neonatology department of Pakistan Institute of Medical Sciences (PIMS), Islamabad from October 2018 till March 2019. The sample size was calculated using WHO calculator. A total of 60 neonates who were born at term or late preterm were included and were randomly divided into two groups. All of them had clinically visible jaundice in the phototherapy range. Infants who were early preterm (<35 weeks) or syndromic, had sepsis or any other infection (diagnosed with clinical history and blood counts), hyperbilirubinemia in the exchange transfusion range or developing within first 24 hours of birth and conjugated hyperbilirubinemia (conjugated bilirubin >2mg/dl) were excluded. Group A (Intervention group) was given phototherapy and zinc sulphate at dose of 5mg twice daily for 5 days while Group B (Control group) was given phototherapy alone. The primary outcome was to see the change in total serum bilirubin which were sent at 0, 24 and 72 hours for both groups. Qualitative data was described in percentage while all quantitative variables were expressed as mean. SPSS version 21 was used to analyze data. Independent T test was applied to see the significance. P value < 0.05 was considered statistically significant.

## RESULTS

In group A, 56.6% neonates were male and 43.3% were female while in group B, 73.3% neonates were male and 26.7% were female. More than half of the neonates were delivered through normal vaginal delivery in both groups; 56.6% and 53.3% in group A and B respectively. The percentage of different blood groups of the mother and the baby in both groups is given in Table-1.

The mean age (Day of life) at which the neonates were hospitalized with jaundice was 4.96 in group A and 6.5 in group B ( $p=0.07$ ). In group A, the mean gestational age was 37.4 weeks while in group B, it was 38.1 weeks ( $p=0.09$ ).

The mean Total bilirubin in group A was 16.94 mg/dl and in group B was 17.02 mg/dl ( $p=0.46$ ), which at 24 hours decreased to 14.58 mg/dl and 14.34 mg/dl respectively ( $p=0.39$ ). There was no significant difference in mean Total bilirubin at 72 hours in both groups; 12.06 mg/dl in group A and 11.45 mg/dl in group B ( $p=0.20$ ). A comparison of total serum bilirubin in both groups at different time intervals is given in Table-2.

The treatment plan in both groups significantly decreased the total bilirubin after 72 hours as shown in table 3. In group A, the mean total bilirubin decreased from 16.94 mg/dl to 12.06 mg/dl ( $p<0.00001$ ). In group B, it decreased from 17.02 mg/dl to 11.45 mg/dl ( $p<0.00001$ ).

**Table-1: Comparison of demographic characteristics of newborns and mothers before intervention.**

	Group A (N=30)	Group B (N=30)
<b>1. Gender</b>		
Male	17 (56.6 %)	22 (73.3 %)
Female	13 (43.4 %)	8 (26.7 %)
<b>2. Mode of Delivery</b>		
NVD	17 (56.6 %)	16 (53.3 %)
C-Section	13 (43.4 %)	14 (46.7 %)
<b>3. Mother's Blood Group</b>		
A Positive	7 (23.4%)	7 (23.4 %)
B Positive	5 (16.7 %)	6 (20 %)
AB Positive	2 (6.7 %)	5 (16.7 %)
O Positive	12 (40 %)	8 (26.6 %)
A Negative	1 (3.3 %)	0 (0 %)
B Negative	1 (3.3 %)	0 (0 %)
AB Negative	1 (3.3 %)	0 (0 %)
O Negative	1 (3.3 %)	4 (13.3 %)
<b>4. Baby's Blood Group</b>		
A Positive	4 (13.3 %)	9 (30 %)
B Positive	11(36.7 %)	14 (46.7 %)
AB Positive	1 (3.3 %)	0 (0 %)
O Positive	10 (33.4 %)	6 (20 %)
A Negative	0 (0 %)	1 (3.3 %)
B Negative	1 (3.3 %)	0 (0 %)
AB Negative	3 (10 %)	0 (0 %)
O Negative	0 (0 %)	0 (0 %)

**Table-2: Comparison mean total bilirubin in both groups at different time intervals (in mg/dL).**

	Group A	Group B	P Value
Mean Age (Day of life)	4.96 ± 2.64	6.5 ± 3.23	0.07
Gestational Age (weeks)	37.4 ± 1.71	38.1 ± 1.58	0.09
Mean Total Bilirubin at 0 hour	16.94 ± 3.04	17.02 ± 3.24	0.46
Mean Total Bilirubin at 24 hours	14.58 ± 3.50	14.34 ± 3.30	0.39
Mean Total Bilirubin at 72 hours	12.06 ± 3.36	11.45 ± 2.35	0.20

**Table-3: Comparison of effectiveness of treatment plan in both groups (in mg/dL).**

	Mean Total Bilirubin at 0 hour	Mean Total Bilirubin at 72 hours	P value
Group A	16.94 ± 3.04	12.06 ± 3.36	<0.00001
Group B	17.02 ± 3.24	11.45 ± 2.35	<0.00001

## DISCUSSION

Our study showed no significant benefit of adding zinc sulphate in the treatment of neonatal jaundice when compared to the previous treatment of phototherapy alone. Similar results were observed in a recent study in which 90 normal term neonates were enrolled and no significant difference was found with the addition of zinc sulphate at a dose of 5mg twice daily [6]. These results were also shared by Patton *et al*, who found no difference with the similar oral dose of zinc sulphate [7]. The results of our study are contrary to those observed by Hashemian *et al*, who not only found a significant reduction in total serum bilirubin but also a reduction in phototherapy duration with zinc sulphate dose of 10mg per day. However, in this study only those newborns were enrolled who had total serum bilirubin >20 mg/dl [8]. In another study done by Mohammedzadeh *et al*, the dose of zinc sulphate given was 10mg twice daily for five days, given to low birth weight premature infants. The mean decline in total serum bilirubin was only significant at 24 hours while it was non-significant at 48, 72, 96 and 120 hours of treatment [9]. Nabavizadeh *et al*, also used 10 mg twice daily dose of zinc sulphate and found no difference in serum bilirubin levels at 0, 6, 12, 24 hour and one week of treatment, when compared to the control group [10]. Rana *et al*, conducted a clinical trial on the effect of zinc gluconate on neonates presenting with hyperbilirubinemia. A total of 294 newborns were included, out of which 148 were given zinc gluconate 10 mg twice daily. Although no significant difference was found in the total serum bilirubin at 72 hours in the zinc or control group, the duration of phototherapy was found to be reduced in the former [11].

A meta-analysis done recently by Sharma *et al*, compared the results of 6 interventional studies to see the effect of zinc supplementation on hyperbilirubinemia. In all of them zinc sulphate was given except one in which zinc gluconate was given [12]. In only one study by Babae *et al*, a significant reduction in transcutaneous bilirubin was observed at 3<sup>rd</sup> to 5<sup>th</sup> day. The remaining five studies used total serum bilirubin as a measuring tool and found no significant difference in the intervention and control group [13].

Kacho *et al*, found a significant difference in the mean length of phototherapy duration when zinc sulphate was given at 5mg dose twice daily. The mean length of phototherapy was 3.6 days in the intervention group and 4.1 days in the control group ( $p= 0.017$ ). However, no significant difference was

found in the serum bilirubin or serum zinc levels before or after intervention in both groups [14]. Similar results were shared by Maamouri *et al*, who found significant reduction in phototherapy duration and weight gain at 3<sup>rd</sup> and 7<sup>th</sup> day of life in the zinc group. It was also found that zinc supplementation could significantly improve weight gain at 72 hour. [15]. Kumar *et al*, also had similar findings [16]. A meta-analysis done by Yang *et al*, on five randomized controlled trials concluded that zinc sulphate therapy showed no difference in total serum bilirubin, however significantly reduced phototherapy duration. [17].

Prophylactic zinc sulphate therapy of 10mg/day in premature, low birth weight (<1800 grams) newborns was found to reduce total serum bilirubin, reduction in weight gain and phototherapy duration [18].

Mosayebi *et al*, conducted a study to find the effect of phototherapy on serum zinc levels and found that phototherapy could significantly increase serum zinc level in newborn having total serum bilirubin > 18mg/dl. They further stated that in some neonates the increase in serum zinc level after phototherapy reached toxic levels and therefore suggested avoidance of zinc supplementation at this bilirubin levels. The zinc levels did not increase much in newborns with moderate hyperbilirubinemia i.e., total serum bilirubin <18mg/dl [19].

A different combination of zinc salt i.e., zinc acetate was given in another study at a dose of 10mg/day. The study comprised of 100 neonates, 50 of which were given zinc acetate. A significant reduction in the total serum bilirubin was found in the zinc group however, the no significant difference was found in the requirement or duration of phototherapy in the two groups [20].

The above studies showed that zinc sulphate is either effective at higher doses in decreasing hyperbilirubinemia or it only reduces the phototherapy duration. It is evident from present and other studies that 5mg twice daily dose is ineffective in treatment of hyperbilirubinemia.

## CONCLUSION

Although zinc has a role in inhibition of enterohepatic circulation, it is not effective in the treatment of jaundice in neonates. Further studies are required with higher doses of zinc sulphate.

**AUTHORS CONTRIBUTION**

**Ayesha Waheed:** Paper writing, literature review and data collection.

**Iqtada Haider Shirazi:** Incharge of the project.

**Asma Mustafa:** Statistical analysis

**Yasir Waheed:** Entry of Data in SPSS.

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