

# WITHDRAWN: Zinc Supplementation in Preterm Neonates with Jaundice: Is It Beneficial?

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## Research

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## EDITORIAL NOTE:

The full text of this preprint has been withdrawn by the authors while they make corrections to the work. Therefore, the authors do not wish this work to be cited as a reference. Questions should be directed to the corresponding author.



# **Abstract**

**Background:** Neonatal jaundice is a common neonatal disease which had adverse effect in the neonates especially preterm neonates when the level of indirect bilirubin is high enough to pass the blood brain barrier causing bilirubin encephalopathy or kernicterus.

**Aim:** The aim of this study is to investigate the value of zinc (Zn) supplementation in preterm neonates with jaundice and if it will be beneficial or not.

**Patients and methods:** A prospective randomized clinical trial (RCT) study, identification number is TCTR20200504007, which was done at Tanta University Hospital (TUH) from July 2016 to March 2018 on 200 preterm neonates suffering from neonatal jaundice. The studied neonates were divided into 2 groups: group 1, which received Zn and phototherapy, and group 2, which received phototherapy only and did not take Zn. In the group 1, 100 preterm neonates with jaundice received Zn as 0.6 ml(cm<sup>3</sup>) of zinc origin/kg/day orally through oro/nasogastric tube divided into 2 doses (/12 hours) which is equal 1.2 mg elemental zinc/kg/day orally for 10 day.

**Results:** There was no significant difference in serum bilirubin between the 2 groups in the 2<sup>nd</sup>, 4<sup>th</sup> and 6<sup>th</sup> day of admission while the serum bilirubin was significantly decreased in neonates who were treated by Zn and phototherapy in group 1, compared with neonates of group 2 who were treated with phototherapy only in the 8<sup>th</sup>, 9<sup>th</sup> and 10<sup>th</sup> day of admission where the p value was 0.045\*, 0.027\* and 0.004\* respectively.

**Conclusion:** Zn administration in jaundiced preterm neonates is beneficial in decreasing serum bilirubin.

**Recommendation:** Zn supplementation for jaundiced preterm neonates.

## **Introduction:**

Neonatal jaundice is a common and widespread neonatal disease which had adverse effect in the neonates especially in the preterm neonates when the level of indirect bilirubin is high enough to pass the blood brain barrier causing bilirubin encephalopathy or kernicterus. Jaundice is common in preterm neonates than full term neonates due to short red blood cells(RBCS) life span, decrease the activity of liver enzymes responsible for the metabolism of bilirubin and liver immaturity, relatively decreased milk intake in comparison with full term with increased the enterohepatic recirculation and lastly weak blood brain barrier with relatively increased risk of kernicterus.[1].

Hyperbilirubinemia or neonatal jaundice occurs in neonates due to the increased levels of indirect or unconjugated bilirubin as a result of increased its production after the destruction of RBCS due to its relatively short life span. The mechanism of bilirubin excretion is that the bilirubin is excreted in the bile into the duodenum where it will be expelled out the body through the stool [2–4].

The main lines of the management of neonatal jaundice including phototherapy blood exchange transfusion in severe cases [5, 6]. Other lines of treatments include high-dose intravenous immunoglobulin and in some cases phenobarbital administration may be given [7, 8].

Some researches stated that one of the methods that could be used to treat indirect hyperbilirubinemia is to use a Zn solution [9]. Some studies stated that the use of zinc supplementation in cases of neonatal jaundice can decrease the serum bilirubin levels by decreasing the enterohepatic cycle of indirect bilirubin [10]. The oral supplementation of Zn sulfate rises the bilirubin excretion and declines its serum level [3, 11].

Since the bilirubin excretion capacity in preterm neonates is less effective both in the hepatic tissues due to liver immaturity and also through the intestinal tract due to relatively poor intestinal movement if compared to full term neonates. Oral administration of Zn salts cause decrease in bilirubin secretion in the bile and adsorb unconjugated bilirubin. The Zn stores from the mother to her neonates occur mainly in the third trimester, so preterm neonates are liable to low serum Zn levels with subsequent loss of its benefits to these neonates [10–12]

The aim of this study is to investigate the value of Zn supplementation in jaundiced preterm neonates and if it will be beneficial or not.

## Patient And Methods:

This research was a prospective randomized clinical trial (RCT) study, identification number is TCTR20200504007, which was done at Tanta University Hospital (TUH) from July 2016 to March 2018 on 200 preterm neonates suffering from neonatal jaundice (neonatal indirect hyperbilirubinemia). The examined neonates who are 200 cases were divided into 2 groups, we had numbered the neonates from 1 to 200 and we had chosen the odd number for neonates of group 1(intervention group) and even numbers for neonates of group 2(control group) in which group 1 consisted of 100 neonates who received Zn in addition to phototherapy (intervention group), and group 2 consisted of 100 neonates who received phototherapy only and did not receive Zn (control group).

This study was done in TUH and approved by ethical committee; Informed consent was taken from the parents of all neonates.

### Inclusion criteria

- 1) gestational age < 37 weeks
- 2) bilirubin level (16–19 mg/dl)
- 3) normal serum zinc levels (7.6–15.3 mmol/l)

### Exclusion criteria

- 1) gestational age ≥ 37 weeks
- 2) Zn supplementation to mothers
- 3) previous Zn supplementation to neonates before admission
- 4) neonatal sepsis
- 5) respiratory distress

## **Intervention:**

In the intervention group, 100 preterm neonates with jaundice received Zn as 0.6 cm of zinc origin/kg/day orally through oro/nasogastric tube divided into 2 doses(12 hours) which is equal 1.2 mg elemental zinc/kg/day orally for 10 day(zinc origin 10 mg/5 ml syrup is produced by Egyptian Group for pharmaceutical Industries "EGPI" For: Origin International Pharma, every 100 ml syrup contain 0.8793 gram Zn sulfate heptahydrate which contain 0.2 gram elemental Zn) along with double phototherapy according to standard protocol. In the Control group, 100 preterm neonates with jaundice did not receiving Zn but only received double phototherapy according to the standard protocol. The neonatal enteral intake recommendation of elemental Zn is from 0.8 to 3 mg/Kg/day [13]. Zn requirements for term neonate are 0.8 mg/kg/day, while in preterm neonates may need up to 3 mg/kg/day [13].

## **Biochemical assays:**

A venous blood sample (1 ml) was taken from each preterm neonate using a sterile butterfly needle. Each blood sample was separated into 2 parts (1/2 ml each). The first part was taken in a tube which contained 4 mg of K<sub>2</sub>EDTA for estimation of Reticulocytes Percent (RP) and hemoglobin levels (Hb). The second part was taken in a serum separator tube, and serum samples were separated after centrifugation and stored at -20 °C until total bilirubin levels were measured.

RP and Hb levels were measured using an automated hematology analyzer (Sysmex® XT-1800i, Japan). Serum total bilirubin was measured, according to the manufacturer's instructions (Roche® Diagnostics, Germany) using the colorimetric method. The colorimetric method of total bilirubin assessment depends on the reaction between bilirubin and the diazonium salt of sulphanilic acid to yield azobilirubin that measured at 535 nm using Shimadzu® (Japan) Spectrophotometer. Serum total bilirubin concentration was expressed as mg/dl.

## **Statistical analysis:**

Statistical analysis was done using the Statistical Package for Social Science (SPSS) version 20. Data were expressed as mean ± SD. Statistical comparison among groups was performed by t-test, Chi-square ( $\chi^2$ ) test for comparison between two groups. Statistical significance was set at p values > 0.05.

## **Results:**

This study was done on 200 neonates suffering from neonatal jaundice, the studied neonates were divided into 2 groups: group 1(100 neonates) who were treated by zinc and phototherapy(intervention group) and group 2(100 neonates) who were treated by phototherapy and placebo (distilled water) (control group), none of the neonates had any side effects of zinc sulfate syrup(no allergy, no diarrhea, no vomiting)

Table 1  
Comparative characteristics between group 1&2 on admission (2nd day of life)

		Group 1 (n = 100)	Group 2 (n = 100)	t. test	P. value
<b>Weight (kg)</b>	Mean ± S.D	2262 ± 95	2246 ± 112	0.142	0.892
<b>Gestational Age (Weeks)</b>	Mean ± S.D	35.7 ± 0.6	35.8 ± 0.5	1.279	0.202
<b>Bilirubin levels (mg/dl)</b>	Mean ± S.D	17.7 ± 1.1	17.6 ± 1.2	0.609	0.540
<b>Hemoglobin levels(gm/dl)</b>	Mean ± S.D	14.3 ± 0.7	14.2 ± 0.8	0.939	0.348
<b>Reticulocytic count (%)</b>	Mean ± S.D	7.45 ± 0.58	7.51 ± 0.49	0.792	0.430
		N	%	N	%
<b>Mode of delivery</b>	NVD	17	34	18	36
	CS	33	66	32	64
<b>Sex</b>	Male	27	54	29	58
	Female	23	46	21	42

\*P. value is significant if < 0.05 NVD: Normal vaginal delivery. CS: Cesarean section.

Table 1 showed comparison between the two groups as regard weight in kg, gestational age in weeks, bilirubin levels by mg/dl, hemoglobin levels by gm/dl, reticulocytic count (%), mode of delivery(NVD or CS) and sex(male or female) where there were no significant difference between the 2 groups.

Table 2  
Comparison between group 1&2 as regard serum bilirubin on admission and at 10th day of admission

		At 1st day of admission (2nd day of life)	At 10th day of admission (11th day of life)	t. test	P. value
<b>Serum bilirubin (mg/dl)</b>	<b>Group 1</b>	17.7 ± 1.1	7.5 ± 1.1	35.569	0.001*
	<b>Group 2</b>	17.6 ± 1.2	7.9 ± 1		

\*P. value is significant if < 0.05

Table 2 showed comparison between the 2 groups as regard serum bilirubin at the 1st day of admission (2nd day of life) and at the 10th day of admission (11th day of life) where there was significant difference with p value = 0.001\* in group 1 and p value = 0.001\* in group 2

Table 3  
Comparison between group 1 & 2 as regard serum bilirubin between the 2nd and 9th day of admission

	Group 1	Group 2	t. test	P. value
Time (Days)	Serum bilirubin (mg/dl)			
2nd day of admission	17.1 ± 2	17.1 ± 2.1	0.068	0.945
4th day of admission	15.1 ± 1.7	15.2 ± 1.8	0.403	0.687
6th day of admission	12.8 ± 1.4	13 ± 1.3	1.048	0.296
8th day of admission	10 ± 1	10.3 ± 1.1	2.023	0.045*
9th day of admission	8.8 ± 0.97	9.1 ± 0.94	2.224	0.027*

\*P. value is significant if < 0.05

Table 3 revealed no significant difference between the 2 groups in the 2nd, 4th and 6th day of admission while there were significant differences between the 2 groups in the 8th and 9th day of admission where the p value was 0.045\* and 0.027\* respectively

Table 4  
Comparison between group 1 & 2 as regard serum bilirubin at the 10th day of admission

Serum bilirubin (mg/dl) at the 10th day of admission	Group 1 (n = 100)	Group 2 (n = 100)
Mean ± SD	7.5 ± 1.1	7.9 ± 1
t. test	2.694	
P. value	0.004*	

\*P. value is significant if < 0.05

Table 4 revealed significant difference between the two groups with p value is 0.004\*.

## Discussion:

This study demonstrated comparison between 2 groups (where the 1st group received zinc in addition to phototherapy and the 2nd group received phototherapy only without Zn) where the results showed decreased serum bilirubin from the 2nd to the 10th day of admission in both groups where there were significant differences between the 2 groups in the 8th, 9th day and 10th days of admission with superiority of the group taking Zn in the drop of bilirubin levels where the p value was 0.045\* and 0.027\*, 0.004\* respectively.

Some studies were done on the effect of Zn administration on serum bilirubin where the results of these studies demonstrated the importance of Zn administration in decreasing the serum bilirubin levels which

agreed with the results of our study of the beneficial effect of zinc administration in reducing the bilirubin levels [9].

In agreement with the results of this study which revealed a decline in bilirubin levels in neonates who were supplied by Zn syrup, there was a study done by Babaei et al. (2014) which found that giving of oral zinc to the neonates would lead to decline in their serum bilirubin levels [12].

The finding of our study in the beneficial effect of Zn in preterm neonate in decreasing the serum bilirubin levels was agreed with some studies which found significant decrease in serum bilirubin levels in preterm infants who were given Zn supplementation if compared with those who did not receive Zn supplementation [14].

The results of our study that showed the therapeutic effect of zinc administration in decreasing indirect hyperbilirubinemia in preterm neonates were agreed with the results of some studies which attributed that to the effect of oral Zn sulfate intake in increasing the number of bowel movements, with increased excretion of bilirubin in the stool with subsequent decrease in the enterohepatic cycle, thereby reducing serum bilirubin levels [15].

Some studies showed that higher levels of Zn had protective effects against hyperbilirubinemia and this in agreement with our results that Zn supplementation was associated with decreased in serum bilirubin [16].

In disagreement with our results, some studies showed no significant reduction of serum bilirubin in Zn administration (17), and also there were some studies in which their results were against our results and their results revealed that there was no effect of administration of Zn on the value of serum bilirubin in neonates (18)

Also, Kumar et al.'s study showed that there was no clinical benefit in using a zinc solution to treat neonatal jaundice which was in disagreement with our results in this study. [19]

Zn is an important trace element in humans. Zn is valuable for the functions of certain enzymes especially the liver enzymes, zinc participates in cell division and growth, intestinal electrolyte absorption, immune response [20, 21]

Zn administration to the neonates is safe if it was given in the right dose. Zinc administration is considered high if it was more than 20 mg/Kg/day as it may influence the absorption of other trace elements such as copper and vitamin A. Zn is essential for all age group especially for preterm neonates. In this population, high requirements to catch up growth, compensate for poor intestinal absorption. In addition, preterm birth has low hepatic stores of Zn which is formed in the late months of pregnancy. [22, 23]

Total bilirubin levels also showed a weak negative correlation with blood zinc concentrations. As regard the relation between bilirubin metabolism in the liver and Zn, the studies showed negative correlation. Zn

is involved in healthy liver function and metabolism as well as Zn cause suppression of the enterohepatic circulation. [24, 25]

Zn is essential for protein synthesis especially in preterm newborns. The nutrition of the preterm neonates to catch up growth may elevate zinc consumption so zinc supplementation may be needed even if the preterm neonates had initial normal serum zinc levels and Preterm neonates may have higher zinc requirements than previously recommended.[26]

The results of these studies which with or against our study raise the attention of the need of further studies in the same topic to reach a solid recommendation to use or not to use zinc supplementation in preterm neonates with jaundice.

## **Conclusions**

Zn administration in jaundiced preterm neonates is beneficial in decreasing serum bilirubin.

## **Abbreviations**

Zn: Zinc

RCT: Randomized clinical trial

NVD: Normal vaginal delivery

CS: Cesarean section

## **Declarations Section**

## **Ethical Approval and Consent to participate**

This RCT was approved by the Ethics Committee, Thai Clinical Trials Registry (TCTR) identification number is TCTR20200504007. Written informed consent was signed from the parents of all neonates.

## **Consent for publication**

All authors and participates in this research had approved the publication of this research in Italian journal of pediatrics.

## **Availability of data and materials**

The data and materials of this research are available with the researcher

# **Competing interests**

The authors declare that there was no competing of interest

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# **Authors' contributions**

Elfarargy MS: Concept and designed the study, analyzed data and drafted the manuscript , Al-Ashmawy GM: Collected the data and helped in data analysis , Abu-Risha S: Help in the doing of investigations , Khattab H: Collect investigation and help in writing the manuscript

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# **Recommendation:**

Zn supplementation for jaundiced preterm neonates.

# **Limitation of the study:**

the relatively limited number of cases in this study.

# **Conflict of interest:**

No conflict of interest is present

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