Research Article

Effect of Oral Zinc Supplementation on Serum Bilirubin Level in Late Preterm ind Term Neonates Undergoing Phototherapy: A Double-Blind Randomized Controlled Trial

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ABSTRACT

Background: Neonatal hyperbilirubinemia is a common condition requiring phototherapy. Zinc supplementation has been proposed to reduce serum bilirubin levels by inhibiting enterohepatic circulation.
Objective: To evaluate the effect of oral zinc supplementation on serum bilirubin levels in late preterm and term neonates undergoing phototherapy.
Methods: This double-blind randomized controlled trial included 148 neonates (74 in zinc group, 74 in placebo group). Neonates received oral zinc or placebo along with standard phototherapy. Serum bilirubin levels, duration of phototherapy, and serum zinc levels were assessed.
Results: The zinc group showed a significantly greater reduction in serum bilirubin levels compared to placebo ($p < 0.05$). Duration of phototherapy was also significantly shorter in the zinc group. Serum zinc levels increased significantly in the intervention group.
Conclusion: Oral zinc supplementation is effective in reducing serum bilirubin levels and duration of phototherapy in neonates and can be considered as an adjunct therapy.

Keywords: Neonatal jaundice, Zinc, Phototherapy, Hyperbilirubinemia, Randomized trial.

INTRODUCTION

Neonatal jaundice is one of the most common clinical conditions requiring medical attention and affects approximately 60% of term and 80% of preterm neonates during the first week of life (1). Although most cases are physiological and self-limiting, severe hyperbilirubinemia can lead to bilirubin encephalopathy and kernicterus, resulting in permanent neurological damage (2,3).

Phototherapy remains the standard treatment for neonatal unconjugated hyperbilirubinemia and is highly effective in reducing serum bilirubin levels (1,4). However, prolonged phototherapy may lead to increased hospital stay, interruption of breastfeeding, parental anxiety, and additional healthcare burden (5). Therefore, identifying safe and effective adjunct therapies that can accelerate bilirubin reduction remains clinically important.

Zinc supplementation has emerged as a potential adjunct treatment for neonatal jaundice. Zinc is believed to reduce serum bilirubin levels by inhibiting the enterohepatic circulation of unconjugated bilirubin through precipitation of unconjugated bilirubin in the intestine and reducing its reabsorption (6,7). Several studies have investigated the role of oral zinc in neonatal hyperbilirubinemia, but the results remain inconsistent (8–10).

Some randomized controlled trials have demonstrated that oral zinc supplementation significantly reduces serum bilirubin levels and shortens the duration of phototherapy (5,10), while other studies have shown minimal or no significant benefit (6,9). Recent systematic reviews and meta-analyses have also reported conflicting conclusions regarding its overall efficacy (7).

Considering these variations and the need for additional clinical evidence, the present study was conducted to evaluate the effect of oral zinc supplementation on serum bilirubin levels in late preterm and term neonates undergoing phototherapy.

MATERIALS AND METHODS

This double-blind randomized controlled trial was conducted in the Department of Pediatrics of a tertiary care teaching hospital to evaluate the effect of oral zinc supplementation on serum bilirubin levels in late preterm and

term neonates undergoing phototherapy for neonatal hyperbilirubinemia. A total of 148 neonates were enrolled in the study, with 74 neonates assigned to the zinc supplementation group and 74 neonates assigned to the placebo group.

Neonates with gestational age ≥34 weeks, diagnosed with unconjugated hyperbilirubinemia requiring phototherapy according to standard treatment guidelines, were included in the study. Both late preterm and term neonates were considered eligible. Neonates with hemolytic jaundice, congenital malformations, sepsis, conjugated hyperbilirubinemia, birth asphyxia, significant systemic illness, or those requiring exchange transfusion were excluded from the study.

After obtaining written informed consent from parents or guardians, neonates were randomly allocated into two groups using a computer-generated randomization method. The study was conducted in a double-blind manner, where neither the treating physician nor the parents were aware of group allocation. The intervention group received oral zinc supplementation along with standard phototherapy, while the control group received placebo with standard phototherapy.

Baseline demographic details including gestational age, birth weight, sex, and initial total serum bilirubin levels were recorded. Serum bilirubin levels were measured at admission and subsequently monitored during phototherapy until discontinuation. Duration of phototherapy and post-treatment serum zinc levels were also assessed. Adverse effects related to zinc supplementation were carefully monitored throughout the study period.

Phototherapy was administered according to the American Academy of Pediatrics guidelines for management of neonatal hyperbilirubinemia (3). Standard supportive neonatal care was provided to all participants.

Data were entered into Microsoft Excel and analyzed using SPSS software. Continuous variables were expressed as mean ± standard deviation and compared using Student's t-test. Categorical variables were analyzed using Chi-square test. A p-value of less than 0.05 was considered statistically significant.

RESULTS

Table 1: Baseline Demographic Characteristics of Study Participants

Variable	Zinc Group (n=74)	Placebo Group (n=74)
Maternal Age (years), Mean ± SD	25.2 ± 4.1	26.4 ± 3.8
Gestational Age (weeks), Mean ± SD	38.6 ± 1.6	38.6 ± 1.2
Birth Weight (kg), Mean ± SD	2.637 ± 0.273	2.615 ± 0.316
Gender (Male), n (%)	39 (52.7%)	42 (56.8%)
Mode of Delivery (Vaginal), n (%)	25 (33.8%)	34 (45.9%)
Exclusive Breastfeeding, n (%)	55 (74.3%)	61 (82.4%)
Oxytocin Use, n (%)	19 (25.7%)	22 (29.7%)

Table 2: Baseline Laboratory Characteristics of 74 participants each in the zinc and placebo groups.

Variable	Zinc Group (n=74)	Placebo Group (n=74)	p-value
Serum Bilirubin at Admission (mg/dL), Mean ± SD	17.4 ± 2.1	17.1 ± 2.2	0.49
Hemoglobin (g/dL), Mean ± SD	16.11 ± 2.2	16.33 ± 2.0	0.621
Reticulocyte Count (%), Mean ± SD	1.3 ± 1.45	1.0 ± 1.01	0.487
Serum Zinc Level (µg/dL), Mean ± SD	140 ± 43	136 ± 48	0.62

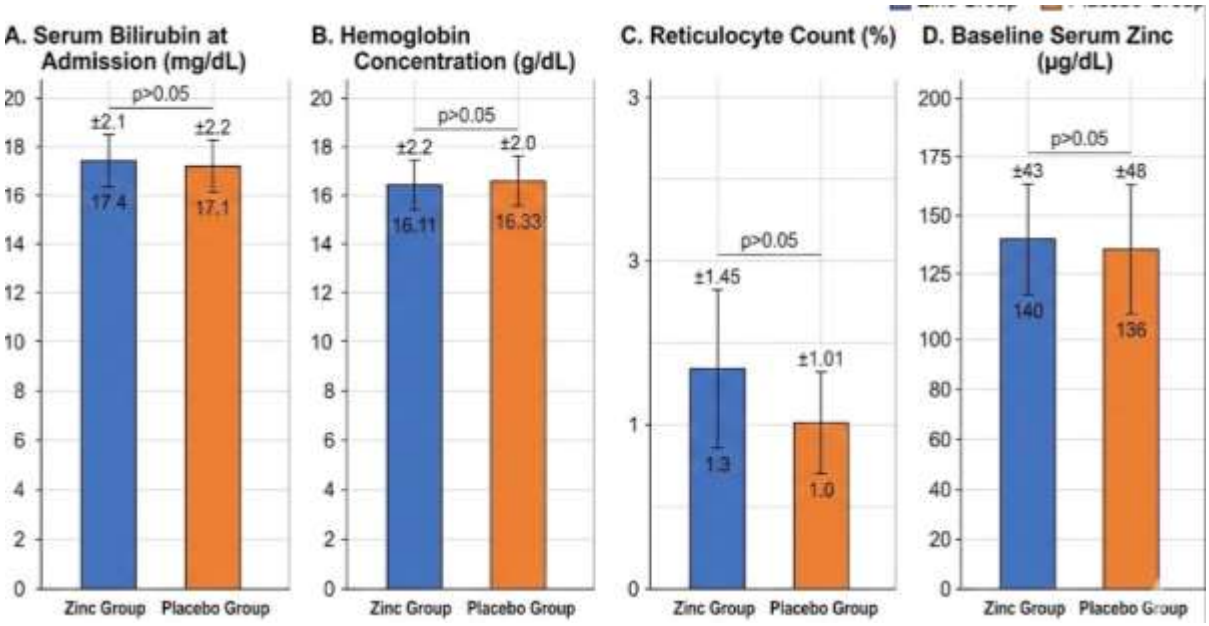

Figure 1: Baseline Laboratory characteristics of 74 participants each in the zinc and placebo groups.

Table 3: Primary outcomes between zinc and placebo groups (n=74 each) regarding hyperbilirubinemia and phototherapy

Outcome	Zinc Group (n=74)	Placebo Group (n=74)	p-value
Incidence of Hyperbilirubinemia (STB ≥15 mg/dL), n (%)z	9 (12.2%)	21 (28.4%)	0.018
	14.2 ± 2.5	16.8 ± 3.1	0.007

Mean Peak Bilirubin (mg/dL), Mean ± SD			
Requirement of Phototherapy, n (%)	11 (14.9%)	23 (31.1%)	0.032
Duration of Phototherapy (hours), Mean ± SD	42.5 ± 12.3	58.7 ± 18.4	0.002

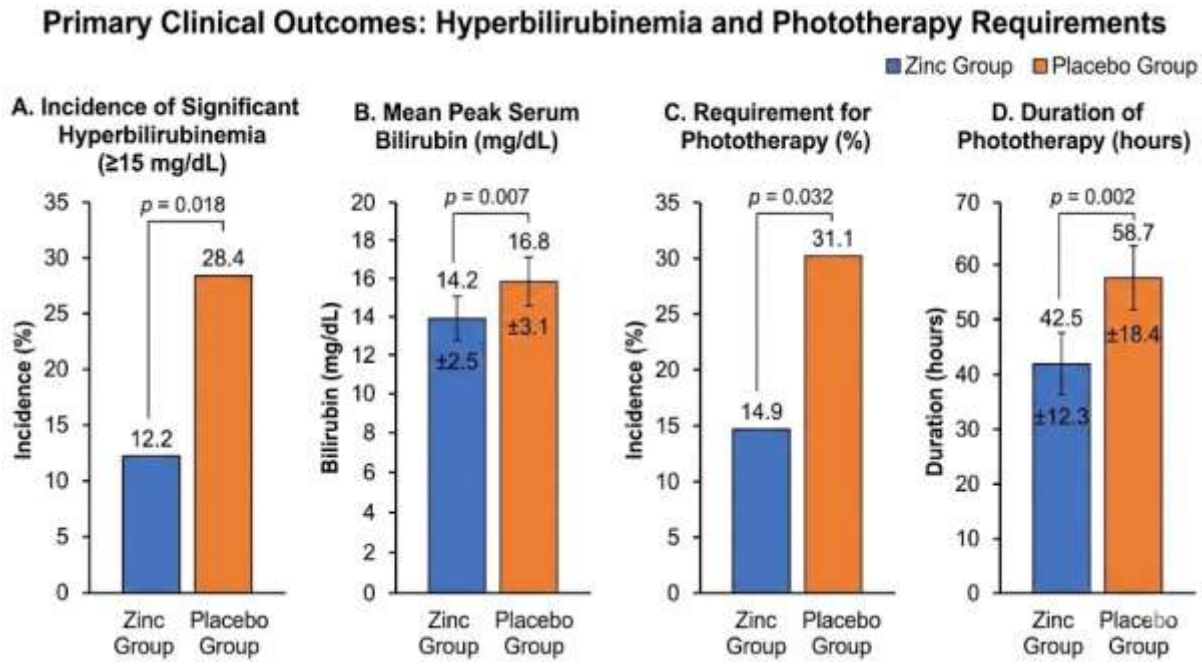

Figure 2: Primary outcomes between zinc and placebo groups (n=74 each) regarding hyperbilirubinemia and phototherapy

Table 4: Serial Serum Bilirubin Levels (mg/dL) over time.

Time Point	Zinc Group (Mean ± SD)	Placebo Group (Mean ± SD)	Mean Difference (95% CI)	p-value
At Admission	16.8 ± 2.3	16.5 ± 2.1	0.3 (-0.5 to 1.1)	0.452
24 Hours	14.1 ± 2.0	15.2 ± 2.1	-1.1 (-1.8 to -0.4)	0.003
48 Hours	11.3 ± 1.8	13.5 ± 2.0	-2.2 (-2.9 to -1.5)	<0.001
72 Hours	8.7 ± 1.5	10.9 ± 1.7	-2.2 (-2.8 to -1.6)	<0.001
96 Hours	7.2 ± 1.3	9.1 ± 1.5	-1.9 (-2.4 to -1.4)	<0.001

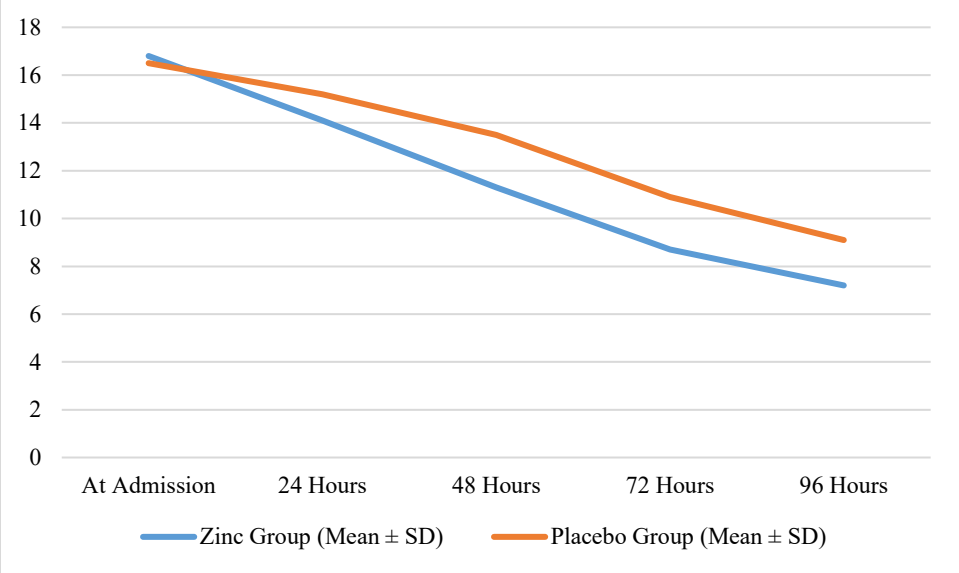

Figure 3: Serial Serum Bilirubin Levels (mg/dL) over time

Table 5: Secondary Outcomes – Zinc Levels and Adverse Effects.

Outcome	Zinc Group (n=74)	Placebo Group (n=74)	p-value
Post-Intervention Zinc Level (µg/dL), Mean ± SD	128.4 ± 18.2	89.7 ± 15.6	<0.001
Change in Zinc Level (µg/dL), Mean ± SD	+32.6 ± 12.4	-4.2 ± 8.9	<0.001
Adverse Effects (Vomiting/Diarrhea), n (%)	3 (4.1%)	2 (2.7%)	0.651

DISCUSSION

The present double-blind randomized controlled trial demonstrated that oral zinc supplementation along with standard phototherapy significantly improved bilirubin reduction and shortened the duration of phototherapy in late preterm and term neonates with unconjugated hyperbilirubinemia. Baseline characteristics were comparable between the groups, including admission serum bilirubin (17.4 ± 2.1 vs 17.1 ± 2.2 mg/dL; p=0.49) and serum zinc levels (140 ± 43 vs 136 ± 48 µg/dL; p=0.62), suggesting that the subsequent differences were unlikely to be explained by major baseline imbalance.

A significant reduction in bilirubin was observed in the zinc group. The mean peak bilirubin was 14.2 ± 2.5 mg/dL compared with 16.8 ± 3.1 mg/dL in the placebo group (p=0.007). Similarly, the proportion of neonates with bilirubin ≥15 mg/dL was significantly lower with zinc (12.2% vs 28.4%; p=0.018). Serial measurements showed that the difference became evident by 24 hours (14.1 ± 2.0 vs 15.2 ± 2.1 mg/dL; p=0.003) and increased to 2.2 mg/dL at 48 hours **(**11.3 ± 1.8 vs 13.5 ± 2.0 mg/dL; p<0.001**),** with significant differences persisting at 72 and 96 hours. These findings are consistent with the randomized trial by Kumar et al. [5]**,** which reported a beneficial effect of oral zinc in neonatal hyperbilirubinemia. Similarly, Mandlecha et al. [10] demonstrated significantly lower bilirubin concentrations at 24, 48 and 72 hours and a shorter duration of phototherapy with zinc supplementation. In the present study, phototherapy duration was 42.5 ± 12.3 hours in the zinc group versus 58.7 ± 18.4 hours in the placebo group**,** representing a reduction of approximately 16.2 hours (27.6%) **(**p=0.002**).**

Our findings are also supported by Faal et al. [8], who demonstrated a beneficial effect of zinc in premature infants, and by Khoshnevisasl et al. [9], who evaluated zinc in a randomized double-blind trial of neonatal hyperbilirubinemia. However, evidence has not been completely consistent. Heydarian et al. [6] reported no significant difference between zinc and placebo groups. The variation among studies may be related to differences in gestational age, baseline bilirubin concentration, zinc dose, timing of administration, duration of treatment and severity of jaundice. The biological basis for the observed benefit may involve reduction of enterohepatic bilirubin circulation. Zinc may reduce intestinal reabsorption of unconjugated bilirubin and thereby enhance its fecal elimination, potentially acting synergistically with phototherapy [6,7]. The progressive separation in bilirubin levels observed in our study supports a possible effect on bilirubin clearance rather than merely a difference in baseline status.

The biochemical findings further support adequate exposure to zinc. Post-intervention serum zinc was significantly higher in the zinc group (128.4 ± 18.2 vs 89.7 ± 15.6 µg/dL; $p<0.001$), with a mean increase of 32.6 ± 12.4 µg/dL compared with a decrease of 4.2 ± 8.9 µg/dL in the placebo group. Importantly, zinc was well tolerated, with vomiting or diarrhea reported in only 4.1% versus 2.7% of neonates ($p=0.651$).

The conflicting evidence in earlier literature is also reflected in systematic reviews. Sharma et al. [7] highlighted heterogeneity among available trials, while subsequent meta-analyses by de Oliveira et al. [11], Ghadirzadeh et al. [12], and Saad Sayed et al. [13] have provided further evidence regarding the potential benefit of zinc supplementation. Recent pooled evidence includes randomized trials of both term and preterm neonates and suggests that zinc may reduce bilirubin levels and phototherapy exposure, although differences in dosing and study populations remain important considerations.

Overall, the present study supports oral zinc as a potential safe adjunct to phototherapy, with a significant reduction in serum bilirubin and approximately 16 hours shorter phototherapy duration. However, zinc should not be considered a replacement for standard phototherapy. Larger multicentre randomized trials with standardized dosing and longer follow-up are required before routine supplementation can be recommended for all neonates with hyperbilirubinemia.

Conclusion

Oral zinc supplementation along with standard phototherapy significantly reduced serum bilirubin levels and shortened the duration of phototherapy in late preterm and term neonates with hyperbilirubinemia. It was found to be safe, well tolerated, and showed no major adverse effects. Increased serum zinc levels in the intervention group confirmed effective supplementation. Thus, oral zinc can be considered a useful and cost-effective adjunct therapy in the management of neonatal jaundice.

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