

EFFECT OF ORAL ZINC SUPPLEMENTATION ON SERUM BILIRUBIN LEVELS IN NEONATES UNDERGOING PHOTOTHERAPY: AN OPEN-LABEL RANDOMIZED CONTROLLED TRIAL

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ABSTRACT

Background: Neonatal hyperbilirubinemia affects 60–80% of newborns and may lead to serious complications if untreated. Phototherapy is the standard treatment, but adjuncts like zinc may reduce enterohepatic circulation of bilirubin.

Objectives: To evaluate the effect of oral zinc supplementation on serum bilirubin levels and duration of phototherapy in neonates.

Methods: An open-label randomized controlled trial was conducted in a tertiary care hospital over 18 months. A total of 100 neonates (≥ 35 weeks gestation) requiring phototherapy were randomized into two groups: phototherapy + zinc (5 mg/day) and phototherapy + placebo. Serum bilirubin levels were measured daily, and duration of phototherapy and hospital stay were recorded.

Results: Baseline characteristics were comparable. There was no significant difference in serum bilirubin levels between groups on day 1, 2, or 3 ($p > 0.05$). However, the zinc group had significantly shorter phototherapy duration ($p = 0.041$) and reduced hospital stay ($p = 0.043$).

Conclusion: Oral zinc supplementation does not significantly reduce serum bilirubin levels but decreases phototherapy duration and hospital stay, suggesting a beneficial adjunctive role.

Keywords: Hyperbilirubinemia, Neonatal; Zinc; Phototherapy & Bilirubin.

INTRODUCTION

Neonatal hyperbilirubinemia is a common condition resulting from increased bilirubin production and immature hepatic conjugation. While most cases are benign, severe hyperbilirubinemia may lead to kernicterus. Phototherapy converts unconjugated bilirubin into water-soluble forms but may require prolonged hospitalization. Zinc has been proposed as an adjunct therapy due to its ability to reduce enterohepatic circulation by binding bilirubin in the intestine. However, existing evidence is inconsistent, necessitating further evaluation.

Objectives

To assess the effect of oral zinc on serum bilirubin levels

To evaluate its impact on duration of phototherapy and hospital stay

Methods

Study Design and Setting

Open-label randomized controlled trial conducted over 18 months in a tertiary care hospital.

Sample Size

Based on prior studies, 50 neonates per group (total n=100) were included, accounting for 10% attrition.

Inclusion Criteria

Neonates ≥ 35 weeks gestation

Hyperbilirubinemia requiring phototherapy

Exclusion Criteria

Direct hyperbilirubinemia

Major congenital anomalies

Prior zinc supplementation

Ethical Clearance Number

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METHODOLOGY

Eligible neonates were randomized into:

Group A: Phototherapy + oral zinc (5 mg/day)

Group B: Phototherapy + placebo

Both groups received standard phototherapy. Serum bilirubin levels were measured daily. Outcomes included bilirubin levels, duration of phototherapy, and hospital stay.

Statistical Analysis

Data were analyzed using SPSS.

Continuous variables: mean $\pm$ SD (t-test)

Categorical variables: Chi-square/Fisher's exact test

$p < 0.05$ considered significant

RESULTS

Baseline characteristics (maternal age, gestational age, birth weight, gender, APGAR scores) were comparable ($p > 0.05$).

Total Bilirubin on day 1, 2 and 3 compared between the groups among late preterm and Term babies

		Phototherapy + Zinc Group	Placebo Group	
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Total Bilirubin	Gestational age	N	“Mean total bilirubin mg/dL”	± SD	N	“Mean total bilirubin mg/dL”	± SD	p value
Day 1	Late preterm	5	17.48	± 2.11	7	15.70	± 2.59	0.235
	Term	45	14.98	± 2.46	43	15.22	± 2.62	0.599
Day 2	Late preterm	5	13.04	± 2.08	7	12.12	± 2.66	0.545
	Term	45	10.57	± 2.13	43	11.41	± 2.13	0.072
Day 3	Late preterm	1	11.69		2	10.20	± 1.26	-
	Term	2	9.65	± 0.49	9	10.56	± 1.18	0.328

Among late preterm babies, the phototherapy plus zinc group had a mean bilirubin of 17.48 mg/dL (SD $\pm$ 2.11) based on 5 cases, while the placebo group had 15.70 mg/dL (SD $\pm$ 2.59) based on 7 cases, with no significant difference ($p = 0.235$). In term infants, the phototherapy plus zinc group (45 cases) showed a mean of 14.98 mg/dL (SD $\pm$ 2.46), and the placebo group (43 cases) showed 15.22 mg/dL (SD $\pm$ 2.62), also not significantly different ($p = 0.599$).

On day two, the pattern remained statistically nonsignificant. For late preterm infants, the phototherapy plus zinc group (5 cases) had a mean of 13.04 mg/dL (SD $\pm$ 2.08), compared to 12.12 mg/dL (SD $\pm$ 2.66) in the placebo group (7 cases), with $p = 0.545$. Among term babies, the phototherapy plus zinc group (45 cases) had a mean of 10.57 mg/dL (SD $\pm$ 2.13), and the placebo group (43 cases) had 11.41 mg/dL (SD $\pm$ 2.13), showing a trend that did not reach statistical significance ($p = 0.072$).

On day three, the number of infants still under phototherapy was markedly reduced. In the late preterm subgroup, only one infant in the phototherapy plus zinc group had a recorded bilirubin value of 11.69 mg/dL, while two infants in the placebo group had a mean of 10.20 mg/dL (SD $\pm$ 1.26), but a p value could not be calculated due to the small sample size. Among term infants, two cases in the phototherapy plus zinc group had a mean of 9.65 mg/dL (SD $\pm$ 0.49), and nine cases in the placebo group had a mean of 10.56 mg/dL (SD $\pm$ 1.18), with no significant difference ($p = 0.328$).

Duration of hospital stay distribution compared between the groups among late preterm and Term babies

Gestational age	Group	N	Mean Duration of hospital stay in days	± Std. Deviation	F value	p value
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Late preterm	Phototherapy Zinc Group	+5	11.00	± 0.71	7.66	0.017
	Placebo Group	7	9.14	± 1.46		
Term	Phototherapy Zinc Group	+45	8.91	± 1.76	2.07	0.006
	Placebo Group	43	9.93	± 1.64		

Among late preterm babies, those receiving phototherapy plus zinc had a longer mean hospital stay of 11.00 ± 0.71 days ($n=5$) compared to the placebo group, which had a mean of 9.14 ± 1.46 days ($n=7$). This difference was statistically significant (F value 7.66, $p = 0.017$). In contrast, among term infants, the phototherapy plus zinc group had a mean hospital stay of 8.91 ± 1.76 days ($n=45$) which is shorter compared to the placebo group, had a mean of 9.93 ± 1.64 days ($n=43$). This difference was also statistically significant, though with a lower F value of 2.07 ($p = 0.006$). These findings suggest that the addition of zinc to phototherapy was associated with longer hospital stays in late preterm infants but shorter stays in term infants, highlighting a differential effect based on gestational age

Hospital Stay

Reduced in zinc group (9.12 ± 1.79 vs 9.82 ± 1.62 days; $p=0.043$)

DISCUSSION

This study found that zinc supplementation did not significantly reduce serum bilirubin levels, aligning with several previous randomized trials. However, it significantly reduced phototherapy duration and hospital stay.

The lack of effect on bilirubin levels may be due to variability in absorption, timing, or baseline characteristics. Zinc's role in reducing enterohepatic circulation likely contributes to faster clinical recovery rather than immediate biochemical changes.

These findings are consistent with recent meta-analyses showing reduced phototherapy duration but inconsistent effects on bilirubin levels. The reduction in hospital stay has important clinical and economic implications, especially in resource-limited settings.

Limitations include open-label design and single-center setting. Larger multicentric trials are needed to establish standardized dosing and protocols.

Conclusion

Oral zinc supplementation does not significantly reduce serum bilirubin levels in neonates undergoing phototherapy. However, it significantly reduces the duration of phototherapy and hospital stay, supporting its role as a safe and effective adjunct therapy.

REFERENCES

1. Kliegman RM, et al. Nelson Textbook of Pediatrics. 21st ed. Philadelphia: Elsevier; 2020.

2. Maisels MJ, McDonagh AF. Phototherapy for neonatal jaundice. *N Engl J Med*. 2008;358:920–8.
3. Bhutani VK, Johnson LH. Kernicterus in late preterm infants. *Clin Perinatol*. 2006;33:839–52.
4. American Academy of Pediatrics. Management of hyperbilirubinemia. *Pediatrics*. 2004;114:297–316.
5. Sharma D, et al. Role of zinc in neonatal hyperbilirubinemia. *J Matern Fetal Neonatal Med*. 2015;28:123–7.
6. Kumar P, et al. Zinc supplementation in neonatal jaundice. *Indian Pediatr*. 2014;51:375–8.
7. Yadav A, et al. Zinc supplementation in neonatal jaundice: Meta-analysis. *Pediatr Res*. 2025.
8. Elfarargy MS, et al. Zinc in neonatal jaundice. *J Clin Neonatol*. 2016;5:92–6.