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Zinc Supplementation Accelerates Bilirubin Reduction in Neonates with Hyperbilirubinemia: A Double-Blind Randomized Clinical Trial

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Abstract

Background: Neonatal hyperbilirubinemia affects up to 80% of infants, and despite phototherapy as standard care, zinc inhibits heme oxygenase, lowers bilirubin and CO, and offers antioxidant benefits. This study evaluated the effect of zinc supplementation on the incidence and severity of neonatal hyperbilirubinemia.

Methods: A double-blind, block-randomized trial was conducted from December 2024 to February 2025 at Prof. Dr. R. D. Kandou Hospital NICU. Neonates with serum bilirubin >5 mg/dL were randomized to receive zinc 5 mg, zinc 10 mg, or placebo, all with phototherapy. Bilirubin levels were measured at baseline, 72 hours, and 120 hours, and outcomes were analyzed using bivariate and multivariate methods.

Results: Ninety neonates, median age 3.0 days; 67% male; 62% birth weight ≥2.5 kg, were evenly distributed among groups with no significant differences at baseline. By day 3, the 10 mg zinc group showed significantly lower median bilirubin levels (5.3 mg/dL) compared to other groups (p=0.027). By day 5, bilirubin levels further declined across all groups: 3.5 mg/dL (placebo), 2.5 mg/dL (5 mg), and 2.4 mg/dL (10 mg) (p=0.025). Hyperbilirubinemia resolution by day 5 was achieved in 67% (placebo), 90% (zinc 5 mg), and 87% (zinc 10 mg) (p=0.044). Multivariate analysis revealed that 5 mg zinc significantly increased the odds of bilirubin resolution (OR 8.0; 95% CI 1.48–44.22; p=0.016), whereas 10 mg did not. Vomiting occurred in 13.3% of neonates receiving 10 mg zinc.

Conclusions: Zinc 5 mg supplementation significantly accelerates bilirubin reduction compared to 10 mg zinc or placebo in neonates with hyperbilirubinemia.

Keywords: Hyperbilirubinemia, Newborn, Phototherapy, Randomized Controlled Trial, Zinc.

Introduction

Neonatal hyperbilirubinemia is a common condition during the neonatal period (1, 2). Although most cases are benign and require no treatment, it remains one of the leading causes of neonatal hospital admission (3–5). Jaundice develops in 60% of term and 80% of preterm infants within the first week of life (1, 2, 4), and more than half of term infants exhibit visible jaundice (serum bilirubin > 5 mg/dL) between days 2 and 4. The highest risk of severe hyperbilirubinemia coincides with peak bilirubin levels on days 3–6 of life (1, 6).

According to the 2016 Global Burden of Disease Study, neonatal jaundice accounted for 1,309.3 deaths per 100,000 live births in the first six days of life, ranking seventh among global causes of neonatal mortality, with the most significant burden in low and middle-income countries (7). Indonesia is among the ten countries with the highest neonatal

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mortality rates, at 13.5 per 1,000 live births (6, 8). Several Indonesian hospitals report noteworthy incidence figures for term infants: Dr. Sardjito Hospital observed that 85% of healthy term newborns had bilirubin ≥ 5 mg/dL and 23.8% had bilirubin ≥ 13 mg/dL; Dr. Kariadi Hospital, Semarang, reported a 13.7% prevalence of neonatal jaundice; Dr. Soetomo Hospital, Surabaya, documented rates of 30% in 2000 and 13% in 2002; and Sanglah Hospital, Bali, recorded 15.09% in 2015 (9).

Hyperbilirubinemia results from excessive serum bilirubin accumulation, clinically manifesting as yellow discoloration of the skin, sclera, and mucous membranes (2, 8, 10). Visible jaundice appears when total serum bilirubin exceeds 5 mg/dL (1, 10). Elevated indirect bilirubin can cause brain dysfunction and permanent damage (kernicterus) (11). The primary mechanisms are increased bilirubin production from hemoglobin breakdown (hemolysis), reduced hepatic uptake or excretion, or both (1, 12). Hemolysis arises from the physiological transition of fetal hemoglobin (HbF) to adult hemoglobin (HbA) and the shorter lifespan of neonatal erythrocytes (1, 12, 13).

The American Academy of Pediatrics recommends phototherapy as the initial management for neonatal hyperbilirubinemia, with pharmacologic agents reserved for pathological cases (14). Emerging studies link zinc status to bilirubin metabolism: zinc levels correlate inversely with serum bilirubin; zinc administration substantially reduces carbon monoxide (CO) and bilirubin concentrations within 1–6 hours; and zinc inhibits heme-oxygenase, thereby preventing jaundice progression (15–18). Oral zinc supplementation has been shown to lower total serum bilirubin, potentially reducing the need for phototherapy and exchange transfusion and mitigating kernicterus risk (19). Zinc's favorable safety profile, essential roles in cell structure, protein synthesis, immune function (as a cofactor for >200 enzymes), and its antioxidant effects in reducing oxidative stress and hemolysis further support its therapeutic promise (15, 20–22). To date, Indonesian data on zinc's impact on hemolysis and neonatal hyperbilirubinemia are scarce. Therefore, this study investigates the effect of zinc supplementation on the incidence and severity of hyperbilirubinemia in neonates.

Materials and Methods

Study Design

This study adopted an experimental design in the form of a randomized, double-blind clinical trial. The research was conducted at the Neonatal Intensive Care Unit (NICU) of Prof. Dr. R. D. Kandou General Hospital, Manado, from December 2024 to February 2025. All study procedures adhered strictly to the ethical principles outlined in the Declaration of Helsinki (2008) and followed the institutional guidelines for research ethics at Prof. Dr. R. D. Kandou General Hospital. Ethical approval was obtained before study initiation from the hospital's Research Ethics Committee with registered number, 253/EC/KEPK-KANDOU/XII/2024.

Study Population

The study recruited neonates diagnosed with hyperbilirubinemia who were admitted to the NICU during the study period and met the established eligibility criteria. Inclusion criteria were as follows: neonates admitted between December 2024 and February 2025, diagnosed with neonatal jaundice with a serum total bilirubin level exceeding 5 mg/dL, undergoing phototherapy, and possessing complete and accessible medical records. Neonates with severe infections, major hemorrhage, significant congenital anomalies, biliary obstruction, or those who had received exchange transfusion therapy were excluded to ensure the safety and validity of the study outcomes.

A consecutive sampling method was employed, in which all eligible neonates encountered during the study period were invited to participate. A minimum of 30 neonates were enrolled in each group to ensure adequate statistical power.

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Data Collection

Data collection involved both primary and secondary sources. A specifically designed case report form was used to document demographic and clinical data, complemented by electronic medical records for secondary information. Screening was performed for neonates presenting with clinical signs of jaundice upon NICU admission. Confirmed cases underwent baseline laboratory evaluations, including serum total bilirubin measurements, along with other relevant investigations based on clinical indications.

Eligible neonates receiving phototherapy were subsequently recruited and randomized into three groups: zinc 5 mg, zinc 10 mg, or no zinc supplementation. Randomization was achieved through a computer-generated sequence with block randomization to ensure balanced group allocation. Zinc supplementation (Novapharin, Indonesia) was administered orally in powdered form through a 1-CC syringe and masked with identical labeling to maintain blinding. The intervention was discontinued upon the completion of phototherapy. To assess the effectiveness of zinc supplementation, serum bilirubin levels were re-evaluated on day 3 and day 5 following the initiation of the intervention. These measurements aimed to capture the dynamic changes in bilirubin levels during treatment.

Measurements

The independent variable in this study was zinc supplementation (Novapharin, Indonesia) (5 mg, 10 mg, or none), while the dependent variable was the total serum bilirubin level. Confounding variables, such as prematurity status and birth weight, were accounted for during both study design and statistical analysis.

Based on clinical practice guidelines, hyperbilirubinemia was operationally defined as a total serum bilirubin concentration greater than 5 mg/dL requiring phototherapy. Serum bilirubin reassessments were scheduled 72 hours (day 3) and 120 hours (day 5) after baseline measurement to evaluate treatment response. Zinc supplementation (Novapharin, Indonesia) was provided in a carefully prepared powdered formulation, delivered using a 1-CC syringe (Onemed, Indonesia) to ensure precise dosing and minimize discomfort for the neonates.

Statistical Analysis

Data analysis was conducted using Statistical Package for the Social Sciences (SPSS) version 29.0.2.0. Results were presented through comparative tables displaying pre- and post-intervention total serum bilirubin levels across the three groups (zinc 5 mg, zinc 10 mg, and no zinc). The normality of data distribution was assessed using the Shapiro-Wilk test. Normally distributed data were reported as mean ± standard deviation, whereas non-normally distributed data were expressed as median with minimum and maximum values. Group comparisons were made using the Kruskal-Wallis or Chi-square tests as appropriate. Further adjustments for potential confounding variables, such as gestational age, birth weight, and baseline bilirubin level, were performed using analysis of covariance (ANCOVA). A p-value of less than 0.05 was considered statistically significant, with results reported within a 95% confidence interval.

Results

Characteristics of Neonates by Research Group

A total of 90 neonates participated in this clinical trial, evenly distributed into three study groups. In general, the majority of infants were around three days old, with the age distribution of 50% of the sample falling within the range of 2 to 4 days. The sex ratio showed that the number of male infants exceeded that of female infants, with a ratio of approximately 7:3. More than 60% of the neonates in this study had a birth weight of ≥2500 grams, indicating that most infants were in the normal birth weight category. However, there was also a proportion of premature infants that accounted for a portion of the total

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sample. The median duration of phototherapy was 4 days, with an interquartile range (IQR) of 4–5 days, indicating relatively slight variation in the duration of therapy among the infants in this study (Table 1).

Table 1. Characteristics of Neonates in the Study.

Character	Total (n = 90)
	Mean/Median
Age (days)	3.6 ± 2.4
Gender, n (%)	
Man	60 (67)
Woman	30 (33)
Heavy Born (g), n (%)	
< 2.5kg	34 (38)
≥ 2.5kg	56 (62)
Age Gestation (months)	36.8
< 37, n (%)	45 (50)
≥ 37, n (%)	45 (50)

Analysis was also performed to confirm that randomization had successfully distributed neonatal characteristics evenly among the three study groups. Statistical analysis showed no significant differences in key baseline characteristics, including age, sex, and birth weight, indicating that these variables were well matched between groups. Therefore, the differences in outcomes observed in this study are more likely attributable to the zinc supplementation intervention rather than to other uncontrolled variables (Table 2).

Table 2. Baseline Characteristics of the Intervention and Control Groups.

Character	Control (n = 30)	Zn 5mg (n = 30)	Zn 10mg (n = 30)	p-value
	Mean/Median	Mean/Median	Mean/Median	
Age (days)	3.0 ± 1.2	3.8 ± 2.8	4.0 ± 2.8	0.211
Gender, n (%)				
Man	21 (70)	21 (70)	18 (60)	0.638
Woman	9 (30)	9 (30)	12 (40)	
Heavy Born, n (%)				
< 2.5kg	12 (40)	11 (37)	11 (37)	0.954
≥2.5kg	18 (60)	19 (63)	19 (63)	
Age Gestation (weeks)	36.5	37.5	36.5	0.318
< 37, n (%)	18 (60)	11 (37)	16 (53)	0.177
≥ 37, n (%)	12 (40)	19 (63)	14 (47)	

Relationship of Zinc Dose with Changes in Serum Bilirubin Levels and Hyperbilirubinemia Status

Bivariate analysis of the effect of zinc supplementation on bilirubin levels and hyperbilirubinemia status was performed using a visual approach (Fig. 1). Visually, the effect of zinc was more pronounced in reducing total bilirubin levels, with variations between dose groups beginning on day 3 and continuing until day 5. The time factor also played an important role, especially in the first three days, when the decrease in total bilirubin was more pronounced in the group receiving zinc supplementation compared to the control group. The statistical analysis showed that the difference in total bilirubin levels between groups were significant (Table 3).

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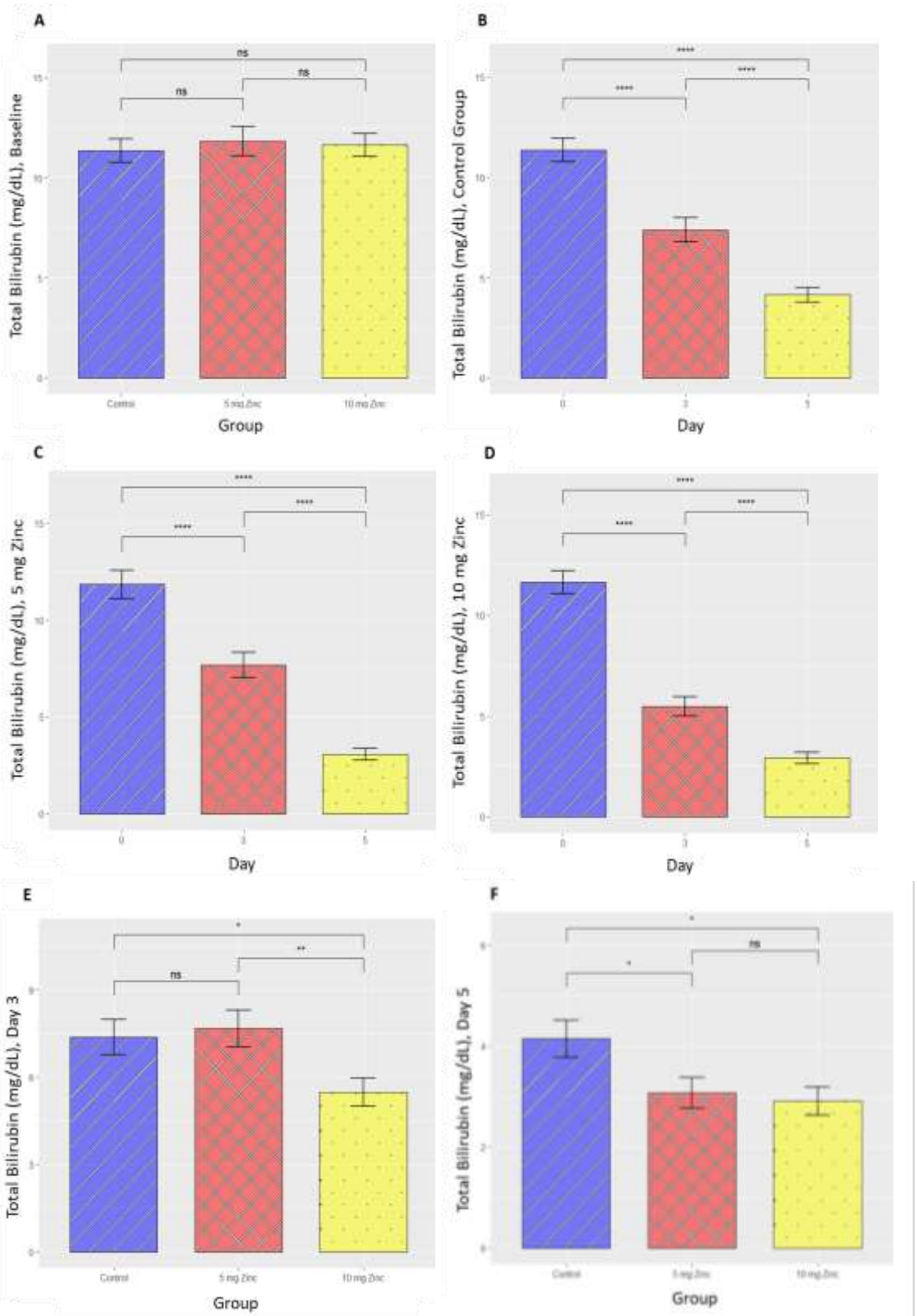

Fig. 1. Distribution and Change of Serum Total Bilirubin Levels according to Group Dose, namely (A) baseline, (B) control, (C) 5 mg Zinc, (D) 10 mg Zinc, (E) Day 3, and (F) Day 5. The ns, *, **, ***, and **** indicate not significant, P< 0.05, P< 0.01, P< 0.001, and P< 0.0001, respectively.

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Table 3. Differences in Bilirubin Levels Over Time and With Prolonged Phototherapy Across Zinc Dose Groups.

Variables	Total (n= 90)	Control (n = 30)	Zn 5mg (n = 30)	Zn 10 mg (n = 30)	p-value
	Median	Median	Median	Median	
Bilirubin Total (mg/dL)					
Beginning	10.9 (9.4 − 12.8)	11.1 (9.0 − 12.9)	10.4 (9.6 − 12.1)	11.1 (9.9 − 12.8)	0.893
Day III	6.3 (4.4 − 8.8)	6.8 (4.9 − 10.2)	6.9 (5.0 − 9.4)	5.3 (3.6 − 7.1)	0.027*
Day V	3.1 (2.1 − 4.3)	3.5 (2.7 − 5.2)	2.5 (2.1 − 4.1)	2.4 (1.7 − 4.1)	0.025*
Hyperbilirubinemia (Bilirubin Total ≥ 5 mg/dL)					
Day III	61 (68)	22 (73)	22 (73)	17 (57)	0.280
Day V	17 (19)	10 (33)	3 (10)	4 (13)	0.044*
Repair Hyperbilirubinemia (Bilirubin Total < 5 mg/dL)					
Day III	29 (32)	8 (27)	8 (27)	13 (43)	0.280
Day V	73 (81)	20 (67)	27 (90)	26 (87)	0.044*

*Significant p-value (p< 0.05).

In terms of improvement of hyperbilirubinemia, which is a qualitative measure of bilirubin in this study, the difference between groups became significant only on day 5 (Table 4). The effectiveness of zinc in accelerating the resolution of hyperbilirubinemia became more apparent in the final phase of treatment compared to the initial phase.

Table 4. Regression Analysis of Zinc's Influence on Serum Bilirubin Levels and Hyperbilirubinemia Resolution.

Variables	Univariate		Multivariate	
	β (95% CI)	p-value	β (95% CI)	p-value
Outcome: Total Bilirubin (Random-Intercept Mixed Model)				
Group (Ref: Control)				
Zinc 5 mg	-0.11 (1.43; 1.21)	0.870	0.22 (-1.05; 1.48)	0.737
Zinc 10 mg	-0.95 (-2.27; 0.37)	0.158	-0.80 (-2.03; 0.43)	0.199
Measurement Time (Ref: Start)				
Day III	-4.76 (-5.36 ; -4.16)	<0.001	-4.76 (-5.36 ; -4.16)	<0.001*
Day V	-8.23 (-8.83 ; -7.63)	<0.001	-8.23 (-8.83 ; -7.63)	<0.001*
Other variables in the multivariate model: birth weight, gestational age				
	Univariate		Multivariate	
	β (95% CI)	p-value	β (95% CI)	p-value
Outcome: Improvement of Hyperbilirubinemia Day III (Logistic Regression)				
Group (Ref: Control)				
Zinc 5 mg	1.00 (0.32; 3.14)	1.000	0.82 (0.08; 8.87)	0.873
Zinc 10 mg	2.10 (0.71; 6.22)	0.179	1.81 (0.04; 92.49	0.768
Other variables in the multivariate model: Total bilirubin level at the start of therapy				
Outcome: Improvement of Hyperbilirubinemia Day V (Logistic Regression)				
Group (Ref: Control)				
Zinc 5 mg	4.50 (1.09; 18.50)	0.037	8.09 (1.48; 44.22)	0.016*
Zinc 10 mg	3.25 (0.89; 11.90)	0.075	4.02 (0.96; 16.83)	0.057
Other variables in the multivariate model: Total and direct bilirubin levels at the start of therapy				

OR = odds ratio, aOR = adjusted odds ratio, CI = confidence interval, *Significant p-value (p< 0.05).

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Regression Analysis of the Efficacy of Zinc Supplementation on Hyperbilirubinemia

The regression model analyses not only confirmed the associations through the strength of association measures, such as mean difference (β), odds ratio (OR), and rate ratio (RR), but also provided a deeper understanding of the effect of zinc supplementation after accounting for confounding factors (Tables 3 and 4). The multivariate models show that the effectiveness of zinc supplementation is more difficult to assess through changes in total bilirubin levels (Table 4). In neonates with hyperbilirubinemia, the decrease in bilirubin levels was influenced more by time than by the dose of zinc administered. Table 4 shows that total bilirubin levels naturally decreased by almost 5 mg/dL on day 3 (95% CI -5.36; -4.16, $p < 0.001$) and by more than 8 mg/dL on day 5 (95% CI -8.83; -7.63, $p < 0.001$), regardless of the dose of zinc received.

The effect of zinc supplementation is more apparent in qualitative bilirubin monitoring, namely through hyperbilirubinemia status. The effect of zinc was most evident on day 5, particularly in the group receiving a dose of 5 mg (Table 4). The odds of improving hyperbilirubinemia in neonates receiving 5 mg of zinc were approximately 8 times greater than in the control group (95% CI 1.48-44.22, $p = 0.016$). However, in the group receiving 10 mg of zinc, this effect was smaller and did not reach statistical significance (OR 4.02; 95% CI 0.96-16.83, $p = 0.057$). This suggests that, although zinc supplementation has the potential to accelerate the improvement of hyperbilirubinemia, its effectiveness may vary depending on the dose administered.

Safety and Side Effect Evaluation of Zinc Supplementation

In this study, four neonates (13.3%) who received zinc supplementation at a dose of 10 mg experienced vomiting, whereas no cases were observed in the 5 mg group. This vomiting was the only side effect identified during the study period.

Discussion

The results of this study indicate that zinc supplementation had a significant effect on reducing total serum bilirubin levels, with differences between treatment groups emerging on day 3 and becoming more pronounced by day 5. These findings are consistent with previous studies that zinc supplementation plays a key role in lowering total serum bilirubin levels and accelerating phototherapy duration in neonates with hyperbilirubinemia. A study conducted by Mandlecha et al., using a double-blind, randomized controlled trial design, showed that 5 mg/day of zinc supplementation significantly accelerated the decline in total serum bilirubin levels compared to placebo (16).

Additionally, research by Boskabadi et al. demonstrated that zinc supplementation during pregnancy effectively reduced the incidence of neonatal hyperbilirubinemia. Their findings revealed that neonates born to mothers who received zinc during the third trimester had higher serum zinc levels, and only 11% of these neonates required phototherapy compared to 36% in the non-supplemented group (23). These findings significantly support the hypothesis that zinc may reduce the severity of neonatal hyperbilirubinemia. Furthermore, a study by Faal et al. demonstrated that zinc supplementation in preterm neonates with hyperbilirubinemia significantly lowered total serum bilirubin levels within the first 48 hours after intervention. Zinc administration was also found to significantly shorten the duration of phototherapy compared to the control group (24).

Conversely, some previous studies have reported no significant effect of zinc supplementation on the management of neonatal hyperbilirubinemia. Khoshnevisasl et al., using a double-blind randomized clinical trial design, reported that 10 mg of zinc supplementation did not result in a statistically significant reduction in total serum bilirubin levels or phototherapy duration compared to

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placebo (25). The inconsistency of findings among studies is likely attributable to heterogeneity in subject characteristics, such as differences in gestational age, birth weight, and severity of hyperbilirubinemia in the study populations. Moreover, variations in bilirubin measurement methodologies and evaluation timing may also contribute to outcome variability. In the context of the present study, the therapeutic effect of zinc appeared more pronounced during specific time intervals that were not captured in the evaluation period of the Khoshnevisasl study.

The mechanism by which zinc supplementation reduces serum bilirubin levels in neonates with hyperbilirubinemia may involve several integrated physiological pathways. One fundamental mechanism is its ability to inhibit the enterohepatic circulation of bilirubin, a process in which bilirubin secreted into the intestinal lumen undergoes reabsorption into systemic circulation via β-glucuronidase-mediated deconjugation. Experimental studies have shown that zinc inhibits the catalytic activity of β-glucuronidase, thereby preventing the reabsorption of conjugated bilirubin and promoting its fecal elimination (16, 26). In addition to its intestinal role, zinc also plays a crucial role in hepatic bilirubin metabolism, particularly by enhancing the catalytic activity of uridine diphosphate-glucuronosyltransferase (UGT1A1, gene ID: 54658), the key enzyme responsible for conjugating bilirubin in hepatocytes. This conjugation biochemically transforms unconjugated bilirubin into a more water-soluble form, facilitating its excretion via the biliary system and eventual elimination in feces (27, 280). Zinc also exhibits notable antioxidant and anti-inflammatory activities, protecting hepatocytes from oxidative damage induced by elevated bilirubin concentrations. Hyperbilirubinemia can cause oxidative stress, impairing liver function. Zinc supplementation, therefore, offers dual therapeutic potential: first, by mitigating structural and functional hepatocyte damage through its antioxidant effects, and second, by optimizing hepatic metabolic capacity for bilirubin via cellular stabilization (29, 30).

For therapeutic use, several clinical studies have assessed various zinc dosages. The International Zinc Nutrition Consultative Group (IZiNCG) recommends a therapeutic zinc dose of 5–10 mg/day for infants under six months with zinc deficiency. These recommendations are based on a comprehensive evaluation of zinc intervention studies, considering both safety and efficacy in infant populations. According to the latest 2024 guidelines of the Australian National Medication Formulary (ANMF), the recommended dose of zinc for neonates is 2–3 mg/kg/day, with a potential increase of up to 6 mg/kg/day as per the ESPGHAN consensus (31, 32).

However, several limitations must be considered when interpreting these results. One key limitation is the lack of statistical significance observed with the 10 mg zinc dose compared to 5 mg. This may suggest a dose-threshold effect, whereby 5 mg represents the optimal dose for enhancing bilirubin metabolism, while higher doses, such as 10 mg, provide no additional benefit. In some cases, high-dose supplementation may trigger compensatory mechanisms, such as enzymatic downregulation or disrupted zinc homeostasis, which could reduce therapeutic efficacy (32, 33). Individual variability in zinc absorption and metabolism may also influence outcomes, with neonates in the 10 mg group potentially exhibiting different retention or excretion patterns than those receiving 5 mg. Another possible factor is sample size, which limited the ability to detect a statistically significant benefit of the 10 mg dose despite a trend toward improved outcomes compared to the control group.

In conclusion, this trial demonstrates that 5 mg of zinc supplementation more effectively reduces total serum bilirubin than 10 mg or no zinc, suggesting that a 5 mg dose may serve as adjuvant therapy in neonates with hyperbilirubinemia, particularly those at high risk (preterm, zinc-deficient, familial jaundice,

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or low birth weight). Future studies should implement 12-hour bilirubin and plasma zinc monitoring to confirm therapeutic adequacy and safety and, expand to multicenter trials with larger, gestational age and birth-weight-matched cohorts that also assess maternal zinc status**.**

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Author contributions
All authors contributed equally to the study's conception, design, data collection, analysis, and interpretation. All authors have reviewed and approved the final version of the manuscript for submission.

Conflict of interest
The authors declare that there is no conflict of interest in this study.

Ethical approval
Ethical approval was obtained before the study's initiation from the hospital's Research Ethics Committee, registered number 253/EC/KEPK-KANDOU/XII/2024.

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