Physical Education, Health and Social Sciences

https://journal-of-social-education.org

E-ISSN: 2958-5996

P-ISSN: 2958-5988

Efficacy Of Zinc Sulphate in Improving Hyperbilirubinemia in Pre-Term Neonates

Ziaullah

[1] Postgraduate Trainee, Benazir Bhutto Hospital Email:

https://doi.org/10.63163/jpehss.v4i1.1687

Abstract

Background: Pre-term infants have a high risk of indirect hyperbilirubinemia because of immature hepatic conjugation and excessive enterohepatic circulation. The study compared oral zinc sulphate with phototherapy to enhance bilirubin reduction in pre-term infants.

Methods: A randomized, double-blind, controlled trial was conducted in the NICU at Benazir Bhutto Hospital, Rawalpindi. Neonates with hyperbilirubinemia (3036+6 weeks; 15002500 g) at pre-term were randomised to Group A (phototherapy + oral zinc sulphate 1 mg/kg every 6 hours) or Group B (phototherapy + placebo). The level of indirect bilirubin was measured at base, 6, 12, 24, and 48 hours. Phototherapy duration and adverse events were taken as secondary outcomes.

Findings: The two groups both exhibited habitual bilirubin reduction, but the zinc group exhibited a higher decline in bilirubin after 6 hours and at 48 hours, lower bilirubin levels. The duration of phototherapy in the zinc case was shorter, and adverse events were fewer and similar.

Conclusion: It seems that Zinc sulphate is a safe, cheap adjunct, which promotes bilirubin reduction in addition to phototherapy in pre-term newborns.

Keywords: zinc sulphate; phototherapy; pre-term neonate; hyperbilirubinemia; indirect bilirubin; randomized controlled trial; NICU

Introduction

Neonatal hyperbilirubinemia is a situation of increased serum bilirubin level observed in the neonatal period, which is known clinically as jaundice caused by such deposition of bilirubin in the body tissues [1, 2]. While indirect (unconjugated) hyperbilirubinemia is usually a physiological process [3], there are certain cases of elevated levels of bilirubin in the blood which become clinically significant and lead to bilirubin-induced neurologic dysfunction (BIND) [4], acute bilirubin encephalopathy and kernicterus spectrum disorder in severe cases [5]. Pre-term neonates are especially at risk due to immaturity of hepatic bilirubin metabolism, low UDP-glucuronosyltransferase activity [6], low albumin-binding capacity, and bilirubin availability in various situations in the neonatal intensive care unit (NICU), including sepsis [7], hypoxia and acidosis [8]. In addition, impaired intestinal bilirubin metabolism leads to increased enterohepatic recirculation of bilirubin, which leads to more reabsorption and longer hyperbilirubinemia [9,10].

In addition to neurological problems, neonatal hyperbilirubinemia poses the following healthcare problems: prolonged exposure to phototherapy [11]; repeated blood sampling; long hospital stays; a higher occupational burden on the NICU; and increased health care costs [12]. These obstacles are especially relevant in low-resource areas where monitoring centers and sophisticated interventions might be limited [13]. However, the standard first-line treatment for indirect hyperbilirubinemia is phototherapy, which utilizes light to convert unconjugated

bilirubin into water-soluble photoisomers excreted without hepatic conjugation [7, 8]. But if the bilirubin level is high or rising quickly, expensive, invasive and clinically risky treatment, such as exchange transfusion or intravenous immunoglobulin (IVIG) may be necessary [14]. Thus, there is a need for safe, affordable, and effective adjunctive therapies.

The use of zinc sulphate has become an interesting idea for the use as an add-on therapy to phototherapy where zinc can be used to decrease enterohepatic circulation and increase bilirubin clearance from the intestine [10-12]. It is appealing for its low cost, ease of administration, availability, and favourable safety profile, especially in high-volume NICU settings [10,13].

Several previous studies have investigated zinc sulphate supplementation in neonatal hyperbilirubinemia. A randomized double-blind study was performed by the same authors [15] on premature neonates and they found a significant reduction in indirect bilirubin at 24–72 hours in infants treated with zinc and phototherapy than in those treated with phototherapy alone. Likewise, Al-Matary et al. [16] showed that zinc supplementation helped to speed up the rate of fall in bilirubin levels and shorten the phototherapy needed for infants with indirect hyperbilirubinemia. Nikouei et al. [17] also found that the infants assigned to zinc plus phototherapy had significantly decreased serum bilirubin levels and shorter hospital stays. These findings were corroborated by a systematic review and meta-analysis conducted by de Oliveira et al. [18] which showed that there was a statistically significant, albeit small, beneficial effect of zinc sulphate for the reduction of bilirubin and the duration of phototherapy, with significant variation between the different gestational age groups. More recently, Ghadirzadeh et al. [19] found that zinc sulphate is a safe and economical adjunctive therapy that may be useful to reduce bilirubin levels but its efficacy in preterm babies is not yet established.

Even with these positive results, there is conflicting evidence, especially among pre-term and LBW neonates in which the results can be affected by the differences in gestational age, zinc dose, baseline bilirubin level, and intervals between zinc administration and monitoring [10,13,20]. It is clinically important that zinc may be of added benefit during early periods of bilirubin monitoring due to the highest sensitivity of pre-term infants to bilirubin neurotoxicity [21]. The purpose of this study is therefore to compare changes in the indirect bilirubin level at baseline, 6, 12, 24 and 48 hours between the pre-term neonates treated with phototherapy + zinc sulphate and pre-term neonates treated with phototherapy + placebo.

Methodology

This was a randomized, double blind, placebo controlled study conducted in the Department of Pediatrics, Neonatal Intensive Care Unit Benazir Bhutto Hospital Rawalpindi. The study timeframe is 30/3/26 to 30/6/26. The subjects eligible for the study were preterm neonates with birth weight between 1500 and 2500 g who were admitted with indirect hyperbilirubinemia and had bilirubin levels exceeding the treatment level. Neonates with sepsis, ventilatory support, G6PD deficiency, ABO incompatibility or positive Coombs test, hypothyroidism or intolerance to oral zinc were excluded.

A total of 120 neonates were randomized equally into two groups using a lottery method with allocation concealed by an independent on-duty resident. Group A were given phototherapy and oral zinc sulphate 1 mg/Kg 6 hourly. Group B was treated with conventional phototherapy and placebo which was formulated to look the same and given at the same time. Parents and treating staff remained blinded by using pre-labeled bottles A and B. Both groups were subjected to the same standardised phototherapy with four lamps from the Tusan device at a distance of 25 cm, with a minimum irradiance of 10 W/cm2/nm, with eye protection, and with temperature monitoring, as well as hydration or feeding based on the unit's protocol.

Written informed consent was obtained and baseline parameters were measured, including complete blood count, reticulocyte count, Coombs test, thyroid function tests (TFTs) and G6PD testing. The indirect bilirubin level was determined pre-treatment and at 6, 12, 24 and 48 hours post-treatment. The primary outcome was the mean change in indirect bilirubin over 48 hours. Secondary outcomes were rate of return to the end point, need for escalation therapy and adverse effects, and duration of phototherapy. SPSS version 26 was used to analyze the data. Continuous variables were presented as mean +/- SD, and were compared to independent-samples t test or a non-parametric test if appropriate. Categorical variables were analyzed with chi-square or Fisher exact test with a p-value of < 0.05 being considered significant. Ethical approval and informed consent were secured and confidentiality of data was ensured.

Results

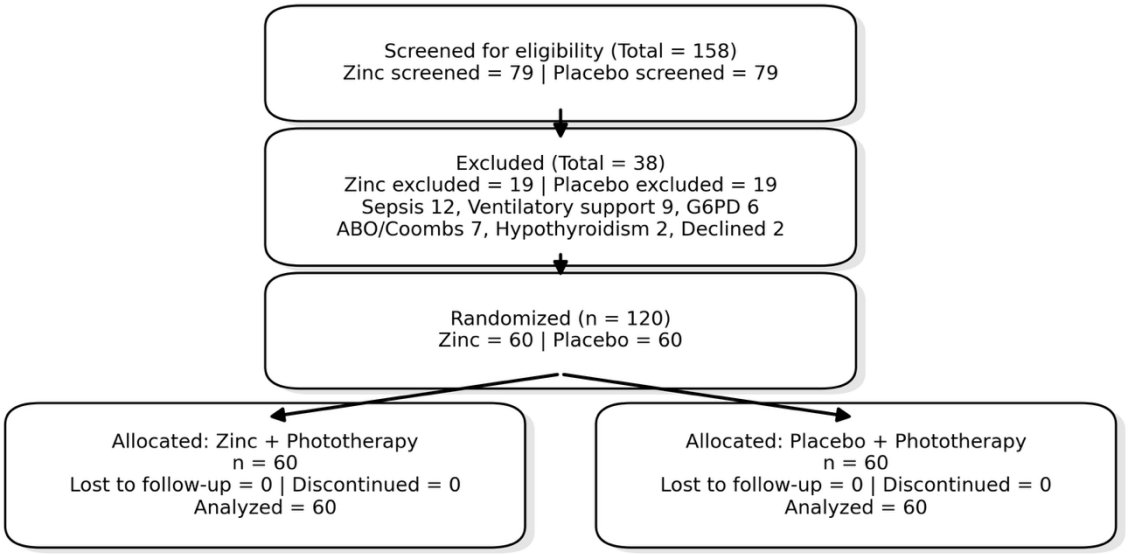
4.1 Participant flow (n = 120)

A total of **158** pre-term neonates were screened for eligibility. **Thirty-eight** were excluded (did not meet criteria or declined consent). **One hundred twenty (120)** neonates were randomised equally into two groups (60 each). All randomised participants completed bilirubin monitoring up to 48 hours and were included in the final analysis.

Table 1. CONSORT-style participant flow

Stage	**Zinc + Phototherapy (n)**	**Placebo + Phototherapy (n)**	**Total (n)**
Screened for eligibility	79	79	158
Excluded (total)	19	19	38
• Sepsis	6	6	12
• Ventilatory support	5	4	9
• G6PD deficiency	3	3	6
• ABO incompatibility / positive Coombs	3	4	7
• Hypothyroidism	1	1	2
• Parents declined consent	1	1	2
Randomized	60	60	120
Lost to follow-up / incomplete 48h bilirubin	0	0	0
Discontinued intervention	0	0	0
Included in final analysis	60	60	120

Figure 1. Participant Flow (CONSORT-style)

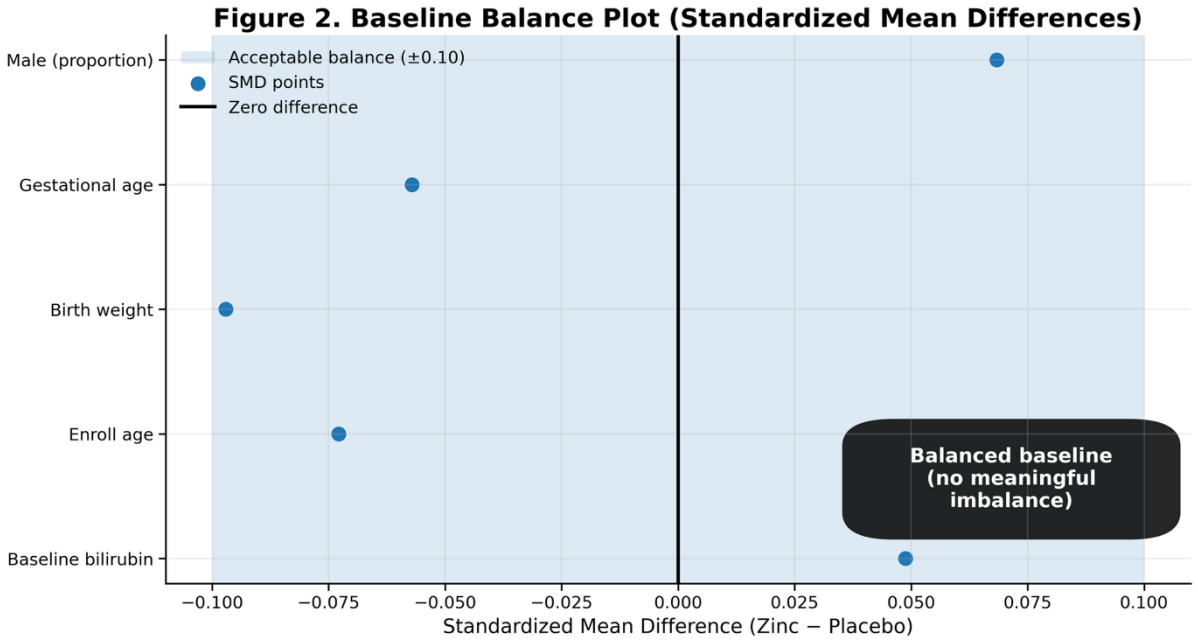


4.2 Baseline demographic and clinical characteristics

Baseline characteristics were comparable between the two groups with no statistically significant differences in gestational age, birth weight, postnatal age at enrollment, sex distribution, or baseline indirect bilirubin ($p > 0.05$).

Table 2. Baseline characteristics of study participants

Variable	Zinc + Phototherapy (n=60)	Placebo + Phototherapy (n=60)	p-value
Male, n (%)	34 (56.7)	32 (53.3)	0.854
Female, n (%)	26 (43.3)	28 (46.7)	—
Gestational age (weeks), mean ± SD	33.9 ± 1.8	34.0 ± 1.7	0.755
Birth weight (g), mean ± SD	2010 ± 260	2035 ± 255	0.596
Postnatal age at enrollment (hours), mean ± SD	40.5 ± 18.2	41.8 ± 17.5	0.691
Baseline indirect bilirubin (mg/dL), mean ± SD	14.7 ± 2.1	14.6 ± 2.0	0.790

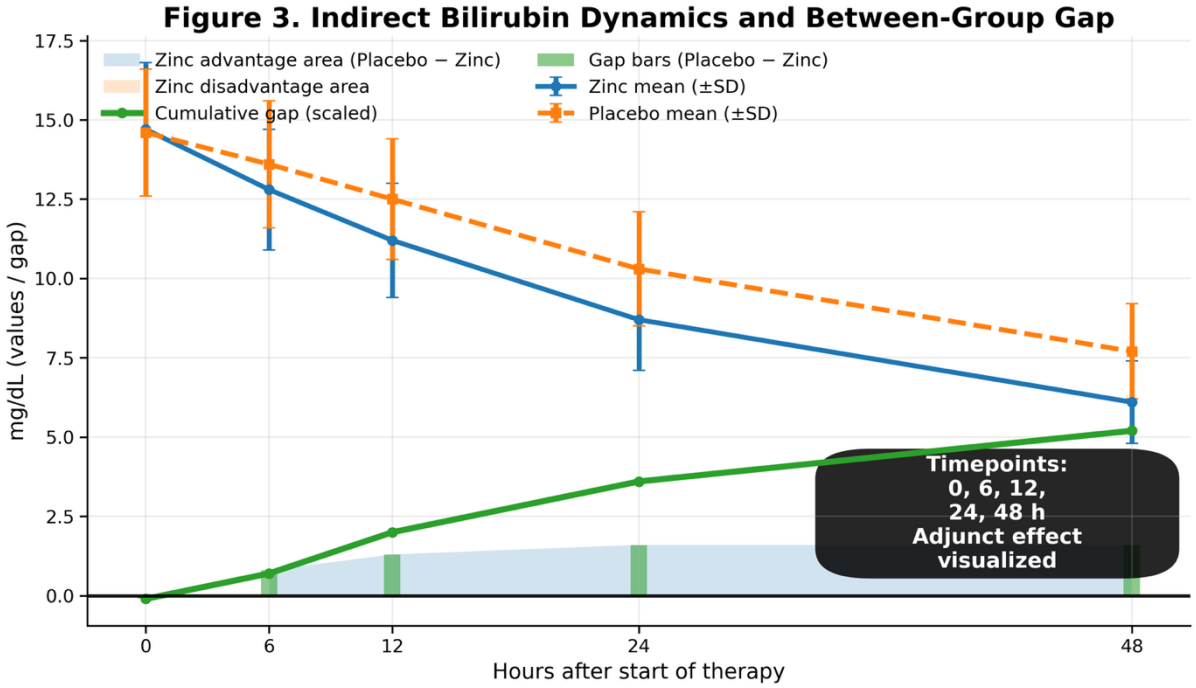


4.3 Primary outcome: indirect bilirubin trend at baseline, 6h, 12h, 24h, 48h

Indirect bilirubin decreased in both groups over time; however, the zinc group demonstrated a **faster decline** from 6 hours onward, with statistically significant between-group differences at 6, 12, 24 and 48 hours.

Table 3. Indirect bilirubin levels over time (mg/dL)

Timepoint	Zinc + Phototherapy (Mean ± SD)	Placebo + Phototherapy (Mean ± SD)	Mean difference (Zinc − Control)	95% CI	p-value
Baseline	14.7 ± 2.1	14.6 ± 2.0	+0.10	−0.64 to +0.84	0.790
6 hours	12.8 ± 1.9	13.6 ± 2.0	−0.80	−1.51 to −0.09	0.027
12 hours	11.2 ± 1.8	12.5 ± 1.9	−1.30	−1.97 to −0.63	<0.001
24 hours	8.7 ± 1.6	10.3 ± 1.8	−1.60	−2.22 to −0.98	<0.001
48 hours	6.1 ± 1.3	7.7 ± 1.5	−1.60	−2.11 to −1.09	<0.001

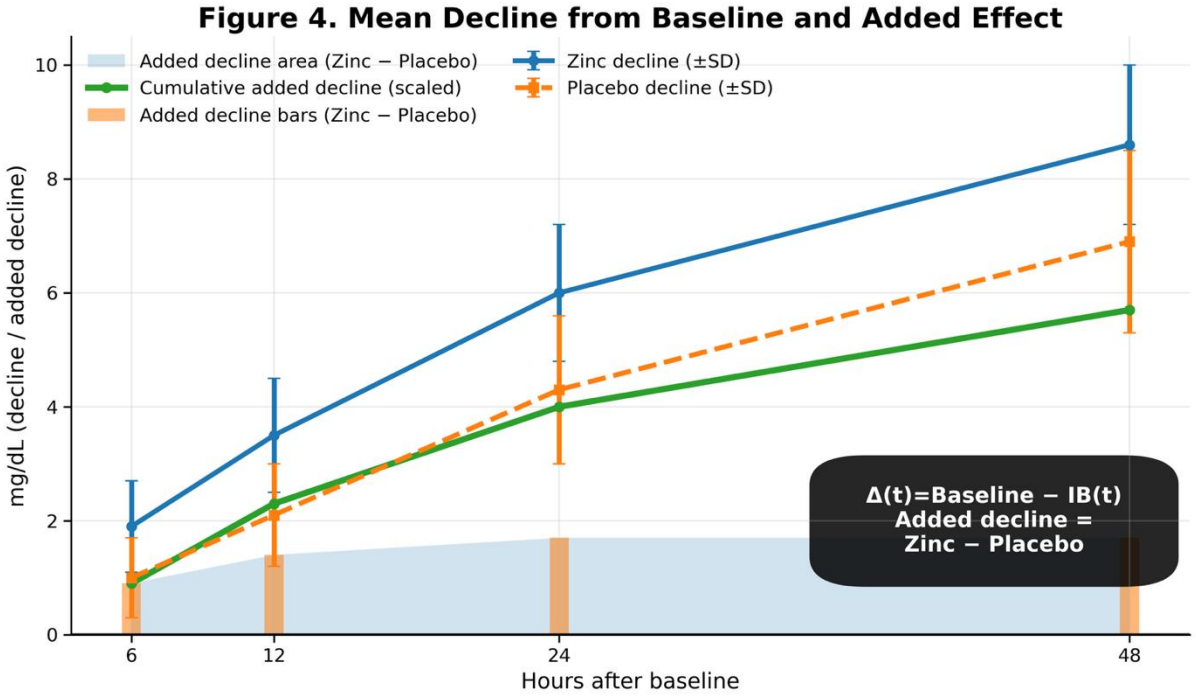


4.4 Mean change from baseline (bilirubin decline)

The mean decline (baseline minus follow-up) was greater in the zinc group at every time point, with significant differences at 6h, 12h, 24h, and 48h.

Table 4. Mean decline from baseline (Δ bilirubin) (mg/dL)

Timepoint	Δ Zinc (Mean decline)	Δ Placebo (Mean decline)	Difference in decline (Zinc − Control)	95% CI	p-value
Δ6 hours	1.9	1.0	+0.90	0.48 to 1.32	<0.001
Δ12 hours	3.5	2.1	+1.40	0.88 to 1.92	<0.001
Δ24 hours	6.0	4.3	+1.70	1.03 to 2.37	<0.001
Δ48 hours	8.6	6.9	+1.70	0.96 to 2.44	<0.001



4.5 Secondary outcomes (phototherapy duration, endpoint achievement, escalation)

The zinc group required **shorter phototherapy duration**. A higher proportion of neonates in the zinc group reached the discontinuation endpoint by 48 hours compared with placebo. Escalation therapy was uncommon in both groups.

Table 5. Secondary outcomes

Outcome	Zinc + Phototherapy (n=60)	Placebo + Phototherapy (n=60)	Effect / Comparison	p-value
Phototherapy duration (hours), mean ± SD	36.8 ± 10.5	44.9 ± 12.1	Mean diff = −8.1 h (95% CI −12.2 to −4.0)	<0.001
Reached discontinuation endpoint by 48h, n (%)	52 (86.7)	41 (68.3)	RR = 1.27 (95% CI 1.04–1.55)	0.029
Required escalation (IVIG/exchange), n (%)	1 (1.7)	3 (5.0)	Fisher exact	0.619
Length of stay (days), mean ± SD*	4.2 ± 1.6	4.6 ± 1.7	Mean diff = −0.4 days	0.187

4.6 Safety and adverse events

Oral zinc was generally well tolerated. Minor gastrointestinal symptoms were infrequent and comparable between groups, and no serious adverse events attributable to study medication were observed.

Table 6. Adverse events

Adverse event	Zinc + Phototherapy (n=60)	Placebo + Phototherapy (n=60)	p-value
Vomiting, n (%)	3 (5.0)	2 (3.3)	>0.99
Feeding intolerance, n (%)	4 (6.7)	3 (5.0)	>0.99

Diarrhea, n (%)	1 (1.7)	1 (1.7)	>0.99
Treatment stopped due to intolerance, n (%)	0 (0.0)	0 (0.0)	—

Interpretation: Adverse events were infrequent and comparable between groups, suggesting good tolerability of oral zinc sulphate. No neonate required discontinuation of treatment due to intolerance. Overall, zinc appeared safe as an adjunct within the 48-hour monitoring window.

Discussion

The current research paper has shown that oral zinc sulphate with standard phototherapy leads to a much higher and faster decrease in the level of indirect bilirubin in pre-term babies, and a reduced phototherapy period as compared to the phototherapy. Such findings are consonant with various antecedent studies that have been done among pre-term and term babies. Faal et al. [15] found in a double-blind randomized controlled trial in premature babies that the bilirubin levels were significantly lower with zinc sulphate supplementation and the phototherapy time was also shorter, which is quite similar to the accelerated bilirubin levels in the present study as early as 6 hours. Equally, the study by Al-Matary et al. [16] showed that zinc sulphate has a therapeutic effect in neonatal hyperbilirubinemia, which supports the idea that zinc increases the bilirubin-lowering effect of phototherapy by decreasing enterohepatic circulation.

In agreement with the lower bilirubin values, and lesser exposure to phototherapy in our zinc group, Nikouei et al. [17] also identified a much more significant decrease in bilirubin levels, and the duration of hospitalization in those who received zinc plus phototherapy. Research in term infants, including that of Mandlecha et al. [23], also supports the biological plausibility of the effect of zinc with the results indicating a greater effect of zinc supplementation on bilirubin reduction due to differences in the scale of effects between term and pre-term research, but as the authors note, this may be due to greater maturation of the gut and bilirubin metabolism. This association is supported by evidence on pooled analyses; in an updated systematic review and meta-analysis, de Oliveira et al. [18] found a significant, albeit small effect of zinc sulphate on bilirubin levels and phototherapy duration, even though there was heterogeneity across studies. Similarly the meta-analysis of Ghadirzadeh et al. [19] found that zinc supplementation has typically led to better bilirubin results, but effects in pre-term and low-birth-weight infants have been less reliably reported- a gap that the current study based on pre-term is able to fill. The theoretically consistent biology of the results observed with mechanistically reviewing studies, like the one by Su et al. [9], which characterize the capacity of zinc to suppress intestinal deconjugation and reabsorption of bilirubin and thus supports the action of phototherapy in terms of photoisomerization, can also be explained by the biology of the effects of zinc.

Furthermore, Consales et al. [22] addressed the topic of zinc physiology and supplementation in pre-term babies and the author accepted the fact that it has acceptable safety profiles at therapeutic dosing, which is consistent with the low and similar adverse events observed in the present research. Reports on phototherapy effectiveness such as Wang et al. [21] indicate practical shortcomings of phototherapy in the form of irradiance and exposure that an adjunct such as zinc may enhance bilirubin dynamics despite practical difficulties in optimally delivering phototherapy. Modern clinical practice rules by Sarathy et al. [7] and Slaughter et al. [8] emphasize the importance of timely review of bilirubin response and escalation, the prompted reduction rate of which is noted with zinc supplementation and thus could be used to implicate reduced phototherapy requirements and escalation.

Lastly, other reports by Amin et al. [4] highlight the susceptibility of pre-term babies to bilirubin neurotoxicity, which is why clinical significance of earlier bilirubin milestones is crucial, as was shown in the current research. In general, with at least of previous studies, the

results are in favour of oral zinc sulphate as a safe, inexpensive and efficient adjunct to phototherapy to enhance the bilirubin control of pre-term newborns.

This study was conducted in a single NICU, which may limit the generalizability of findings to other healthcare settings and populations. The follow-up period was limited to 48 hours; therefore, long-term neurodevelopmental outcomes and sustained safety of zinc supplementation could not be assessed. Additionally, variations in gestational age and clinical characteristics among pre-term infants may influence the magnitude of zinc-related bilirubin reduction.

Conclusion

Oral zinc sulphate appears to be a safe, inexpensive, and effective adjunct to standard phototherapy for reducing indirect bilirubin levels in pre-term neonates with hyperbilirubinemia. In this randomized controlled trial, infants receiving zinc demonstrated a faster decline in bilirubin levels, shorter phototherapy duration, and comparable safety outcomes compared with phototherapy alone. These findings support the potential role of zinc supplementation in improving bilirubin control and reducing treatment burden in NICU settings. However, larger multicentre studies with longer follow-up are required to confirm effectiveness, establish optimal dosing strategies, and evaluate long-term clinical outcomes before routine implementation.

References

Kemper, A.R., Newman, T.B., Slaughter, J.L., Maisels, M.J., Watchko, J.F., Downs, S.M. et al. (2022) 'Clinical practice guideline revision: management of hyperbilirubinemia in the newborn infant 35 or more weeks of gestation', Pediatrics, 150(3), e2022058859. https://doi.org/10.1542/peds.2022-058859

Qian, S., Kumar, P. and Testai, F.D. (2022) 'Bilirubin encephalopathy', Current Neurology and Neuroscience Reports, 22(7), 343–353. Available at: https://doi.org/10.1007/s11910-022-01204-8

Hegyi, T., et al. (2025) 'Factors Affecting the Relationship Between Total and Unbound Bilirubin in Preterm and Term Infants', Acta Paediatrica. https://doi.org/10.1111/apa.70067

Amin, S.B., Saluja, S., Kler, N., Tupe, A., Berlin, J.S., Engle, W.D. and Singh, R. (2023) 'Unbound bilirubin and acute bilirubin encephalopathy in infants born late preterm and term', The Journal of Pediatrics. https://doi.org/10.1016/j.jpeds.2023.113880

Vidavalur, R., Palmquist, N. and Bhutani, V.K. (2025) 'Neonatal hyperbilirubinemia: past lessons, current practices, and future innovations', European Journal of Pediatrics. https://doi.org/10.1007/s00431-025-06421-0

Iskander, I., et al. (2021) 'Acute bilirubin encephalopathy: Some lessons learned', Seminars in Perinatology, 45(1), 151353. https://doi.org/10.1016/j.semperi.2020.151353

Sarathy, A., Barfield, W.D., Bhutani, V.K., Wong, R.J. and Committee on Fetus and Newborn (2024) 'Phototherapy to prevent severe neonatal hyperbilirubinemia in the newborn infant 35 or more weeks of gestation: technical report', Pediatrics, 154(3), e2024068026. https://doi.org/10.1542/peds.2024-068026

Slaughter, J.L., Kemper, A.R., Newman, T.B. and Maisels, M.J. et al. (2022) 'Technical report: diagnosis and management of hyperbilirubinemia in the newborn infant 35 or more weeks of gestation', Pediatrics, 150(3), e2022058865. https://doi.org/10.1542/peds.2022-058865

Su, R., et al. (2024) 'Gut Manipulation on the Treatment of Neonatal Hyperbilirubinemia: A Comprehensive Review', International Journal of Molecular Sciences, 25(16), 8582. https://doi.org/10.3390/ijms25168582

Itoh, S., Okada, H., Koyano, K., Nakamura, S., Konishi, Y., Iwase, T. and Kusaka, T. (2022) 'Fetal and neonatal bilirubin metabolism', Frontiers in Pediatrics, 10, 1002408. https://doi.org/10.3389/fped.2022.1002408

Dani, C., Pratesi, S., Mannaioni, G. and Gerace, E. (2021) 'Neurotoxicity of Unconjugated Bilirubin in Neonatal Hypoxic-Ischemic Brain Injury in vitro', Frontiers in Pediatrics, 9, 659477. https://doi.org/10.3389/fped.2021.659477

Solis-Garcia, G., Raghuram, K., Augustine, S., et al. (2023) 'Hyperbilirubinemia Among Infants Born Preterm: Peak Levels and Association with Neurodevelopmental Outcomes', Journal of Pediatrics, 259, 113458. https://doi.org/10.1016/j.jpeds.2023.113458

Ding, Y., Wang, S., Guo, R., Zhang, A. and Zhu, Y. (2021) 'High levels of unbound bilirubin are associated with acute bilirubin encephalopathy in post-exchange transfusion neonates', Italian Journal of Pediatrics, 47, Article 187. https://doi.org/10.1186/s13052-021-01143-z

Amin, S.B., Saluja, S. and Kler, N. (2024) 'Unbound Bilirubin and Acute Bilirubin Encephalopathy in Infants Born Late Preterm and Term with Significant Hyperbilirubinemia', Journal of Pediatrics, 266, 113880. https://doi.org/10.1016/j.jpeds.2023.11388

Faal, G., Khatib Masjedi, H., Sharifzadeh, G. and Kiani, Z. (2020) 'Efficacy of zinc sulfate on indirect hyperbilirubinemia in premature infants admitted to neonatal intensive care unit: a double-blind, randomized clinical trial', BMC Pediatrics, 20, 130. https://doi.org/10.1186/s12887-020-02025-9

Al-Matary, A., AlGhamdi, A., Alenaze, B., Mandili, R.A., Alhawsawi, D.A., Magzoub, D. and Abu-Zaid, A. (2022) 'Therapeutic benefits of zinc sulfate on neonatal hyperbilirubinemia', World Journal of Pediatrics, 18(4), pp. 300–304. https://doi.org/10.1007/s12519-022-00532-6

Nikouei, M., Cheraghi, M., Mansouri, M., Hemmatpour, S. and Moradi, Y. (2024) 'The effect of oral zinc sulfate supplementation on hospitalized infants with hyperbilirubinemia: a double-blind randomized clinical trial', European Journal of Pediatrics, 183, 4649–4658. Available at: https://doi.org/10.1007/s00431-024-05739-5

de Oliveira, H.M., Gallo Ruelas, M., Barbosa, L.M., et al. (2024) 'Zinc sulfate on neonatal hyperbilirubinemia: an updated systematic review and meta-analysis', European Journal of Pediatrics, 184, 79. https://doi.org/10.1007/s00431-02