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THE IMPACT OF URSODEOXYCHOLIC ACID ON UNCONJUGATED HYPERBILIRUBINEMIA IN TERM NEONATES UNDERGOING PHOTOTHERAPY

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Abstract

Background: *Neonatal jaundice affects approximately 60% of term newborns. Unconjugated hyperbilirubinemia is primarily managed with phototherapy, which carries risks including mother–infant separation, dehydration, and skin rash. Ursodeoxycholic acid (UDCA), a hydrophilic bile acid with an established safety profile in pediatric cholestatic liver disease, may enhance bilirubin elimination by reducing enterohepatic circulation and providing hepatoprotection.*

Objectives: *To evaluate whether adjunctive oral UDCA combined with phototherapy accelerates bilirubin clearance in term neonates with unconjugated hyperbilirubinemia compared to phototherapy alone.*

Methods: *This randomized controlled trial was conducted at the Department of Paediatrics, Sheikh Zayed Medical College/Hospital, Rahim Yar Khan, Pakistan (December 2024–May 2025). Seventy-six term neonates (≥37 weeks) with non-hemolytic indirect hyperbilirubinemia were randomized 1:1 to intensive phototherapy plus oral UDCA 10 mg/kg/day (n=38) or phototherapy alone (n=38). Total serum bilirubin (TSB) was measured at baseline and at 24, 48, and 72 hours.*

Results: *Baseline characteristics were comparable between groups. The UDCA group demonstrated significantly greater TSB reduction at 72 hours (8.5 ± 1.5 vs. 7.0 ± 1.8 mg/dL; p<0.001; mean difference 1.4 mg/dL; 95% CI: 0.89–1.91) and shorter phototherapy duration (30.4 ± 6.2 vs. 42.1 ± 7.5 hours; p<0.001). More UDCA-treated infants achieved TSB <10 mg/dL by 48 hours (79% vs. 50%; p=0.003). No adverse effects were observed in either group.*

Conclusions: *Adjunctive UDCA significantly accelerated bilirubin reduction and shortened phototherapy duration in term neonates without adverse effects. These findings support UDCA as a potentially safe and effective supplement to phototherapy in neonatal unconjugated hyperbilirubinemia, though confirmation by larger multicentre trials is warranted.*

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INTRODUCTION

Neonatal hyperbilirubinemia is among the most common conditions encountered in neonatal practice, affecting approximately 60% of term infants and nearly all preterm infants during the first week of life [1]. Although typically self-limiting, an excess of unconjugated bilirubin is neurotoxic and, if inadequately managed, may cause bilirubin-induced neurological dysfunction or kernicterus, making timely and effective intervention essential [1,2].

Intensive phototherapy remains the cornerstone of treatment for significant unconjugated hyperbilirubinemia in term neonates. It acts by converting bilirubin into more hydrophilic photoisomers that are readily excreted via bile and urine [2,16]. Although phototherapy has substantially reduced the need for exchange transfusions, it is not without drawbacks. Prolonged inpatient care, enforced mother–infant separation, and short-term adverse effects, including dehydration, hyperthermia, skin rashes, and gastrointestinal disturbances, represent clinically important concerns [3]. Emerging evidence also suggests potential long-term sequelae, including retinal changes, melanocytic nevi, and predisposition to allergic disorders, further underscoring the need for adjunctive strategies that can safely reduce phototherapy exposure [3,15].

Several pharmacological agents, including metalloporphyrins, phenobarbital, clofibrate, and activated charcoal, have been investigated for their theoretical capacity to enhance bilirubin clearance, but none has achieved broad clinical endorsement owing to insufficient efficacy or unacceptable safety profiles [4,5,20]. Ursodeoxycholic acid (UDCA), a hydrophilic dihydroxy bile acid with an established safety record in pediatric cholestatic liver disease, has emerged as a promising candidate [4,6]. Through multiple complementary mechanisms, including stimulation of bile flow, inhibition of enterohepatic bilirubin recirculation, and antioxidant and anti-apoptotic hepatoprotective effects, UDCA may facilitate bilirubin clearance in neonates [4,6]. Published randomized trials have yielded mixed results, with some reporting significant improvements in bilirubin clearance and reductions in phototherapy duration, and others finding no clinically meaningful benefit [7,8,13].

Despite a growing body of evidence, a definitive consensus on the clinical utility of UDCA in neonatal unconjugated hyperbilirubinemia remains elusive, particularly in resource-limited South Asian settings. The present study was therefore designed to evaluate, in a randomized controlled trial, whether adjunctive oral UDCA accelerates bilirubin clearance and reduces phototherapy duration in term neonates with non-hemolytic unconjugated hyperbilirubinemia. Our primary hypothesis was that neonates receiving UDCA in addition to phototherapy would demonstrate a significantly greater reduction in TSB at 72 hours compared with those receiving phototherapy alone.

METHODS

This was a single-centre, parallel-group, randomized controlled trial conducted in the Department of Pediatrics, Sheikh Zayed Medical College/Hospital, Rahim Yar Khan, Pakistan, from December 2024 to May 2025. The study protocol was approved by the Institutional Ethics Review Board (IREB Reference No.119/IRB/SZMC/SZH) in accordance with the Declaration of Helsinki. Written informed consent was obtained from the parents or legal guardians of all participants prior to enrollment. The consent process was conducted in the participants' native language, and documentation was recorded in a pre-designed proforma before any study procedure was initiated.

Eligible participants were term neonates (gestational age 37–41 weeks) admitted for phototherapy with non-hemolytic indirect hyperbilirubinemia. Inclusion criteria were: postnatal age above 24 hours; birth weight 2,500–4,000 g; exclusive breastfeeding; TSB 12–20 mg/dL; and direct bilirubin less than 2 mg/dL at the time of admission. Neonates were excluded if they had hemolytic disease (Rh or ABO incompatibility, G6PD deficiency), neonatal sepsis, congenital infections, cholestatic jaundice (biliary atresia or neonatal hepatitis), inborn errors

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of metabolism affecting bilirubin handling (Crigler-Najjar syndrome or Gilbert syndrome), hypothyroidism, significant cephalohaematoma or severe bruising, or if their parents declined participation.

A consecutive sampling technique was employed to recruit eligible neonates during the study period. Randomization was performed using a lottery system with sequentially numbered, sealed opaque envelopes, achieving a 1:1 allocation ratio and maintaining allocation concealment until the point of enrollment. Given the nature of the oral intervention, the trial was conducted in an open-label fashion. To minimize the risk of detection bias, laboratory technicians performing TSB analyses were kept blinded to group assignment. The absence of a placebo arm is acknowledged as a limitation; however, the use of objective, laboratory-based primary endpoints substantially mitigates the risk of performance and detection bias.

Group A (intervention) received intensive phototherapy plus oral UDCA 10 mg/kg/day administered in two divided doses every 12 hours. UDCA was prepared by dissolving a 300-mg UDCA capsule (Ursobil®) in distilled water, with dosing adjusted by body weight. Group B (control) received intensive phototherapy alone. Both groups were treated with LED phototherapy units (spectral range 430–480 nm) at irradiance levels conforming to American Academy of Pediatrics (AAP) guidelines, administered continuously except during feeding and brief care episodes. All infants received supportive care including frequent breastfeeding or supplemental feeds as clinically indicated. UDCA was initiated concurrently with phototherapy and continued until phototherapy was discontinued, up to a maximum of 72 hours.

The primary outcome was the absolute reduction in TSB from baseline to 72 hours. TSB was measured at baseline (prior to commencing phototherapy) and at approximately 24, 48, and 72 hours after the start of treatment. Blood samples (0.5 mL) were obtained by heel prick or venipuncture and analysed using a spectrophotometric bilirubin analyser validated for neonatal samples (APEL BR-5200P, Japan), calibrated per the manufacturer's protocol [9]. Secondary outcomes included total phototherapy duration (hours), length of hospital stay (days), proportion of infants achieving TSB <10 mg/dL by 48 hours, UDCA-related adverse events (vomiting, diarrhoea, rash, or feeding intolerance), and the need for exchange transfusion. All data were recorded in a standardized pre-designed proforma.

Sample size was calculated based on the primary outcome. A minimum of 38 neonates per group was required to detect a between-group difference in mean TSB of 0.9 mg/dL at 72 hours, with 90% power and a two-sided alpha of 0.05, based on data from comparable prior trials [10,11]. Recruitment was initially targeted at 40 per group to allow for attrition; however, 76 neonates (38 per group) completed the study with no losses to follow-up. The observed mean TSB difference of 1.4 mg/dL exceeded the a priori assumption of 0.9 mg/dL; a post-hoc power calculation confirmed that the study achieved greater than 95% power for the observed effect size.

Data were analysed using IBM SPSS Statistics (version 23.0). Continuous variables were expressed as mean ± standard deviation (SD) and compared between groups using independent samples t-tests, after verifying normality with the Shapiro-Wilk test and homogeneity of variance with Levene's test. Where distributional assumptions were not met, the Mann-Whitney U test was used. Categorical variables were compared using the Chi-square test or Fisher's exact test as appropriate. Since TSB was assessed at three time points (24, 48, and 72 hours), Bonferroni correction was applied to adjust for multiple comparisons, with the corrected significance threshold set at $p<0.017$. For the primary and secondary comparisons, statistical significance was defined as a two-tailed p-value <0.05. Mean differences were reported with 95% confidence intervals (CIs). All analyses were conducted on an intention-to-treat basis, including all randomized participants in their originally assigned groups.

RESULTS

Eighty neonates were assessed for eligibility during the study period. Four were excluded prior to

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randomization: two for confirmed G6PD deficiency, one for a positive direct Coombs test indicating ABO incompatibility, and one due to parental refusal of participation. The remaining 76 neonates were randomized, with 38 allocated to each group. No withdrawals, dropouts, or treatment crossovers occurred during the 72-hour follow-up period, ensuring complete data for all randomized participants.

Baseline characteristics were well matched between the two groups and are summarized in Table 1. Mean birth weight was 3.2 ± 0.4 kg in the UDCA group and 3.1 ± 0.4 kg in the control group (p=0.290). Mean age at admission was 5.4 ± 1.3 days in the UDCA group and 5.3 ± 1.5 days in the control group (p=0.886). Groups did not differ significantly in gestational age, sex distribution, or baseline TSB. No infant had clinical or laboratory evidence of haemolysis or any comorbidity known to affect bilirubin metabolism.

Table 1. Baseline characteristics of study participants.

Characteristic	UDCA + Phototherapy (n=38)	Phototherapy Alone (n=38)	*p-value*
Male sex, n (%)	20 (53%)	18 (47%)	0.650[1]
Age at admission (days)	5.4 ± 1.3	5.3 ± 1.5	0.886[2]
Birth weight (kg)	3.2 ± 0.4	3.1 ± 0.4	0.290[2]
Gestational age (weeks)	39.1 ± 1.2	39.0 ± 1.1	0.700[2]
Initial TSB (mg/dL)	16.0 ± 2.0	15.8 ± 2.1	0.750[2]

[1]Chi-square test; [2]Independent samples t-test. Values are expressed as mean ± SD or n (%) as appropriate. TSB: total serum bilirubin. P-values reported to three decimal places.

Both groups demonstrated statistically significant within-group reductions in TSB over the course of treatment (p<0.001, baseline to 72 hours, for each group). However, the rate of bilirubin decline was consistently greater in the UDCA group at all time points. At 24 hours, mean TSB was 12.1 ± 1.5 mg/dL in the UDCA group versus 12.7 ± 1.4 mg/dL in the control group (mean difference 0.6 mg/dL; p=0.072; not significant after Bonferroni correction). At 48 hours, mean TSB was 9.3 ± 1.2 versus 10.3 ± 1.3 mg/dL, respectively (mean difference 1.0 mg/dL; 95% CI: 0.45–1.55; p=0.002), which remained significant after Bonferroni correction. At 72 hours, mean TSB was 7.5 ± 1.1 mg/dL in the UDCA group versus 8.9 ± 1.2 mg/dL in the control group (mean difference 1.4 mg/dL; 95% CI: 0.89–1.91; p<0.001). Overall, the UDCA group achieved a mean absolute TSB reduction of 8.5 mg/dL from baseline (approximately 53%), compared with 7.0 mg/dL (approximately 44%) in the control group. The bilirubin trends across all time points are illustrated in Figure 1.

A significantly greater proportion of UDCA-treated infants achieved TSB <10 mg/dL by 48 hours: 30 of 38 (79%) versus 19 of 38 (50%) in the control group (p=0.003, Chi-square; proportion difference 29%; 95% CI: 9%–49%). By 72 hours, all infants in both groups had achieved TSB <10 mg/dL and phototherapy was discontinued per protocol. The bilirubin response showed similar directional trends across subgroups by sex and baseline bilirubin category, though a formally powered stratified analysis is not reported in this manuscript.

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Figure 1. Mean total serum bilirubin (± SE) over 72 hours of treatment in both groups.

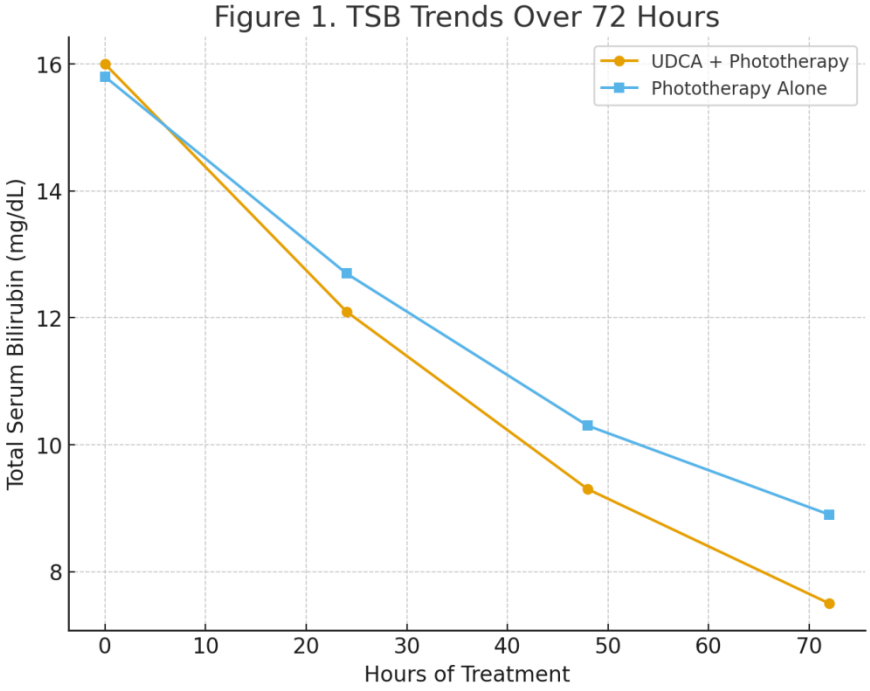
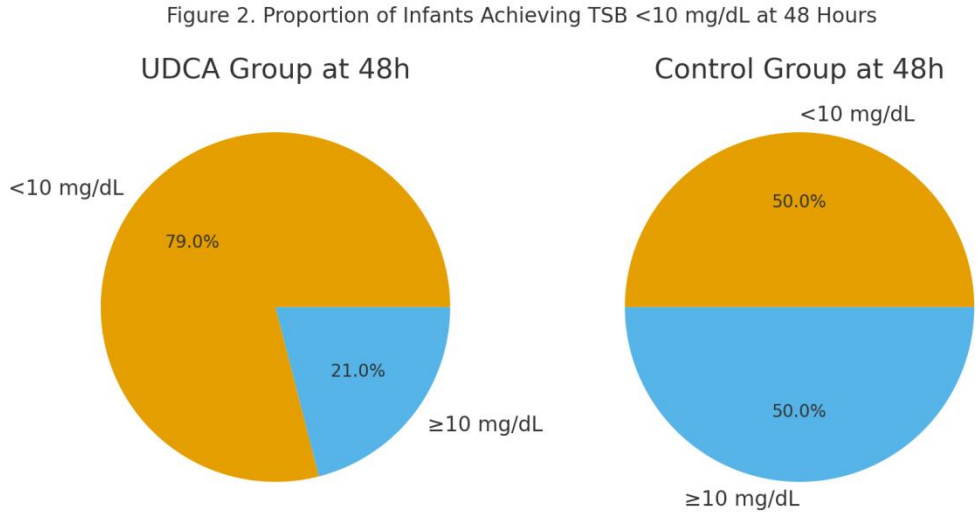


Figure 2. Proportion of neonates achieving TSB <10 mg/dL by 48 hours of treatment.



Treatment outcome data are presented in Table 2. Infants in the UDCA group required significantly shorter phototherapy than controls (30.4 ± 6.2 hours vs. 42.1 ± 7.5 hours; mean difference 11.7 hours; 95% CI: 8.8–14.6 hours; $p<0.001$). This corresponded to a shorter hospital stay in the UDCA group (2.0 ± 0.3 days vs. 2.7 ± 0.4 days; mean difference 0.7 days; 95% CI: 0.53–0.87 days; $p<0.001$). No infant in either group required escalation to exchange transfusion. UDCA was well tolerated throughout the treatment period; no adverse effects—including vomiting, diarrhoea, rash, or feeding intolerance—were recorded in the intervention group. Liver function parameters remained within normal limits. A small number of infants in both groups developed transient, self-

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limiting heat rash attributable to phototherapy exposure; no cases of bronze baby syndrome or bilirubin encephalopathy were identified. Telephone follow-up at one week post-discharge revealed no rebound hyperbilirubinemia requiring readmission in either group.

Table 2. Treatment outcomes in UDCA + phototherapy vs. phototherapy-alone groups.

Outcome	UDCA + Phototherapy (n=38)	Phototherapy Alone (n=38)	*p-value*
TSB at 72 h (mg/dL)	7.5 ± 1.1	8.9 ± 1.2	<0.001[2]
Absolute TSB reduction at 72 h (mg/dL)	8.5 ± 1.5	7.0 ± 1.8	0.001[2]
Phototherapy duration (hours)	30.4 ± 6.2	42.1 ± 7.5	<0.001[2]
Hospital stay (days)	2.0 ± 0.3	2.7 ± 0.4	<0.001[2]
TSB <10 mg/dL by 48 h, n (%)	30 (79%)	19 (50%)	0.003[1]
Exchange transfusion required, n	0	0	–
Adverse effects observed, n	0	0	–

[1]Chi-square test; [2]Independent samples t-test. Values are expressed as mean ± SD or n (%) as appropriate. Adverse effects refers to any drug-related events attributable to UDCA (e.g., gastrointestinal upset, rash). No infant in either group required exchange transfusion or developed major complications. Ninety-five percent confidence intervals for primary and secondary outcome mean differences are reported in the text.

DISCUSSION

This randomized controlled trial demonstrated that adjunctive oral UDCA significantly improved bilirubin control in term neonates with non-hemolytic unconjugated hyperbilirubinemia. Compared with phototherapy alone, neonates who received UDCA alongside intensive phototherapy achieved a greater TSB reduction at 72 hours (mean difference 1.4 mg/dL; 95% CI: 0.89–1.91; p<0.001) and required approximately 12 fewer hours of phototherapy. These findings are consistent with our primary hypothesis and extend the existing evidence base to a South Asian tertiary care setting.

Our results align with earlier randomized trials reporting a beneficial effect of UDCA on neonatal jaundice. Hassan et al. [9] demonstrated significantly lower bilirubin levels at 12, 24, and 36 hours and a shorter phototherapy duration in UDCA-treated infants in a 200-neonate RCT. Similarly, Honar et al. [10] reported that UDCA at 10 mg/kg/day significantly accelerated bilirubin decline and reduced phototherapy duration compared with phototherapy alone. The somewhat smaller reduction in phototherapy duration observed in the present study, relative to Honar et al. [10], may reflect differences in the phototherapy cessation threshold or the baseline severity of jaundice in the control group.

More recent evidence further supports these findings. Zarkesh et al. [7] reported that UDCA combined with phototherapy resulted in significantly lower bilirubin levels at discharge and a reduced rate of rehospitalization compared with phototherapy alone. A meta-analysis by Lazarus et al. [12] encompassing eight RCTs (1,116 infants) found that UDCA significantly reduced phototherapy duration and improved 48-hour bilirubin reduction, although between-study heterogeneity was considerable. The standardized protocol and pre-specified endpoints employed in the present study contribute methodological clarity to this body of literature.

Not all prior studies have demonstrated benefit. Mirzarahimi et al. [8] found no significant differences in bilirubin course or phototherapy

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duration between the UDCA and control groups, and Akefi et al. [13] observed only early bilirubin improvement without a meaningful reduction in phototherapy hours or length of stay. These discrepancies likely reflect differences in phototherapy protocols, patient selection criteria, and UDCA dosing regimens. Notably, some earlier trials enrolled infants with hemolytic conditions, in which the rate of bilirubin production may exceed UDCA's excretory capacity [6]. The strict exclusion of hemolytic jaundice in the present study likely contributed to the more consistent treatment response observed.

The dose of 10 mg/kg/day used in this study is consistent with the most widely used regimen in the literature [10,11]. A higher dose of 15 mg/kg/day has been explored by Gharehbaghi et al. [11], with some evidence of more rapid bilirubin decline; however, available meta-analyses have not confirmed dose-dependent superiority [12]. In the present study, UDCA demonstrated an excellent tolerability profile, consistent with its established safety record in pediatric hepatology [4,6].

The clinical implications of these findings are meaningful. A reduction in phototherapy duration of approximately 12 hours facilitates earlier maternal–infant reunion, decreases exposure to phototherapy-associated complications such as dehydration and skin rash [3], and may help alleviate pressure on neonatal unit resources. These benefits are of particular relevance in resource-constrained healthcare settings.

This study has several limitations that must be acknowledged. The single-centre design and sample size of 76 neonates restrict the generalizability of findings to broader populations and clinical contexts. The open-label design, while unavoidable given the nature of the oral intervention, introduces potential performance bias; this risk is substantially mitigated, however, by the use of objective laboratory-based primary endpoints and blinding of laboratory personnel. Although allocation concealment was maintained through sequentially numbered sealed opaque envelopes, a formal randomization sequence registry was not established, which is a methodological limitation. The planned stratified analysis by sex and baseline bilirubin category could not be adequately powered at this sample size and remains to be addressed in future research. Furthermore, long-term neurodevelopmental outcomes and bile acid kinetics were not evaluated. Future studies should prioritize multicentre, placebo-controlled RCTs with larger and more diverse samples, subgroup analyses in preterm infants and those with hemolytic jaundice, dose-optimization and prophylactic-use trials, and mechanistic investigations of fecal bilirubin and bile acid excretion. Such research would provide the evidence needed to consider incorporating UDCA into standard neonatal jaundice management guidelines.

CONCLUSION

Adjunctive oral UDCA at 10 mg/kg/day, combined with intensive phototherapy, significantly accelerated bilirubin reduction and shortened phototherapy duration in term neonates with non-hemolytic unconjugated hyperbilirubinemia, with no observed adverse effects in this study. While these findings are encouraging, they are derived from a single-centre trial with a modest sample size and should be interpreted with appropriate caution. Confirmation by larger, multicentre, placebo-controlled randomized controlled trials is necessary before broad clinical recommendations can be made. If replicated, UDCA may represent a safe, low-cost, and effective adjunct to standard phototherapy, particularly in resource-limited neonatal care settings.

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