DOI: 10.7860/JCDR/2025/80533.22074

Original Article

Paediatrics Section

Effect of Ursodeoxycholic Acid on Unconjugated Hyperbilirubinemia in the Term Neonates Treated with Phototherapy: A Prospective Interventional Study

CHINTHAPUVU VIVEK[1], SHRISHAIL M GIDAGANTI[2], RAGHAVENDRA H GOBBUR[3], MALLANGOUDA M PATIL[4]

ABSTRACT

Introduction: Neonatal hyperbilirubinemia affects 60–80% of term neonates in the first week of life. Phototherapy (PT) is the standard treatment; however, prolonged PT has limitations. Ursodeoxycholic Acid (UDCA) is a potential adjuvant therapy to enhance bilirubin clearance.

Aim: To evaluate UDCA as a safe and useful adjuvant to PT in term neonates with Unconjugated Hyperbilirubinemia (UCHB) by comparing bilirubin reduction, PT duration, and length of hospital stay.

Materials and Methods: A prospective interventional study was conducted at the Level 3 Neonatal Intensive Care Unit (NICU) of Shri BM Patil Medical College, Hospital and Research Institute, Vijayapura, Karnataka, India, from January 2024 to January 2025. Total 100 term neonates were allocated into two groups: Group 1 (n=50) received oral UDCA (10–15 mg/kg/day) with PT, and Group 2 (n=50) received standard PT alone. Total Serum Bilirubin (TSB) levels were measured at admission, 24 hours, and 48 hours. PT duration, NICU stay, and adverse effects were assessed. The independent samples t-test or the Mann–Whitney U test was used to compare continuous variables, and the Chi-square test or Fisher's-exact's test was used to assess categorical variables. A p-value <0.05 was considered significant.

Results: Baseline characteristics such as gestational age (38.4±1.2 vs 38.2±1.3 weeks), birth weight (2.79±0.43 vs 2.76±0.40 kg), and gender distribution were comparable between groups. The decline in TSB at 48 hours was 9.3±1.75 mg/dL in the UDCA+PT group versus 9.8±1.90 mg/dL in the PT-only group (p=0.175). The mean PT duration was 47.84±2.50 hours in the UDCA group and 48.22±5.50 hours in the control group (p=0.66). UDCA was well tolerated, with only mild vomiting observed in three neonates.

Conclusion: The UDCA may modestly enhance bilirubin clearance, but differences in bilirubin reduction, PT duration, and NICU stay were not statistically significant. Larger randomised controlled trials are needed.

Keywords: Bilirubin clearance, Neonatal care, Neonatal jaundice, Phototherapy duration

INTRODUCTION

Neonatal Unconjugated Hyperbilirubinemia (UCHB) affects 60–80% of term neonates and an even higher percentage of preterm infants in the first week of life [1]. Accumulation of Unconjugated Bilirubin (UCB) leads to jaundice, which can progress to severe hyperbilirubinemia (TSB >20 mg/dL), increasing the risk of Acute Bilirubin Encephalopathy (ABE) and kernicterus, leading to irreversible neurological damage [2]. Timely management is essential to prevent these complications.

Neonatal jaundice arises due to increased bilirubin production from the shorter lifespan of foetal erythrocytes (70-90 days vs. 120 days in adults) [3], immature hepatic conjugation due to low Uridine Diphosphate-Glucuronosyltransferase (UGT1A1) activity [4], and increased enterohepatic circulation due to high β-glucuronidase levels in the gut [5]. While most cases resolve spontaneously, severe cases require medical intervention.

The American Academy of Paediatrics (AAP) recommends Phototherapy (PT) as the primary treatment [6]. PT converts UCB into water-soluble isomers for excretion but has complications such as dehydration, electrolyte imbalance, oxidative stress, and potential disruption of maternal-infant bonding [7]. Exchange transfusion, used in severe cases, carries risks such as haemodynamic instability, infections, and Necrotising Enterocolitis (NEC) [8]. These challenges have driven interest in adjuvant therapies to enhance bilirubin clearance and reduce PT duration.

Several pharmacological agents have been explored, including phenobarbital (induces bilirubin conjugation but is sedative) [9], clofibrate (a Peroxisome Proliferator-activated Receptor (PPAR) agonist) with unclear neonatal safety [10], D-penicillamine (limited efficacy) [11], and probiotics (inconclusive impact on bilirubin recycling) [12]. UDCA, a hydrophilic bile acid used in cholestatic liver diseases [13], has emerged as a promising adjuvant. It enhances biliary bilirubin excretion via Bile Salt Export Pump (BSEP) and Multidrug Resistance-associated Protein 2 (MRP2) transporters [14], reduces enterohepatic circulation, and has anti-inflammatory and antioxidant properties [15,16].

Cuperus FJ et al., (2009) found that UDCA accelerated bilirubin metabolism in Gunn rats [7], and Mendez-Sanchez N et al., (1998) observed enhanced bilirubin turnover in rodents [8]. However, clinical evidence remains limited. Bhardwaj S et al., (2020) showed that UDCA with PT led to faster bilirubin decline than PT alone [3]. Honar N et al., (2016) found that UDCA reduced PT duration by 24 hours [5], while Hasan AM et al., (2015) reported significant reductions in TSB levels and hospitalisation [4]. Large-scale trials are needed to confirm UDCA's efficacy and safety before routine use.

Given PT limitations, the risks of prolonged bilirubin exposure, and the economic burden of extended hospital stays, an effective adjuvant therapy is necessary. UDCA's potential cost-effectiveness and non invasiveness make it a promising candidate.

Hence, the present study was conducted to assess UDCA's role in term neonates with UH receiving PT, evaluating its impact on bilirubin reduction, PT duration, and hospitalisation, particularly in resource-limited settings where advanced PT and exchange transfusion may be inaccessible.

MATERIALS AND METHODS

The present prospective interventional study was conducted at the Level 3 NICU of Shri BM Patil Medical College, Hospital and Research Institute, Vijayapura, Karnataka, India, over a period of one year, from January 2024 to January 2025. The study was approved by the Institutional Ethics Committee (ref. no.: BLDE(DU)/IEC/963/2022-23). It adhered to the Declaration of Helsinki guidelines, with informed parental consent obtained.

Inclusion criteria: Full-term neonates (>37 weeks gestation), birth weight >2 kg, clinically stable, diagnosed with UCHB (TSB>13 mg/dL requiring PT as per AAP guidelines [6]) were included.

Exclusion criteria: Neonates with congenital anomalies, systemic sepsis, metabolic disorders, haemolytic disease, or direct hyperbilirubinemia (>20% of TSB) were excluded.

Sample size calculation: A total of 100 neonates (50 per group) were enrolled, determined using G*Power 3.1.9.4 with power 80% and a 5% level of significance, based on Hasan AM et al., [4].

Randomisation was performed using a computer-generated allocation sequence created with random-number software.

Study Procedure

Participants were assigned to either the intervention (UDCA+PT) or control (PT only) group in a 1:1 ratio.

UDCA+Phototherapy (PT) group: Received oral UDCA (10 mg/kg/day) with standard PT.

Control group: Received standard PT alone.

Term neonates on exclusive breastfeeding with TSB>13 mg/dL were treated with double-surface Light-emitting Diode (LED) phototherapy. UDCA (10 mg/kg/day for 2 days) was administered orally or via nasogastric tube with breast milk or sterile water. Phototherapy was administered per AAP guidelines [6], with TSB monitored every 24 hours until levels fell below 10 mg/dL. Exchange transfusion was to be considered if bilirubin exceeded critical thresholds. Collected data included birth weight, gestational age, Appearance, Pulse, Grimace, Activity, and Respiration (APGAR) scores, bilirubin levels (baseline and serial measurements), PT duration, hydration status, and adverse effects (diarrhoea, vomiting).

STATISTICAL ANALYSIS

Statistical Packages of Social Sciences (SPSS) version 20.0 was used to analyse the data. The independent samples t-test or Mann-Whitney U test was used to compare continuous data, and the Chi-square test or Fisher's-exact's test was used to assess categorical variables. A p-value <0.05 was considered significant.

RESULTS

There is no significant differences in gestational age, birth weight, APGAR scores, gender distribution, or maternal blood group between the two groups (p>0.05) has been depicted in [Table/Fig-1]. The comparable baseline characteristics ensure homogeneity of the study population, strengthening the reliability of outcome analysis.

Clinical parameters such as heart rate, respiratory rate, oxygen saturation, and capillary refill time showed no statistically significant differences between the groups (p>0.05), indicating comparable physiological status at admission [Table/Fig-2].

The mean TSB and UCB levels were compared over different time points between the two groups. TSB and UCB were compared in both groups (UDCA+PT and PT alone) at admission, 24 hours, and 48 hours; the results showed no statistically significant differences (p>0.05) [Table/Fig-3].

The duration of PT was shorter in the UDCA+PT group; however, the differences in PT duration and NICU stay were not statistically significant [Table/Fig-4].

Parameters	UDCA+Phototherapy group (n=50) (case)	Phototherapy-only group (n=50) (control)	p-value
Gestational age (weeks)	38.4±1.2	38.2±1.3	0.412
Birth weight (kg)	2.79±0.43	2.76±0.4	0.528
Mode of delivery (NVD/LSCS/Elective LSCS)	11/36/03	08/42/00	0.763
APGAR score at birth	8±0.0	8±00	0.621
APGAR score at 5 min	9±0.0	9±0.0	0.654
Neonatal gender (M/F)	24/26	31/19	0.734
Maternal blood group A/B/O/ AB	17/13/18/02	18/17/13/02	0.834

[Table/Fig-1]: Baseline characteristics of both groups.
NVD: Normal vaginal delivery; LSCS: Lower segment caesarean section

Parameters	UDCA+Phototherapy group (n=50) (case)	Phototherapy-only group (n=50) (control)	p-value
Heart rate (bpm)	142±9	143±8	0.621
Respiratory rate (breaths/min)	51±6	50±5	0.543
Capillary filling time (sec)	2.3±0.4	2.4±0.5	0.698
SpO_2 right upper limb (%)	98.5±1.2	98.3±1.4	0.814
SpO_2 left lower limb (%)	97.8±1.3	97.6±1.5	0.792

[Table/Fig-2]: Clinical parameters of both groups at admission.
Clinical parameters such as heart rate, respiratory rate, oxygen saturation, and capillary filling time, showed no statistically significant differences between the groups (p>0.05), thereby indicating comparable physiological status at the time of admission [Table/Fig-2].

Time point	UDCA+Phototherapy group (n=50) (case)	Phototherapy-only group (n=50) (control)	p-value
TSB at admission	18.2±3.12	18.42±2.4	0.693
TSB at 24 hours	13.1± 2.25	13.9±2.19	0.07
TSB at 48 hours	9 .3± 1.75	9.8±1.9	0.175
UCB at admission	17.83±2.92	18.12±0.4	0.488
UCB at 24 hours	12.9±2.0	13.6±2.12	0.092
UCB at 48 hours	9.08±1.7	9.73±1.9	0.074

[Table/Fig-3]: Serum bilirubin levels (in mg/dL) of both groups at different intervals.

Parameters	UDCA+Phototherapy group	Phototherapy-only group	p-value
Duration of PT (hours)	47.84±2.5	48.22±5.5	0.66
NICU stay (days)	3.02±0.24	3.0±0.2	0.651

[Table/Fig-4]: Impact on PT and NICU stay.

There were no adverse effects such as diarrhoea or abdominal distension; only three cases had vomiting in the UDCA+PT group.

DISCUSSION

The present study compared UDCA+PT versus PT alone in term neonates. Baseline characteristics, including gestational age (38.4±1.2 vs. 38.2±1.3 weeks) and birth weight (2.79±0.43 vs. 2.76±0.40 kg), were similar (p>0.05). Findings align with Bhardwaj S et al., (2020) and Honar N et al., (2016), who also reported no significant pretreatment differences [3,5]. Vital signs at admission included heart rate (142±9 vs. 143±8 bpm, p=0.621) and respiratory rate (51±6 vs. 50±5 breaths/min, p=0.543). Our findings are consistent with Hasan AM et al., (2015) [4], indicating that UDCA does not impact early clinical stability.

Serial bilirubin measurements indicated a modest reduction in UCB levels in the UDCA+PT group compared to the PT alone group. At admission, UCB levels were 18.2±3.12 mg/dL in the UDCA+PT group versus 18.42±2.40 mg/dL in the PT group (p=0.693). At 24 hours, the levels were 13.1±2.25 mg/dL in the UDCA+PT group versus 13.9±2.19 mg/dL in the PT group (p=0.07). At 48 hours, UCB levels decreased to 9.3±1.75 mg/dL in the UDCA+PT group versus 9.8±1.90 mg/dL in the PT group (p=0.175).

The PT duration (47.84±2.5 vs 48.22±5.5 hours, p=0.66) and NICU stay (3.02±0.24 vs 3.0±0.2 days, p=0.651) were similar in both groups.

In a study performed by Honar N et al., the mean total bilirubin in the intervention group was 12±1.6, 10±1.1, and 9.8±0.2 mg/dL at 12, 24, and 48 hours after the beginning of PT, respectively [5]. By contrast, these measures were 14.4±1.3, 12.5±1.4, and 10.1±1.1 mg/dL in the control group, respectively (p<0.05). The mean time required for PT to decrease bilirubin to <10 mg/dL was 15.5±6 and 44.6±13.3 hours in the case and control groups, respectively (p=0.001).

Another study by Hasan AM et al., reported that the mean TSB in group A was 11.7±1.5, 8.8±1.1, and 7.6±0.9 mg/dL at 12, 24, and 36 hours after the start of Ursodiol plus PT, while in group B these measures were 14.6±1.6, 13.2±5.8, 10.2±1.4, and 9.1±0.8 mg/dL at 12, 24, 36, and 48 hours, respectively (p<0.001). The duration of PT in groups A and B was 23.2±5.6 and 41.1±7.2 hours, respectively (p<0.001) [4].

Both of the above studies reported statistically significant reductions in bilirubin, but their groups did not have similar baseline TSB values; bilirubin levels were lower in those groups compared with controls. In our study, similar TSB ranges were observed in both groups to avoid bias.

The UDCA was well tolerated, with only three cases of mild vomiting consisting of a few milliliters of milk after the first dose, subsiding spontaneously without intervention. No severe adverse effects were noted, consistent with UDCA+PT studies by Bhardwaj S et al., (2020) and Mohammed S et al., (2020) [3,17].

Limitation(s)

The present study is a single-centre study and findings may not be generalisable to diverse healthcare settings. Confounding variables like uncontrolled factors (feeding patterns, genetic variations, maternal health) may influence outcomes.

CONCLUSION(S)

The UDCA used as an adjunct to PT in term neonates with unconjugated hyperbilirubinemia was found to be safe and well-tolerated, with only mild vomiting observed in a few cases. The mean reduction in TSB at 24 and 48 hours was slightly higher in the UDCA group compared with the PT-only group, but this difference was not statistically significant. Similarly, no significant differences were observed in PT duration or NICU stay. However, the trend toward faster bilirubin decline and reduced PT duration suggests a potential clinical advantage that warrants further investigation. Future studies with larger sample sizes, diverse populations, and longer follow-up periods are recommended to validate these findings and determine the optimal clinical utility of UDCA in neonatal jaundice management.

REFERENCES

[1] Maisel MJ. Neonatal jaundice. Pediatr Rev. 2006;27(12):443-53.
[2] Hameed NN, Vilms R, Bhutani VK. Severe neonatal hyperbilirubinemia and adverse short-term consequences in Baghdad, Iraq. Neonatology. 2011;100(1):57-63.
[3] Bhardwaj S, Gupta S, Jagrwal S, Meena M. Effect of oral ursodeoxycholic acid on indirect hyperbilirubinemia in neonates treated with phototherapy at a tertiary care centre, Jaipur. Eur J Mol Clin Med. 2020;7(11):5738-47.
[4] Hasan AM, Abdulrahman A, Husain RH. Effect of ursodeoxycholic acid in lowering neonatal indirect hyperbilirubinemia: A randomized controlled trial. Merit Res J Med Med Sci. 2015;3(9):402-05.
[5] Honar N, Saadi EG, Saki F, Pishva N, Shakibazad N, Teshnizi SH. Effect of ursodeoxycholic acid on indirect hyperbilirubinemia in neonates treated with phototherapy. J Pediatr Gastroenterol Nutr. 2016;62(1):97-100.
[6] American Academy of Pediatrics Subcommittee on Hyperbilirubinemia. Management of hyperbilirubinemia in the newborn infant 35 or more weeks of gestation. Pediatrics. 2004;114(1):297-316. Doi: 10.1542/peds.114.1.297.
[7] Cuperus FJ, Hafkamp AM, Havinga R, Vitek L, Zelenka J, Tiribelli C, et al. Effective treatment of unconjugated hyperbilirubinemia with oral bile salts in Gunn rats. Gastroenterology. 2009;136(2):673-82.e1.
[8] Mendez-Sanchez N, Brink MA, Paigen B, Carey MC. Ursodeoxycholic acid and cholesterol induce enterohepatic cycling of bilirubin in rodents. Gastroenterology. 1998;115(3):722-32.
[9] Hansen TW. The epidemiology of neonatal jaundice. Pediatr Med. 2021;4:18.
[10] Kaplan M, Muraca M, Hammerman C, et al. Imbalance between pro-oxidant and anti-oxidant mechanisms in newborns: The basis for pharmacologic strategies. Semin Perinatol. 2014;38(6):425-32.
[11] Bhutani VK, Stark AR, Lazzeroni LC, Poland R, Gourley GR, Kazmierczak S, et al. Predischarge screening for severe neonatal hyperbilirubinemia identifies infants at risk for adverse outcomes. J Pediatr. 2013;162(3):477-82.e1.
[12] Shapiro SM. Definition of the clinical spectrum of kernicterus and bilirubin-induced neurologic dysfunction (BIND). J Perinatol. 2003;23(5):368-69.
[13] Maisels MJ, Bhutani VK, Bogen D, Newman TB, Stark AR, Watchko JF. Hyperbilirubinemia in the newborn infant ≥35 weeks' gestation: An update with clarifications. Pediatrics. 2019;124(4):1193-98.
[14] Hansen TW. Pathophysiology of neonatal jaundice. Clin Perinatol. 2011;38(3):643-59.
[15] Beuers U, Bilir BM, Newton J, et al. Molecular pathogenesis of bile acid-induced hepatocyte injury. J Hepatol. 2020;72(4):746-63.
[16] Watchko JF, Tiribelli C. Bilirubin-induced neurologic damage – mechanisms and management approaches. N Engl J Med. 2013;369(21):2021-30.
[17] Mohammed S, Bashir T, Saeed H, Khan Y. The safety profile of ursodeoxycholic acid in neonatal jaundice: A cohort study. J Trop Pediatr. 2020;66(2):175-81.

PARTICULARS OF CONTRIBUTORS:
1. Postgraduate Student, Department of Paediatrics, BLDE Medical College and Research Institute, Vijayapura, Karnataka, India.
2. Assistant Professor, Department of Paediatrics, BLDE Medical College and Research Institute, Vijayapura, Karnataka, India.
3. Professor, Department of Paediatrics, BLDE Medical College and Research Institute, Vijayapura, Karnataka, India.
4. Professor and Head, Department of Paediatrics, BLDE Medical College and Research Institute, Vijayapura, Karnataka, India.

NAME, ADDRESS, E-MAIL ID OF THE CORRESPONDING AUTHOR:
Dr. Raghavendra H Gobbur,
Professor, Department of Paediatrics, BLDE Medical College and Research Institute, Vijayapura-586103, Karnataka, India.
E-mail: rhgobbur@gmail.com

PLAGIARISM CHECKING METHODS: [Jain H et al.]
- Plagiarism X-checker: May 13, 2025
- Manual Googling: Aug 05, 2025
- iThenticate Software: Aug 07, 2025 (10%)

ETYMOLOGY: Author Origin

EMENDATIONS: 7

AUTHOR DECLARATION:
- Financial or Other Competing Interests: None
- Was Ethics Committee Approval obtained for this study? Yes
- Was informed consent obtained from the subjects involved in the study? Yes
- For any images presented appropriate consent has been obtained from the subjects. NA

Date of Submission: **May 12, 2025**
Date of Peer Review: **Jun 26, 2025**
Date of Acceptance: **Aug 09, 2025**
Date of Publishing: **Dec 01, 2025**