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Research Paper

Effect of Ursodeoxycholic Acid in Lowering Neonatal Indirect Hyperbilirubinemia

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ABSTRACT:

BACKGROUND:

Neonatal hyperbilirubinemia is one of the most frequent conditions in newborns. Around 60% of term and nearly 80% of preterm infants show visible jaundice during the first postnatal week.

OBJECTIVE:

This study evaluated whether adding ursodeoxycholic acid (UDCA) to conventional phototherapy accelerates the decline of indirect bilirubin in neonates.

PATIENTS AND METHODS:

A randomized controlled trial was carried out in the Neonatal Care Unit at Sulaimani Pediatric Teaching Hospital between February 2014 and February 2015. Two hundred neonates with indirect hyperbilirubinemia were enrolled and randomly assigned to:
-**Group A** (n=100): Oral UDCA 10 mg/kg/day in two divided doses plus phototherapy.
- **Group B** (n=100): Phototherapy alone.

Randomization used a computer-generated block sequence (block size 4). Allocation was concealed in sealed opaque envelopes. Outcome assessors were blinded.

RESULTS:

In Group A, mean total bilirubin declined to 11.7 ± 1.5, 8.8 ± 1.1, and 7.6 ± 0.9 mg/dL at 12, 24, and 36 hours, respectively. In Group B, bilirubin fell more slowly: 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. The average phototherapy duration was 23.2 ± 5.6 hours in Group A versus 41.1 ± 7.2 hours in Group B.

CONCLUSION:

The addition of UDCA to phototherapy significantly hastened bilirubin reduction and shortened treatment duration by 17.9 hours compared with phototherapy alone.

KEYWORDS: Neonatal jaundice, Indirect hyperbilirubinemia, Phototherapy, Ursodeoxycholic acid.

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Iraqi Postgraduate Medical Journal, 2026; Vol.25 (2): 219-224
DOI: 10.52573/ipmj.2025.164374 *Received: August 27, 2024* *Accepted: September 9, 2024*

INTRODUCTION:

jaundice, caused by increased serum bilirubin, presents as a yellowish discoloration of the skin and sclera and is among the most common clinical findings in newborns. It occurs in about 60% of full-term and up to 80% of preterm infants during the first postnatal week[1]. Although usually benign, excessive bilirubin may lead to bilirubin-induced neurological dysfunction, such as acute encephalopathy and kernicterus, which can cause lasting developmental impairment if untreated [2]. Phototherapy remains the primary treatment for unconjugated hyperbilirubinemia. It converts bilirubin into water-soluble photoisomers that are more readily eliminated [3]. In severe or unresponsive cases, exchange transfusion may be needed, though this procedure is invasive and associated with significant risks [4]. While phototherapy is effective, it often requires prolonged hospitalization, contributing to parental stress and increasing healthcare costs [5]. Therefore, investigators have explored adjuvant pharmacological therapies to enhance bilirubin clearance and shorten therapy duration. Agents such as metalloporphyrins, phenobarbital, clofibrate, activated charcoal, and bile salts have been studied, but none have gained widespread acceptance for routine neonatal care [6]. Ursodeoxycholic acid (UDCA), a hydrophilic bile acid commonly used in cholestatic liver disease, enhances bile flow, reduces intestinal bilirubin reabsorption, and has hepatoprotective properties [7,8]. These effects make it a potential adjunct in treating neonatal jaundice. Several randomized trials have suggested that UDCA may accelerate bilirubin decline and reduce phototherapy requirements. Studies from Turkey and India published in 2020 showed favorable outcomes [9,10], and meta-analyses in 2022 supported these findings, although they rated the overall quality of evidence as low due to variability among trials [11,12]. Recent mechanistic reports (2024) also highlight UDCA's potential in reducing enterohepatic circulation and protecting hepatocytes[13]. However, not all evidence is supportive. A double-blind RCT in 2025 by ZadKarami et al. found no significant difference between UDCA and placebo [14].

According to the 2022 American Academy of Pediatrics (AAP) guideline, phototherapy remains the first-line intervention, with escalation to intensive phototherapy, IV fluids, IVIG for isoimmune hemolysis, or exchange transfusion when necessary [23]. UDCA is not part of these recommendations and is still considered investigational.

Given these uncertainties, integrating recent trial data with established guidelines is important to clarify UDCA's potential role in the modern management of neonatal hyperbilirubinemia.

PATIENTS AND METHODS:

This randomized controlled trial was conducted at the "Neonatal Care Unit of Sulaimani Pediatric Teaching Hospital" between February 2014 and February 2015. A total of 200 term neonates with indirect hyperbilirubinemia were enrolled.

Study Groups:

- Group A (n=100): Received oral ursodeoxycholic acid (UDCA) at 10 mg/kg/day in two divided doses in addition to standard phototherapy.
- Group B (n=100): Received phototherapy alone.

Randomization and Allocation:

Participants were randomized using a computer-generated sequence with blocks of four to ensure balanced group sizes. Group assignments were concealed in sequentially numbered, sealed opaque envelopes prepared by an independent staff member not involved in patient care. Envelopes were opened only after confirmation of eligibility.

Because placebo phototherapy was not feasible, the trial was open-label. However, bilirubin measurement and outcome evaluation were performed by laboratory staff who were blinded to group assignment. Phototherapy was delivered according to standardized protocols to minimize bias.

Sample Size:

Based on an expected moderate effect size (0.5), significance level ($\alpha=0.05$), and power (80%, $\beta=0.2$), a minimum of 86 neonates per group was required. To account for possible dropouts (15%), the final sample size was increased to 200.

Eligibility Criteria:

Inclusion criteria:

- Term neonates, 3–8 days old.
- Birth weight 2.5–4 kg.
- Exclusively breastfed.
- Total serum bilirubin 14–20 mg/dL
- - Direct bilirubin <2 mg/dL.

Exclusion criteria:

- - ABO or Rh incompatibility.
- - Prematurity.
- - Neonatal sepsis.
- - Infants of diabetic mothers.
- - Direct hyperbilirubinemia.

Study Procedures:

All neonates underwent detailed history taking (birth weight, age of jaundice onset, family history), full physical examination, and laboratory testing, including CBC, blood group and Rh typing, and total and direct bilirubin. Bilirubin was measured from heel-prick samples using the micro-method. Phototherapy lamps were placed 20 cm from the infant, with a maximum bulb half-life of 250 hours.

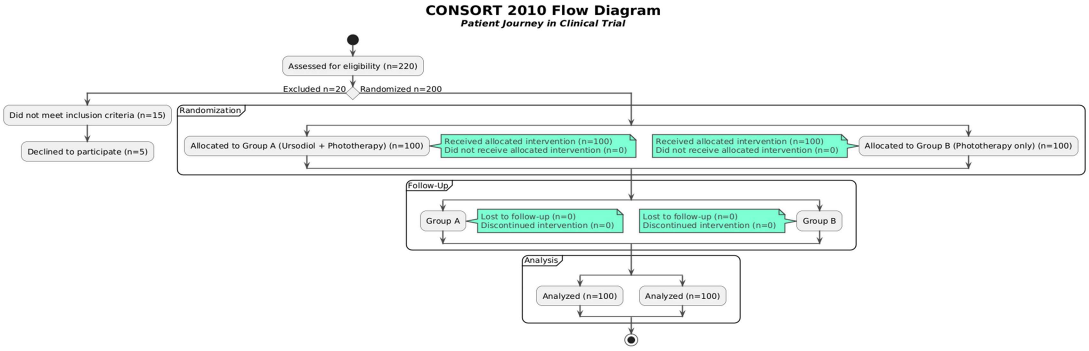
Ethics:

Approval was obtained from the Iraqi Board for Medical Specialization and the Institutional Review Board of Sulaimani Pediatric Teaching Hospital (Approval No: 28-3/2014). Informed parental consent was obtained in the local language.

Statistical Analysis:

Data were analyzed using SPSS v20. Repeated measures ANOVA compared bilirubin levels between groups, with Bonferroni correction for multiple comparisons. Both intention-to-treat and per-protocol analyses were conducted. Confidence intervals and effect sizes (Cohen's d) were reported, and $p < 0.05$ was considered statistically significant.

RESULTS:



Baseline Characteristics:

No significant differences were observed between groups regarding age, weight, sex, gestational age, delivery mode, or feeding status. “All baseline comparisons were non-significant ($p>0.05$ for all variables).”

Table 1: Differences regarding age, weight, sex, gestational age, delivery mode, or feeding status

Characteristic	Group A (Mean ± SD / n%)	Group B (Mean ± SD / n%)	P-value
Age (days)	5.4 ± 1.4	5.3 ± 1.5	0.886
Weight (kg)	3.2 ± 0.4	3.1 ± 0.4	0.287
Male	56 (56%)	51 (51%)	0.471
Female	44 (44%)	49 (49%)	
Gestational Age	38.6 ± 1.1	38.7 ± 1.2	0.732
Delivery Mode (Vaginal)	70 (70%)	68 (68%)	0.76
Feeding (Exclusive BF)	100 (100%)	100 (100%)	-

Table 2: Total Serum Bilirubin (TSB).

Time Point	Group A (Mean ± SD)	Group B (Mean ± SD)	Mean Difference (95% CI)	P-value	Cohen’s d
On admission	16.3 ± 1.7	16.5 ± 2.9	-0.2 (-1.1, 0.7)	0.852	0.09
12 hours	11.7 ± 1.5	14.6 ± 1.6	-2.9 (-3.5, -2.3)	0.001*	1.9
24 hours	8.8 ± 1.1	13.2 ± 5.8	-4.4 (-5.5, -3.3)	0.001*	1.7
36 hours	7.6 ± 0.9 (n=8)	10.2 ± 1.4 (n=93)	-2.6 (-3.5, -1.7)	-	-
48 hours	0 (n=0)	9.1 ± 0.8 (n=49)	-	-	-

Table 3: Duration of Phototherapy.

Group	Duration (hours, Mean ± SD)	P-value	95% CI	Cohen’s d
Group A	23.2 ± 5.6	0.001*	-21.2, -16.5	2.5
Group B	41.1 ± 7.2			

Adverse events:

No side effects such as diarrhea, vomiting, or intolerance were observed in the UDCA-treated group. Safety monitoring confirmed no complications during hospitalization.,No clinically significant changes in liver enzymes were observed between baseline and discharge.

DISCUSSION:

Physiological jaundice is almost universal in healthy term neonates, with serum bilirubin levels usually peaking by the second or third day of life [15]. In contrast, the mean age at admission in our study was 5.4 ± 1.4 days in Group A and 5.3 ± 1.5 days in Group B, which is relatively late and consistent with findings by Al-Gabban et al. [16]. This delay may reflect local patterns of healthcare access or cultural practices that influence when families seek medical care.

Male neonates were slightly more affected than females (56% in Group A vs. 51% in Group B). This observation is consistent with prior reports showing male gender as a risk factor for hyperbilirubinemia. Al-Shujairy (2001) reported a male-to-female ratio of 1.43:1 [17], while

Jennifer A. et al. (2005) demonstrated significantly higher bilirubin levels in males than females ($P < 0.001$) [18]. Such differences may be attributed to increased prematurity rates or sex-related variations in bilirubin metabolism.

Our findings show that UDCA, when combined with phototherapy, significantly reduced bilirubin levels at 12, 24, 36, and 48 hours, and shortened phototherapy duration by approximately 18 hours compared with phototherapy alone ($P < 0.05$). Importantly, this magnitude of reduction is clinically relevant, as it corresponds to nearly three-quarters of a day less hospitalization.

Comparison with prior literature demonstrates consistency with several randomized controlled trials. Yilmaz et al. (2020) and Sharma et al. (2020) both reported accelerated bilirubin clearance and reduced phototherapy duration in neonates receiving UDCA alongside phototherapy [9,10]. Zarkesh et al. (2023) confirmed similar findings in Iran, concluding that UDCA effectively reduced both serum bilirubin and hospital stay [20].

Recent meta-analyses further support these observations. Wang et al. (2022) found that UDCA significantly accelerated bilirubin clearance and shortened phototherapy, though the overall evidence quality was low due to study heterogeneity [11]. Li et al. (2022), analyzing 1,116 neonates across eight studies, demonstrated a reduction in phototherapy duration of 18–24 hours [12]. Glen et al. (2022) also concluded that UDCA may represent a novel adjuvant therapy [21]. Taken together, these findings suggest a consistent effect size of approximately one day less phototherapy across diverse settings.

However, conflicting evidence cannot be ignored. Kuitunen et al. (2022) identified only low-quality evidence for UDCA, emphasizing the need for confirmatory trials [22]. Most importantly, a rigorously designed, multicenter, ‘’double-blind trial by ZadKarami et al. (2025) found no significant benefit of UDCA over placebo [14]. Differences in study design,sample size(60 neonates;30 UDCA vs 30 placebo) , and the lower UDCA dose (5mg/kg/day) may contribute to the divergent results’’. This highlights the urgent need for well-powered multicenter studies with standardized protocols before UDCA can be recommended for routine clinical use.

The pharmacological basis for UDCA provides biological plausibility. UDCA reduces intestinal reabsorption of bilirubin by interrupting enterohepatic circulation, stimulates bile flow, and exerts hepatoprotective and cytoprotective effects [13]. Neuroprotective benefits have also been suggested, which could be important for preventing bilirubin-induced neurologic dysfunction.

From a safety perspective, all neonates in our study underwent structured monitoring every six hours, including vital signs, gastrointestinal tolerance, and bilirubin levels. Liver function was checked at baseline and at discharge,No clinically significant changes in liver enzymes were observed. UDCA was compounded in the hospital pharmacy under sterile conditions, stored at room temperature, and dispensed after dose verification using (mL/kg) Each 300 mg Ursodiol capsule was reconstituted in 60 mL of sterile water,and the calculated volume was administered orally to the neonates. Compliance was ensured through nursing logs that documented administration times. No adverse events were reported. While this suggests short-term safety, the lack of systematic long-term safety data—especially regarding neurodevelopment—remains a limitation. Previous reports have generally shown good short-term tolerance of UDCA, but larger follow-up studies are required to confirm long-term safety.

The implications of our findings are clinically relevant. A consistent reduction of 18hours in phototherapy duration translates into shorter hospital stays, decreased risk of phototherapy-related complications (e.g., dehydration, skin rash, parental anxiety), and potential cost savings for healthcare systems. However, without strong confirmatory evidence and given the absence of UDCA in the 2022 American Academy of Pediatrics (AAP) guidelines [23], UDCA should currently be considered only as an investigational adjuvant rather than routine therapy.

Our study has strengths, including its randomized design, standardized phototherapy protocols, and close monitoring. Nonetheless, limitations must be acknowledged: single-center design, relatively small sample size, absence of long-term follow-up, and potential selection bias.because treating clinicians and parents were not blinded ,performance bias cannot be completely excluded. Furthermore, the optimal UDCA dosing regimen remains undefined. These limitations restrict the generalizability of our findings.

CONCLUSION:

This randomized controlled trial indicates that UDCA, when combined with phototherapy, accelerates bilirubin decline and reduces treatment duration by about 18 hours compared to phototherapy alone. These results align with several clinical trials and meta-analyses, although they contrast with the negative findings of a more recent RCT [14]. However UDCA is not currently recommended in major guidelines. Given the conflicting evidence and the fact that UDCA is not currently part of AAP guideline recommendations [23], its use should remain experimental until supported by larger, multicenter studies with long-term safety data.

Future Directions

1. Larger multicenter RCTs are needed to confirm both efficacy and safety of UDCA in neonatal jaundice.
2. Optimal dosing regimens must be standardized to ensure comparability across studies.
3. Long-term follow-up of treated infants is essential to assess neurodevelopmental outcomes and safety beyond the neonatal period.
4. Economic evaluations should be conducted to quantify cost savings and resource utilization associated with reduced hospital stay.
5. Subgroup analyses (e.g., preterm vs. term neonates, hemolytic vs. non-hemolytic jaundice) could help identify populations most likely to benefit. Until such evidence emerges, UDCA should be reserved for research settings rather than routine practice.

AKNOWLEDGMENT:

I wish to express my sincere appreciation to my supervisor , Professor Dr.Adnan M. Hasan ,for suggesting this work and for his valuable advice throughout the study and thesis writing. I also extend special thanks to the staff of the Neonatal Care Unit and Laboratory Department of Sulaimani Pediatrics Teaching Hospital ,as well as my colleagues and the nursing staff for their support in completing of the thesis..

Conflict of interest statement: “The authors declare no conflict of interest.”

Authors’ contribution:

Author 1: data collection, drafting, statistical analysis

Author 2: study design ,supervision, writing review, approval

Funding: This research did not receive any specific grant from funding agencies in the public, commercial or not-for-profit sectors.

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