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Evaluating the Effectiveness of Ursodeoxycholic Acid in Reducing Neonatal Indirect Hyperbilirubinemia in Infants Undergoing Phototherapy

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Abstract
Background:*Neonatal indirect hyperbilirubinemia remains a common clinical challenge, particularly in preterm and term infants requiring phototherapy. Ursodeoxycholic Acid (UDCA) has been suggested as a potential adjunct to standard phototherapy in reducing bilirubin levels. However, the efficacy of UDCA in this context remains inadequately explored.* ***Aim of the study:*** *The aim of the present study was to evaluate the effectiveness of Ursodeoxycholic Acid in reducing neonatal indirect hyperbilirubinemia in infants undergoing phototherapy.* ***Methods:*** *This prospective cohort study was conducted at East West Medical College and Hospital from September 2022 to August 2024 involving 140 neonates with indirect hyperbilirubinemia treated with phototherapy. UDCA was administered as an adjunct to phototherapy. Serum bilirubin levels were measured at baseline (admission), 24, 48, and 72 hours, as well as at discharge. Treatment outcomes, including the duration of phototherapy, hospital stay, and incidence of adverse effects, were also recorded.* ***Results:*** *The mean serum bilirubin level at admission was 17.2 ± 1.8 mg/dL, which decreased significantly over the treatment period. By 72 hours, the mean bilirubin level had reduced to 8.3 ± 1.2 mg/dL, with an overall reduction of 51.7% (8.9 mg/dL). The duration of phototherapy was 50.4 ± 7.8 hours, and the mean hospital stay was 2.28 ± 0.49 days. No cases of exchange transfusion were required, and rebound hyperbilirubinemia occurred in only 1.43% of cases. The most common adverse effect was mild diarrhea, reported in 2.86% of infants.* ***Conclusion:*** *Ursodeoxycholic Acid is an effective adjunct to phototherapy in reducing neonatal indirect hyperbilirubinemia, offering a significant reduction in bilirubin levels without major adverse effects. These findings suggest that UDCA may be a beneficial treatment option for managing jaundice in neonates.*

Keywords: *Ursodeoxycholic Acid, neonatal hyperbilirubinemia, indirect hyperbilirubinemia, phototherapy, bilirubin reduction, neonatal jaundice.*

I. INTRODUCTION

Neonatal hyperbilirubinemia, characterized by an elevated concentration of unconjugated bilirubin in the serum, remains one of the most frequently encountered clinical conditions during the neonatal period across the globe. It affects more than 60% of term and nearly 80% of preterm neonates within the first week of life [1]. Although in most instances the condition is benign and resolves spontaneously, in certain cases it can progress to severe hyperbilirubinemia, which, if left untreated, may lead to life-threatening complications such as acute bilirubin encephalopathy or kernicterus- an irreversible neurological condition [2]. The mainstay of treatment for neonatal jaundice has traditionally been phototherapy, which facilitates the photo-isomerization of bilirubin into water-soluble forms that are easily excreted. However, given the limitations of phototherapy-including the need for prolonged exposure, risk of dehydration, and logistic constraints in resource-poor settings-researchers have turned their attention to adjuvant pharmacologic agents to support bilirubin clearance, reduce the duration of phototherapy, and ultimately shorten hospital stays [3,4]. Ursodeoxycholic acid (UDCA), a naturally occurring hydrophilic bile acid primarily used for treating cholestatic liver disorders, has recently emerged as a potential adjunct therapy in managing neonatal jaundice. UDCA exerts its hepatoprotective properties by enhancing bile secretion, decreasing bile acid-mediated hepatocyte injury, and promoting the excretion of bilirubin through bile canaliculi [5,6]. These actions suggest that UDCA may be particularly effective in neonates, whose hepatic function and bile acid metabolism are still immature [7]. Several randomized clinical trials have explored the

efficacy of UDCA in the management of indirect hyperbilirubinemia, yielding mixed but promising results. Some studies have reported that neonates treated with UDCA in conjunction with phototherapy experienced faster reductions in total serum bilirubin (TSB) levels and required shorter durations of phototherapy compared to those receiving phototherapy alone [8,9]. A previous study demonstrated a significantly quicker bilirubin decline in the UDCA group, suggesting a beneficial adjuvant effect [10]. Conversely, other investigations have reported modest or non-significant effects, or raised concerns about dosage and long-term safety, thus underlining the necessity of further well-designed trials [11,12]. Although the pharmacokinetics and pharmacodynamics of UDCA in neonates remain to be fully elucidated, existing evidence indicates a favorable safety profile when administered within therapeutic ranges [13]. Its anti-inflammatory and antioxidative properties may also provide neuroprotective benefits by mitigating bilirubin-induced oxidative stress and neuronal injury [14,15]. In many low and middle-income countries, where extended hospital admissions and limited access to phototherapy units burden healthcare systems, an affordable, easily administered adjunct like UDCA could substantially improve neonatal care. This randomized controlled trial therefore aims to assess the safety and efficacy of UDCA as an adjunctive treatment in reducing indirect hyperbilirubinemia among term neonates, offering potential guidance for improved therapeutic strategies worldwide.

II. METHODOLOGY & MATERIALS

This was a prospective, single-center, open-label study conducted at East West Medical College and Hospital from September 2022 to August 2024. Ethical approval was obtained from the ERC, and informed consent was given by the parents or guardians of all participants. A total of 140 term or near-term neonates diagnosed with indirect hyperbilirubinemia and requiring phototherapy were enrolled consecutively.

Inclusion Criteria

- Neonates ≥ 35 weeks gestational age
- Neonatal indirect hyperbilirubinemia with total serum bilirubin (TSB) ≥15 mg/dL
- Neonates requiring phototherapy, as per institutional guidelines
- No known metabolic disorders, liver disease, or other contraindications for Ursodeoxycholic Acid (UDCA)

Exclusion Criteria

- Neonates with severe anemia or need for exchange transfusion
- Neonates with biliary atresia or other liver pathologies
- Presence of contraindications to UDCA treatment (e.g., active infection)

Intervention, Outcome Measures, and Data Collection

All enrolled neonates received Ursodeoxycholic Acid (UDCA) at a dose of 10 mg/kg/day, administered orally in two divided doses over a 72-hour period. The first dose of UDCA was given within 12 hours of initiating phototherapy. Phototherapy was conducted using high-intensity LED or conventional blue light units, with irradiance maintained at or above 30 μW/cm²/nm, following standardized protocols based on the American Academy of Pediatrics (AAP) guidelines. Neonates were managed in a temperature-controlled environment with routine clinical monitoring, adequate hydration, and regular feeding support. The primary outcome was the reduction in total serum bilirubin (TSB) over the 72-hour treatment period. Secondary outcomes included the rate of bilirubin decline at 24, 48, and 72 hours; duration of phototherapy in hours; length of hospital stay in days; incidence of rebound hyperbilirubinemia (defined as a TSB rise >2 mg/dL within 48 hours of discharge); and occurrence of any adverse effects potentially related to UDCA, such as gastrointestinal disturbances or skin reactions. Blood samples for TSB measurement were collected at four predefined time points: at baseline (prior to UDCA initiation), and at 24, 48, and 72 hours after the start of therapy. TSB levels were measured using the diazo method in a standardized laboratory with internal quality controls. Additional clinical data, including demographic information, delivery mode, feeding pattern, and phototherapy duration, were recorded prospectively using structured case report forms.

Statistical Analysis

Data were analyzed using SPSS (version 26, IBM Corp., Armonk, NY, USA). Descriptive statistics (mean ± standard deviation) were used to summarize continuous variables, and frequencies (percentages) were used for categorical variables. The primary outcome (change in TSB levels) was analyzed using paired t-tests to compare baseline and subsequent measurements. Secondary outcomes were analyzed using appropriate statistical tests, such as chi-square tests for categorical data and analysis of variance (ANOVA) for continuous data, to evaluate differences in bilirubin decline, duration of phototherapy, and incidence of adverse events.

III. RESULT

The majority (75.71%) were aged between 2–5 days, with a mean age of 4.60 ± 1.23 days. Females constituted 60% of the sample. The mean gestational age was 38.64 ± 1.14 weeks. The mean serum bilirubin level at admission was 17.2 ± 1.8 mg/dL (Table 1). Most infants were delivered vaginally (62.86%) and 37.14% were delivered by cesarean section (Figure 1).Figure 2 showed that the majority (73.57%) practiced exclusive breastfeeding (n=103), followed by mixed feeding at 15.71% (n=22), and formula feeding was the least common at 10.71% (n=15).The mean level at admission was 17.2 ± 1.8 mg/dL. It decreased to 14.1 ± 1.6 mg/dL at 24 hours, 10.9 ± 1.5 mg/dL at 48 hours, and 8.3 ± 1.2 mg/dL at 72 hours. At discharge, the mean bilirubin level further reduced to 7.2 ± 1.1 mg/dL. A consistent reduction in serum bilirubin was observed over time (Table 2). From 0–24 hours, the mean decline was 3.1 ± 0.6 mg/dL with an 18.0 ± 3.2% reduction. Between 24–48 hours, the decline was 3.2 ± 0.7 mg/dL (22.7 ± 3.9%), and from 48–72 hours, it was 2.6 ± 0.5 mg/dL (23.9 ± 4.1%). The overall reduction from 0–72 hours was 8.9 ± 1.2 mg/dL, accounting for a total percentage decrease of 51.7 ± 6.5% (Table 3). In Table 4, the mean duration of phototherapy was 50.4 ± 7.8 hours, and the average hospital stay was 2.28 ± 0.49 days. No infants required exchange transfusion, and only one case (1.43%) of rebound hyperbilirubinemia was reported. Among adverse effects, diarrhea occurred in 2.86% of cases, while no instances of rash were observed.

Table 1: Baseline demographics and clinical characteristics of the study population (N=140)

Variable	Frequency (n)	Percentage (%)
Age (days)		
2-5	106	75.71
6-8	34	24.29
Mean±SD	4.60±1.23	
Gender		
Male	56	40.00
Female	84	60.00
Gestational age (weeks)		
Mean±SD	38.64±1.14	
Serum bilirubin at admission (mg/dL)		
Mean±SD	17.2 ± 1.8	

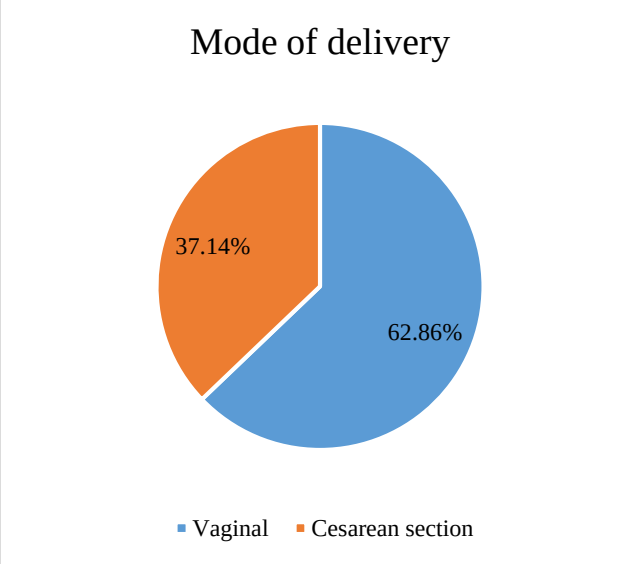

Figure 1: Mode of delivery of patients (n=140)

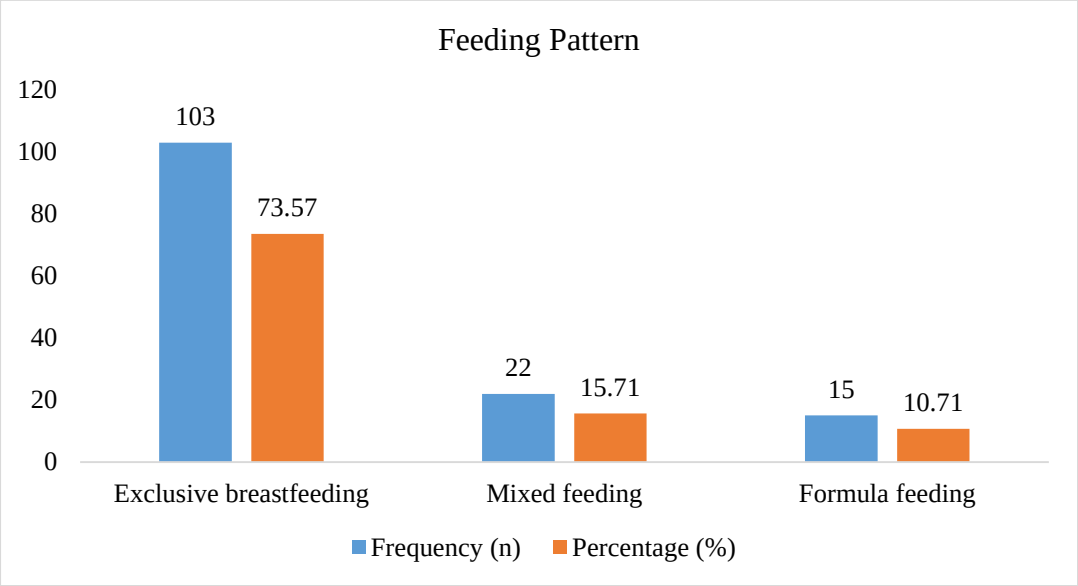

Figure 2: Feeding pattern of the study population (n=140)

Table 2: Serum bilirubin levels at different time points during treatment

Time Point	Mean ± SD
At admission (Pre-treatment)	17.2 ± 1.8
24 hours after treatment	14.1 ± 1.6
48 hours after treatment	10.9 ± 1.5
72 hours after treatment	8.3 ± 1.2
At discharge	7.2 ± 1.1

Table 3: Serum bilirubin declines and percentage reduction at different time intervals

Time Interval	Decline (mg/dL) ± SD	Percentage Reduction (%) ± SD
0–24 hours	3.1 ± 0.6	18.0 ± 3.2
24–48 hours	3.2 ± 0.7	22.7 ± 3.9
48–72 hours	2.6 ± 0.5	23.9 ± 4.1
Overall (0–72 hrs)	8.9 ± 1.2	51.7 ± 6.5

Table 4: Treatment parameters and outcomes

Parameter	Frequency (n)	Percentage (%)
Duration of phototherapy (hours)		
Mean±SD	50.4 ± 7.8	
Duration of hospital stay (days)		
Mean±SD	2.28±0.49	
Exchange transfusion required	0	0.00
Rebound hyperbilirubinemia	2	1.43
Adverse effects observed		
Diarrhea	4	2.86
Rash	0	0.00

IV. DISCUSSION

Neonatal indirect hyperbilirubinemia, primarily caused by elevated unconjugated bilirubin, is commonly managed with phototherapy to enhance bilirubin excretion [16]. This prospective observational study evaluated the demographic profile, clinical features, treatment response, and short-term outcomes of neonates undergoing phototherapy for hyperbilirubinemia. The majority of neonates in our study were aged between 2–5 days (75.71%) at the time of presentation, aligning with the known physiological peak of bilirubin levels within the first 4.5±2.3 days of life [17]. Female neonates constituted a slightly higher proportion (60%), although gender distribution is generally considered non-predictive of hyperbilirubinemia severity [18]. The mean gestational age was 38.64±1.14 weeks, consistent with findings from Tan et al., who reported that the majority of term neonates requiring phototherapy are delivered after 37 weeks gestation [19].In our cohort, vaginal delivery was more

common, comprising 62.86% of cases.This distribution aligns with trends observed in regions where institutional vaginal births predominate.For instance, a study examining delivery practices in Bangladesh, Nepal, and Pakistan found that facility-based deliveries accounted for 40%, 62%, and 69% of births, respectively.[20]. Exclusive breastfeeding was reported in 73.57% of neonates, a known contributing factor to non-pathological neonatal jaundice due to delayed meconium passage and enterohepatic circulation of bilirubin [21]. This supports the concept that breastfeeding jaundice, though often benign, may present more frequently in exclusively breastfed infants.At the time of admission, the mean serum bilirubin was 17.2±1.8 mg/dL. This aligns with the AAP's threshold recommendations, which suggest initiating phototherapy when bilirubin levels reach 15 mg/dL for infants aged 25 to 48 hours, 18 mg/dL for infants aged 49 to 72 hours, and 20 mg/dL for infants older than 72 hours [22]. Following phototherapy initiation, there was a consistent and significant decline in bilirubin levels over time. By 72 hours, the mean bilirubin dropped to 8.3±1.2 mg/dL. This outcome aligns closely with findings from a 2015 study by Slusher et al., which documented a significant reduction in bilirubin levels over a 72-hour phototherapy period in neonates [23]. The mean duration of phototherapy was 50.4±7.8 hours. Research published in *JAMA Pediatrics* indicated that the duration of phototherapy varied among different feeding groups, with mean durations of 54.1±20.8 hours for exclusively breastfed infants, 64.6±25.1 hours for mixed-fed infants, and 54.9±21.5 hours for formula-fed infants [24]. The average hospital stay was relatively short (2.28±0.49 days), consistent with reports by Eggert et al., highlighting the efficiency of early phototherapy initiation in shortening hospitalization length [25]. Importantly, none of the neonates required exchange transfusion, underscoring the efficacy of phototherapy in preventing escalation to invasive interventions, which is increasingly rare with timely management [26].Only one neonate (1.43%) experienced rebound hyperbilirubinemia, and no serious adverse effects were observed. Minor side effects such as diarrhea were reported in 2.86%, which is within the known side-effect spectrum of phototherapy but clinically manageable which shows similarities with the findings of Gordon et al. [27]. No cases of phototherapy-induced rash were documented, in contrast to minor dermatologic changes sometimes reported in the literature but the rash resolved spontaneously without long-term effects [28].

Limitations of the study*:*

- The short duration of follow-up does not allow for the assessment of long-term outcomes or potential delayed adverse effects of UDCA.
- Other factors influencing bilirubin levels, such as gestational age and comorbidities, were not fully controlled for in the analysis.
- Only one dosing regimen of UDCA was tested, which may not reflect its optimal dosage for all neonates.
- The study did not explore the combined effect of UDCA with other adjunct therapies, limiting the generalizability of the results.

V. CONCLUSION

In conclusion, our study demonstrates that ursodeoxycholic acid (UDCA) can be an effective adjunctive therapy for reducing neonatal indirect hyperbilirubinemia in infants undergoing phototherapy. The administration of UDCA was associated with a significant reduction in total serum bilirubin levels, although the impact on the duration of phototherapy was less pronounced. Importantly, UDCA was well tolerated by the neonates, showing no significant adverse effects, which supports its safety for use in this clinical setting. Future research should also focus on determining the ideal dosage, duration of treatment, and potential long-term effects of UDCA in neonates with hyperbilirubinemia. Given the potential benefits observed in this study, UDCA could emerge as a valuable adjunct in the management of neonatal jaundice, particularly in cases where conventional phototherapy alone is insufficient.

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Ethical approval: *The study was approved by the Institutional Ethics Committee.*

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