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ORIGINAL ARTICLE

# Comparison of phototherapy with ursodeoxycholic acid versus phototherapy alone in neonates with hyperbilirubinemia alone.

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**ABSTRACT... Objective:** To compare the mean duration of phototherapy in neonates with indirect hyperbilirubinemia undergoing phototherapy with ursodeoxycholic acid versus phototherapy alone. **Study Design:** Randomized Controlled Trial. **Setting:** Department of Pediatric Medicine, Allied Hospital Faisalabad. **Period:** 20th September 2023 to 19th March 2024. **Methods:** A total of 60 neonates of both genders, presenting within 3-7 days of life with Jaundice were included. Infants with ABO and Rh incompatibility, Glucose-6-phosphate dehydrogenase (G6PD) deficiency, Crigler-Najjar syndrome, Gilbert syndrome, hypothyroidism and the infants with diabetic mothers were excluded. The treatment was assigned according to the following plan – Intervention group: In addition to phototherapy, the patients in this group were administered oral ursodeoxycholic acid suspension in a dose of 30 mg/kg/day every 12 hourly. Comparison group: Patient in this group received phototherapy only. The distance between the phototherapy units and baby was kept 30 centimeters. Bilirubin estimation was done spectrophotometrically using diazo reagent by Malloy and Evelyn method until bilirubin levels fall < 10 mg/dl. Duration of phototherapy to achieve this level was noted. **Results:** The mean age of neonates was 3.89 ± 1.13 days; 58.3% were male. The mean duration of phototherapy in the UDCA group was 1.57 ± 0.68 days, significantly shorter compared with 4.40 ± 1.07 days in the phototherapy-only group. **Conclusion:** This study has shown that duration of phototherapy for bringing bilirubin < 10 mg/dl is lower in ursodeoxycholic acid group compared to phototherapy alone in term neonates with hyperbilirubinemia.

**Key words:** Neonatal Jaundice, Phototherapy, Ursodeoxycholic Acid.

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## INTRODUCTION

Neonatal jaundice is one of the most common clinical conditions encountered in the newborn period, affecting nearly 60% of term and 80% of preterm infants worldwide. It results primarily from the accumulation of unconjugated bilirubin due to increased bilirubin production and immature hepatic conjugation mechanisms in early life. Although physiological in most infants, significantly elevated serum bilirubin levels can progress to severe hyperbilirubinemia, increasing the risk of acute bilirubin encephalopathy and kernicterus[1]—conditions associated with irreversible neurological damage, cerebral palsy, sensorineural hearing loss, and even death. Early identification and effective treatment of neonatal jaundice therefore remain critical components of newborn care.

Phototherapy is the standard therapy for unconjugated hyperbilirubinemia and has substantially reduced the global burden of kernicterus. However, its use is associated with limitations, including prolonged hospitalization, interruption of breastfeeding, dehydration, temperature instability, and, in resource-limited settings, inadequate accessibility or inefficient phototherapy units[2-4] As a result, pharmacological agents that can safely enhance bilirubin clearance have been investigated. Ursodeoxycholic acid (UDCA), a hydrophilic bile acid commonly used in pediatric cholestatic disorders, has shown promise due to its choleretic, cytoprotective, and anti-oxidative properties. Several international studies have demonstrated that UDCA can augment bilirubin excretion and significantly reduce the duration of phototherapy in neonates with indirect hyperbilirubinemia.[5-6]

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Nevertheless, local evidence remains limited, particularly in South Asian populations where neonatal jaundice contributes prominently to hospital admissions and healthcare burden.

In this context, the present study was designed to evaluate the effect of adding UDCA to standard phototherapy on the duration of treatment in neonates with indirect hyperbilirubinemia. The specific objective of this study was to compare the mean duration of phototherapy in neonates receiving phototherapy with UDCA versus phototherapy alone. We hypothesized that neonates treated with UDCA in addition to phototherapy would require significantly fewer hours of phototherapy to achieve safe bilirubin levels compared with those receiving phototherapy alone.

## METHODS

This study was designed as a randomized controlled trial conducted in the Department of Pediatric Medicine, Allied Hospital, Faisalabad from 20th September 2023 to 19th March 2024.

The sample size was calculated using OpenEpi software by applying the formula for mean difference. The duration of phototherapy in the ursodeoxycholic acid group was taken as 3.0 ± 0.58 days, while in the phototherapy alone group it was 5.5 ± 1.35 days. With a power of 80% and a level of significance of 95%, the calculated sample size was 60 patients, with 30 patients allocated to each group.

A non-probability consecutive sampling technique was used for patient enrollment. Inclusion criteria consisted of neonates aged 3–7 days, of either gender, with body weight ≥2.5 kg and gestational age between 38 and 41 weeks, and total serum bilirubin levels between 12 and 22 mg/dL and direct bilirubin level <2 mg/dL. Exclusion criteria included infants with ABO and Rh incompatibility, diagnosed on history and medical record, neonates with glucose-6-phosphate dehydrogenase (G6PD) deficiency, Crigler-Najjar syndrome, Gilbert syndrome, and hypothyroidism documented in medical records were also excluded. In addition, infants born to diabetic mothers, identified through maternal history, were not included in the study.

Ethical approval for the study was obtained from the Institutional Ethical Review Committee, Faisalabad Medical University (FMU) No. 48.ERC/FMU/2022-23/296 dated 11-07-2023 in accordance with established ethical guidelines. Informed consent was obtained from parents of all participants before enrollment in the study. Patient confidentiality was strictly maintained throughout the research process, with all collected data anonymized and stored securely. Additionally, participants were assured of their right to withdraw from the study at any time without repercussions.

The study was commenced after approval from institutional ethics review committee. A total of 60 newborn infants, meeting the inclusion criteria, were enrolled in the study after informed consent of the parents. Demographic data like age (days), gender (male/ female), birth weight (kg), the family history of neonatal jaundice (yes / no) were noted. Laboratory data included total and direct bilirubin from the single laboratory.

The enrolled newborns were assigned into two groups through lottery method using sealed opaque envelopes containing group assignment slips. The treatment was assigned according to the following plan – Intervention group: In addition to phototherapy, the patients in this group were administered oral ursodeoxycholic acid suspension in a dose of 30 mg/kg/day every 12 hourly. Comparison group: Patient in this group received phototherapy only. The distance between the phototherapy units and baby was kept 30 centimeters. During phototherapy, genitalia and both eyes of infants were covered.

Every 12-hourly venous whole blood was taken from all infants and centrifuged at 10000 rpm for 10 minutes and serum thus obtained was assessed immediately for total, direct and indirect serum bilirubin levels. Bilirubin estimation was done spectrophotometrically using diazo reagent by Malloy and Evelyn method until bilirubin levels fall < 10 mg/dl. Duration of phototherapy to achieve this level was noted. All the data was recorded on proforma (attached).

The data was analyzed through SPSS version 23. Age, weight, baseline serum total bilirubin and

duration of phototherapy were presented as mean and standard deviation. Gender and the family history of neonatal jaundice were presented as frequency and percentages. Time (days) to achieve total bilirubin < 10 mg/dl (duration of phototherapy) between the two groups was compared through independent sample t-test. The data was stratified on age groups, gender, family history of neonatal jaundice, birth weight and baseline serum total bilirubin to determine the effect on duration of phototherapy between two groups. Post stratification independent sample t-test was applied and p-value ≤ 0.05 was taken as significant.

## RESULTS

A total of 60 neonates were enrolled, with 30 allocated to each study group. The mean age of the study population was 3.89 ± 1.13 days, and males comprised 58.3% of the sample. Baseline characteristics, including age and gender distribution, were comparable between the two groups (Table-I).

The primary outcome—duration of phototherapy—was significantly different between the groups. The UDCA group required a substantially shorter duration of phototherapy compared with the phototherapy-alone group. Mean duration of phototherapy in the UDCA group was 1.57 ± 0.68 days, while the comparison group required 4.40 ± 1.07 days (Table-II).

Overall, neonates receiving UDCA achieved bilirubin levels <10 mg/dL markedly earlier than those treated with phototherapy alone.

**TABLE-I**

**Baseline characteristics of study participants (N = 60)**

| Variable | Group A (n = 30) | Group B (n = 30) | Total |
|---|---|---|---|
| Mean Age (days) | 4.17 ± 1.15 | 3.83 ± 0.87 | 3.89 ± 1.13 |
| Age Group 3–4 days | 20 (66.7%) | 22 (73.3%) | 42 (70.0%) |
| Gender (Male) | 18 (60.0%) | 17 (56.7%) | 35 (58.3%) |
| Gender (Female) | 12 (40.0%) | 13 (43.3%) | 25 (41.7%) |

**TABLE-II**

**Comparison of duration of phototherapy between groups**

| Outcome | UDCA + Phototherapy (n = 30) | Phototherapy Only (n = 30) |
|---|---|---|
| Duration of Phototherapy (days), Mean ± SD | 1.57 ± 0.68 | 4.40 ± 1.07 |

**TABLE-III**

**Stratification of duration of phototherapy with respect to age groups, gender, family history of neonatal jaundice, birth weight and baseline serum total bilirubin.**

| | | Group A (n=30) | | Group B (n=30) | | P-Value |
|---|---|---|---|---|---|---|
| | | Duration of Phototherapy (Days) | | Duration of Phototherapy (Days) | | |
| | Mean | SD | Mean | SD | | |
| Age (days) | 3-4 | 1.55 | 0.82 | 4.00 | 1.08 | 0.0001 |
| | 5-7 | 1.58 | 0.61 | 4.71 | 0.99 | 0.0001 |
| Gender | Male | 1.59 | 0.62 | 4.39 | 1.20 | 0.0001 |
| | Female | 1.54 | 0.78 | 4.42 | 0.90 | 0.0001 |
| Weight (kg) | ≤3.5 | 1.60 | 0.84 | 4.41 | 1.10 | 0.0001 |
| | >3.5 | 1.55 | 0.60 | 4.38 | 1.06 | 0.0001 |
| F/h of neonatal jaundice | Yes | 2.40 | 0.55 | 3.83 | 1.33 | 0.0001 |
| | No | 1.40 | 0.58 | 4.54 | 1.98 | 0.0001 |
| Baseline bilirubin (mg/dl) | 12-16 | 1.53 | 0.52 | 4.37 | 0.96 | 0.0001 |
| | >16-22 | 1.60 | 0.83 | 4.45 | 1.29 | 0.0001 |

## DISCUSSION

I have conducted this study to compare the mean duration of phototherapy in neonates with indirect hyperbilirubinemia undergoing phototherapy with ursodeoxycholic acid versus phototherapy alone. Mean age was 3.89 ± 1.13 days. The mean age of patients in group A was 4.17 ± 1.15 days and in group B was 3.83 ± 0.87 days. Majority of the patients 42 (70.0%) were 3-4 days ears of age. Out of 60 patients, 35 (58.33%) were males and 25 (41.67%) were females with male to female ratio of 1.4:1. The mean (SD) duration of therapy were 1.57 ± 0.68 days in the group A (phototherapy with ursodeoxycholic acid) and 4.40 ± 1.07 days in the group B (phototherapy alone). Hassan AM et al enrolled 200 neonates randomly divided into two groups, group A (n=100) received Ursodiol in addition to phototherapy, while group B (n=100) received only phototherapy. It was noticed that the duration of phototherapy in group A and group B was 23.2±5.6 hours and 41.1±7.2 hours respectively (p< 0.001).[7] Ughasoro MK et al, from Nigeria, conducted a double-blind-controlled study recruiting neonates who were categorized into the experimental group (n=18, given UDCA plus phototherapy) and the control group (n=22, phototherapy and plain syrup). The mean (SD) duration of therapy were 3.0 ± 0.58 days in the experimental group and 5.5 ± 1.35 days in the control group (p=0.001).[8]

Ursodeoxycholic Acid (UDCA) is a type of hydrophilic bile acid that accounts for about 4% of bile acids in humans and is synthesized by bacterial enzymes in the gallbladder from primary bile acid chenodeoxycholic acid. During oral administration, almost half of the drug, is absorbed in the intestine and enters hepatocytes through the portal circulation. UDCA significantly reduces the secretion of cholesterol into the bile.[9] As it is more hydrophilic than other bile acids, it gradually replaces hydrophobic acids that have accumulated in the bile during cholestasis, thus facilitating bile outflow from the liver/gallbladder. It also reverses the induction of programmed cell death (apoptosis) of indirect bilirubin on hepatocytes and nerve cells[8] that is associated with the protection of brain and liver tissue against indirect bilirubin.

Phototherapy is a cheap, simple, non-invasive method with appropriate effectiveness. This treatment has side effects such as changes in circadian rhythm, dehydration, hypocalcemia, skin rash, and retinal damage.[10] Thus; it seems that applying other methods of treatment in combination with phototherapy that can reduce the duration and increase its efficacy, can be useful. The findings of this study showed that the use of oral UDCA significantly reduced the amount of total bilirubin at the time of discharge which was in line with the study by Honar et al. They conducted a double-blind randomized clinical trial on 80 neonates with jaundice. They were randomly divided into two groups of intervention (receiving 10 mg/kg/ day UDCA in addition to phototherapy), and control (receiving only phototherapy). The mean of total bilirubin in the intervention group was 12±1.6, 10±1.1, and 9.8±0.2 mg/dL 12, 24, and 48 hours after the beginning of phototherapy, respectively. On the contrary, 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 phototherapy to decrease the bilirubin level to <10 mg/dL was 15.5±6 and 44.6±13.3 hours in the case and the control group, respectively, (P=0.001).[11]

In addition, results of Jafari et al. who assessed 96 term neonates with hyperbilirubinemia indicated that oral administration of UDCA at a dose of 10 mg / kg with phototherapy significantly reduced TSB compared with the phototherapy alone. They reported the same efficacy for the dose of 10 versus 20 mg / kg of UDCA.[12] Akefi et al. performed a randomized clinical trial on 220 neonates receiving 10 mg / kg oral UDCA twice daily plus phototherapy and the control group. They found that the mean 12 hours TSB decreased by 2.70 mg / dl in the control versus 3.70 mg / dl in the intervention group. In addition, at 24 hours, the mean TSB diminished by 5.22 mg / dl in the control versus 6.54 mg / dl in the intervention group (p = 0.01).[13]

In the study by El-Gendy et al, duration of phototherapy was significantly shorter among neonates who received UDCA treatment.[14] In another study, UDCA has a beneficial effect in reducing bilirubin levels and duration of hospital admission in neonatal indirect hyperbilirubinemia. In a recent study on mice, UDCA reduces both

plasma and brain bilirubin.[15] It should remember that no adverse effect of this drug was seen in our study. The result of these studies differs from our studies. It may be due to different sample sizes or genetic backgrounds. In a previous meta-analysis by Kuitunen et al[16], they found low-quality evidence that UDCA as an adjuvant to phototherapy decreases the indirect bilirubin. Furthermore, the dose of UDCA was different between studies.[16]

The average duration of treatment for those in the experimental group was shorter than those in the control group and this has been reported by previous studies.[11-13] This may be due to the adjunctive effect of UCDA. This can be explained by the efficacy of phototherapy being proportional to the concentration of bilirubin in the skin. Therefore, as the level of bilirubin is reduced, the relative effectiveness of phototherapy is reduced. This decline in efficacy after 48 hrs can be attributed to the fact that excreted unstable bilirubin isomers (photobilirubin) that are formed revert to natural bilirubin in the intestine and are reabsorbed via the enterohepatic circulation and contribute to the bilirubin load the hepatocytes have to handle.[17] The UDCA has been shown to inhibit the enterohepatic recirculation.[18] Although phototherapy has been assumed to be an innocuous form of treatment and thus should be instituted freely and as long as the jaundice persists, the economic cost of each day spent in the hospital by both mothers and their neonates has not been evaluated. Apart from direct medical costs, other intangible costs like inconveniences, psychological exhaustion, deprived care for the elder siblings of the jaundiced neonate on treatment, etc. can be reduced if the duration of hospitalization is reduced.

A limitation of this study was lack of follow-up on these neonates to monitor for rebound bilirubin levels in both groups as well as to check for any adverse events due to the use of UDCA. However, studies have shown that the average rebound bilirubin level after phototherapy is often below 1 mg per day. Furthermore, previous studies where UDCA was used for cholestasis reported no adverse events.

## CONCLUSION

This study has shown that duration of phototherapy for bringing bilirubin < 10 mg/dl is lower in ursodeoxycholic acid group compared to phototherapy alone in term neonates with hyperbilirubinemia. So, we recommend that phototherapy with ursodeoxycholic acid should be used in order to decrease bilirubin level than phototherapy alone, as this will also reduce hospital stay, without compromising the health of neonate.

## CONFLICT OF INTEREST

The authors declare no conflict of interest.

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| 3 | **Shaiq Mahmood:** Critical review. |
| 4 | **Aamir Naseem:** Data entry. |
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