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Effect of Ursodeoxycholic Acid on Unconjugated Hyperbilirubinemia in Neonates Treated with Phototherapy; A Randomized Control Trial

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Abstract

Background: *Phototherapy is worldwide used treatment for unconjugated hyper bilirubinemia. Some adjuvants like Ursodeoxycholic acid (UDCA) have additive effect with phototherapy in neonates which may reduce the duration of phototherapy.*

Aim of the study: *This study was done to investigate the effect of UDCA on reducing the unconjugated bilirubin and duration of phototherapy.*

Methodology: *This RCT was conducted in Department of Neonatology in Mymensingh Medical College Hospital. Neonates with indirect hyper-bilirubinaemia (above phototherapy level) were enrolled and randomized into two groups: phototherapy plus UDCA (Case Group) and the phototherapy-alone (Control Group). Infants in case group received 10 mg/kg/day UDCA every 12 hours in addition to phototherapy, while the neonates in control group received only phototherapy. TSB level was monitored as per NICU protocol. Phototherapy and UDCA administration were stopped when the TSB level decreased 3 mg/dL below the phototherapy level for the age. The statistical analysis was done using SPSS. The results of the two groups will be compared and analyzed using the Chi-square and student t-tests, as applicable. A P-value less than 0.05 will be considered significant.*

Results: *In this study of 66 cases and 64 controls, postnatal ages on admission averaged 84.55±43.16 and 77.56±56.71 days, respectively (P=0.561). Gestational ages were similar (P=0.868), as were birth weights (P=0.559) and admission weights (P=0.496). ABO positivity was 36.36% in cases and 40.63% in controls (P=0.618), and Rh positivity was 3.03% in cases and 9.38% in controls (P=0.132). Pre-phototherapy total serum bilirubin (TSB) levels were not significantly different (P=0.705), but post-phototherapytotal serum bilirubin (TSB) levels at24-hour, 48-hour, and 72-hour levels showed significant differences (P=0.032, P=0.047, P=0.028, respectively). Phototherapy duration was shorter for cases (P=0). Rebound hyperbilirubinemia occurred in 4.55% of cases and 12.50% of controls (P=0.103).*

Conclusion: *Ursodeoxycholic acid as an adjuvant along with phototherapy can significantly reduce the duration of phototherapy as well as hospital stay than phototherapy alone.*

Keywords: *Ursodeoxycholic Acid, Unconjugated Hyperbilirubinemia, Neonates and Phototherapy.*

1. Introduction

Hyperbilirubinemia is a common neonatal morbidity and a major cause of hospital admission in the neonatal period. Approximately 60-70% of term and 80% of preterm infants develop jaundice in the first

week of life. The pathophysiological mechanisms that pre-dispose newborn infants to hyperbilirubinemia are 1) Increased bilirubin formation from larger RBC mass and shorter RBC lifespan, 2) Decreased hepatic uptake, 3) Impaired conjugation and excretion due to reduced UDPGT activity and 4) Increased absorption from enhanced enterohepatic circulation. Although most of these infants are healthy and will not need therapy, they need to be monitored closely because severe unconjugated hyperbilirubinemia can be potentially toxic to neurons. Most infants with increasing jaundice are treated with phototherapy when it is believed that bilirubin levels can enter the toxic range. Phototherapy reduces serum bilirubin levels by photoisomerization and photooxidation of bilirubin to an excretable form [1]. Although phototherapy is a relatively safe and widely used therapeutic method for the treatment of unconjugated hyperbilirubinemia, it is not free from disadvantages. This method of treatment has hospitalization costs, risks of nosocomial infections, interrupts mother-child bonding and interferes with the social activity of parents. Moreover, phototherapy has some potential complications like temperature instability, skin rash, fluid and electrolyte disorder, risk of retinal degenerative change etc. Therefore, using adjuvant therapies, which reduce the duration of hyperbilirubinemia and phototherapy, can be highly effective [2,3]. Up to now, several drugs, such as phenobarbital, activated charcoal, D-penicillamine, metalloporphyrin, clofibrate, and bile salts, have been used for the treatment of indirect hyperbilirubinemia [4-7]. Several studies have shown that phenobarbital therapy is effective in reducing indirect hyperbilirubinemia and decreasing the duration of phototherapy [8]. Nevertheless, it has complications, including an increase in drowsiness, reduction of breast feeding, dehydration, and neurological disorders [9]. Thus, performing studies on medications with lower complications seems to be necessary. Ursodeoxycholic acid (UDCA) is a bile acid that is widely used in the treatment of cholestatic liver disorders. It protects the liver against oxidative stress, prevents cell apoptosis, stimulates the bile flow, and suppresses the confounding factors in immunological mechanisms [10]. UDCA is well tolerated and has limited complications in the pediatric age group [11]. A study conducted on the effect of UDCA on unconjugated bilirubin (UCB) in rats showed that administration of UDCA induces a large, persistent decrease in plasma UCB concentrations in Gunn rats by increasing its fecal disposal [12]. Some recent RCTs on the effect of UDCA on indirect hyperbilirubinemia in neonates have shown that ursodeoxycholic acid had an additive effect with phototherapy in neonates with indirect hyperbilirubinemia. This drug also reduced the period needed for phototherapy and, consequently, decreased the hospitalization period [13,14]. Owing to the lack of sufficient data about the effect of UDCA on neonatal unconjugated hyperbilirubinemia in Bangladesh, the present study aimed to investigate the effect of UDCA on reducing unconjugated hyperbilirubinemia in infants undergoing phototherapy.

2. Methodology & Materials

This randomized control trial was conducted in the Department of Neonatology at Mymensingh Medical College Hospital, a tertiary care hospital in Mymensingh, Bangladesh. During one year, from May 2022 to April 2023, a total of 130 neonates with indirect hyperbilirubinemia and total serum bilirubin above the phototherapy level were enrolled in the study. On admission, enrolled newborns were randomly assigned into two groups, and the randomization was done by lottery method after collection of informed written consent from parents. Ethical clearance was obtained from the Institutional Review Board (IRB) of MMC to undertake the current study.

Case Group (N=66): Phototherapy plus UDCA

Control Group (N=64): Phototherapy-alone

Inclusion Criteria

- Term and late preterm neonates with unconjugated hyperbilirubinemia with total serum bilirubin above phototherapy level.

Exclusion Criteria

- Preterm neonates with gestational age <34 weeks.
- Sepsis.
- Sick baby.
- Neonates will be treated with exchange transfusion.

Infants in the phototherapy plus UDCA group received 10 mg/kg/day UDCA every 12 hours in addition to phototherapy, while the neonates in the phototherapy-only group received only phototherapy. All the included newborns received standard care during a hospital stay.

Phototherapy was given continuously using fluorescent bulbs. The distance between the baby and the lamp was 25 cm, and during phototherapy, both eyes and, in the case of the male baby, genitalia were covered. In both groups, the TSB level was monitored as per NICU protocol. Phototherapy was stopped when the TSB level fell to 3 mg/dL or below the level at which phototherapy would be indicated for that age. Administration of UDCA was also stopped simultaneously with phototherapy. Rebound TSB was done after 24 hours of stopping phototherapy. Significant bilirubin rebound was defined as the post-phototherapy rise of bilirubin level needing reinstitution of phototherapy.

Data Collection

On the first day of hospitalization, a complete history and physical examination will be done. For each newborn following data will be collected: Birth weight, Gestational age, sex, age on admission, TSB level on admission, percentage of weight loss on admission, presence of ABO or Rh incompatibility, presence of coomb's positivity, TSB level at different time points after starting phototherapy, duration of phototherapy and presence of significant bilirubin rebound.

Statistical Analysis

Data entry and analysis will be carried out using the Statistical Package of Social Science Software program, version 26.0 (SPSS). The results of the two groups will be compared and analyzed using the Chi-square and student t-tests, as applicable. A P-value less than 0.05 will be considered significant.

3. RESULT

Regarding the characteristics of groups Case (N=66) and Control (N=64), the mean postnatal age on admission was 84.55±43.16 and 77.56±56.71 days in groups Case (N=66) and Control (N=64), respectively, with no significant difference (P=0.561). The mean Gestational age (weeks) 37.29±1.31 and 37.31±1.37 days in groups Case (N=66) and Control (N=64), respectively, with no significant difference (P=0.868). The mean birth weight was 2847.58±613.58 and 2923.44±577.77 g in groups Case (N=66) and Control (N=64), respectively, without any significant difference (P=0.559). The mean Admission weight (grams) was 2621.82±570.48 and 2685.16±531.38 g in groups Case (N=66) and Control (N=64), without any significant difference (P=0.496). The mean weight loss for cases was 7.77±3.52%, while for controls it was 94.2±483.5%. Despite the large discrepancy in the control group's weight loss variability, the p-value of 0.511 indicates that the difference in weight loss between the two groups is not statistically significant (Table 1).For the ABO variable, 36.36% cases and 40.63% controls were positive, with a p-value of 0.618, indicating no significant difference between the groups. In terms of the Rh variable, 3.03% of cases and 9.38% of controls were positive, with a p-value of 0.132, again showing no significant difference. Coombs positivity was uniformly negative across both groups, with 100% of cases and controls being negative. No p-value was provided for Coombs positivity due to the lack of variation between groups (Table 2).Table 3 compares total serum bilirubin (TSB) levels before and after starting phototherapy. The mean TSB level before phototherapy was 15.49±3.52 mg/dl in the case group and 13.95±3.67 mg/dl in the control group, with a p-value of 0.705, indicating no significant difference. After 24 hours of phototherapy, the mean TSB levels were 11.89±2.67 mg/dl in cases and 12.78±2.82 mg/dl in controls, with a p-value of 0.032. After 48 hours, the mean TSB levels were 10.32±2.89 mg/dl in cases and 11.39±2.51 mg/dl in controls, with a p-value of 0.047. After 72 hours, the mean TSB levels were 9.61±1.93 mg/dl in cases and 11.33±2.46 mg/dl in controls, with a p-value of 0.028. In all instances, the p-values indicate significant difference between the groups in TSB levels after 24 hour starting phototherapy. Table 4 compares the duration of phototherapy and the presence of rebound hyperbilirubinemia between the case (N=66) and control (N=64) groups. The mean duration of phototherapy was significantly shorter in the case group (31.64±14.68 hours) compared to the control group (50.25±20.38 hours), with a p-value of 0, indicating a statistically significant difference. Regarding rebound hyperbilirubinemia, 4.55% (3 cases) in the case group and 12.50% (8 controls) in the control group experienced it, while 95.45% (63) of cases and 87.50 % (56) of controls did not. The p-value of 0.103 suggests no significant difference between the groups in the occurrence of rebound hyperbilirubinemia.

Table 1. *Baseline characteristics of both groups*

Variables	Case (N=66)	Control (N=64)	P-value
	Mean±SD	Mean±SD	
Postnatal age on admission (hour)	84.55±43.16	77.56±56.71	0.561
Gestational age (weeks)	37.29±1.31	37.31±1.37	0.868
Birth weight (grams)	2847.58±613.58	2923.44±577.77	0.559
Admission weight (grams)	2621.82±570.48	2685.16±531.38	0.496
Weight loss (%)	7.77±3.52	94.2±483.5	0.511

Table 2. *Comparison of blood group incompatibility*

Variables	Case (N=66)		Control (N=64)		P-value
	N	%	N	%	
ABO					
Yes	24	36.36	26	40.63	0.618.
No	42	63.64	38	59.38	
Rh					
Yes	2	3.03	6	9.38	0.132
No	64	96.97	58	90.63	
Coombs positivity					
Yes	0	0.00	0	0.00	-
No	66	100.00	64	100.00	

Table 3. *Comparison of both groups based on TSB level after starting phototherapy*

TSB level (mg/dl)	Case (N=66)	Control (N=64)	P-value
	Mean±SD	Mean±SD	
Before phototherapy	15.49±3.52	13.95±3.67	0.705
TSB level (mg/dl) after phototherapy			
After 24 hours	11.89±2.67	12.78±2.82	0.032
After 48 hours	10.32±2.89	11.39±2.51	0.047
After 72 hours	9.61±1.93	11.33±2.46	0.028

Table 4. *Comparison of phototherapy duration and rebound hyperbilirubinemia in both groups.*

Variables	Case (N=66)		Control (N=64)		P-value
Duration of Phototherapy (hours)	31.64±14.68		50.25±20.38		0
Presence of rebound hyperbilirubinemia					
Yes	3	4.55	8	12.50	0.103
No	63	95.45	56	87.50	

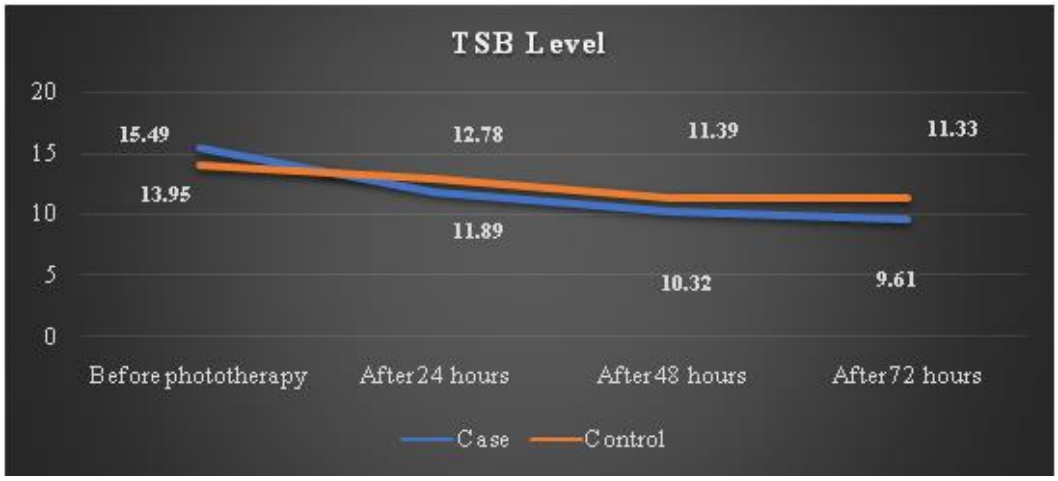

Figure 1. *Comparison of role of decline of average TSB level in both groups*

4. Discussion

Neonatal hyperbilirubinemia is a prevalent condition in newborns, often considered benign. It is defined by a total serum bilirubin (TSB) level greater than 5 mg/dL or above the 95th percentile. Approximately 50% of full-term

infants and nearly all preterm infants experience hyperbilirubinemia at some point in their early days of life [18]. Although most jaundiced infants are generally healthy, elevated bilirubin levels raise concerns due to their potential neurotoxicity, particularly affecting the central nervous system [19].Phototherapy is widely regarded as the primary treatment for reducing bilirubin in neonates. However, it has certain limitations, including high costs and the disruption of the mother-infant relationship, as it requires incubator use and the shielding of the infant's eyes [20]. Thus, the development of adjunctive therapies that can reduce both the duration of phototherapy and the severity of hyperbilirubinemia is highly beneficial [9, 20]. Ursodeoxycholic acid (UDCA), a bile acid commonly used to treat cholestatic liver disorders, offers promise in this regard. UDCA protects the liver against oxidative stress, prevents cellular apoptosis, stimulates bile flow, and regulates immune mechanisms. In pediatric cases, UDCA has been well tolerated with minimal adverse effects, primarily nausea, diarrhea, constipation, and headache [11]. Palmela et al. (2015) conducted an in vitro study showing that UDCA protects human blood-brain barrier endothelial cells from damage caused by unconjugated bilirubin (UCB). Moreover, it was demonstrated that UDCA reduces UCB-mediated neuronal and astrocyte cell death, suggesting its neuroprotective properties [21]. In the present study, we investigated the effect of UDCA combined with phototherapy on unconjugated hyperbilirubinemia, comparing it to treatment with phototherapy alone. The objective was to assess whether this combination could reduce the duration of phototherapy and hospital stay, minimizing associated complications. A total of 130 healthy full-term neonates, aged 2–5 days, with birth weights between 2–3.5 kg and total bilirubin levels ranging from 12–19 mg/dL, were enrolled. No significant differences were found between the groups in terms of sex, mean age, weight, gestational age, or initial bilirubin levels at the start of the study. The mean total bilirubin levels at 24, 48, and 72 hours post-treatment in the case group (phototherapy with UDCA) were 11.89±2.67 mg/dL, 10.32±2.89 mg/dL, and 9.61±1.93 mg/dL, respectively, compared to 12.78±2.82 mg/dL, 11.39±2.51 mg/dL, and 11.33±2.46 mg/dL in the control group (phototherapy alone). These results indicate a significantly greater reduction in bilirubin levels among neonates receiving UDCA in addition to phototherapy [8, 20]. Additionally, the duration of phototherapy was significantly shorter in the UDCA group ($p = 0$), demonstrating the additive benefit of UDCA. Our findings align with those of Honar et al. (2016), who reported a reduction of approximately 24 hours in phototherapy duration when UDCA was used as an adjunct to treat indirect hyperbilirubinemia [8]. Hassan et al. (2015) also supported these findings, concluding that adding oral UDCA to phototherapy significantly improved the treatment outcomes of neonatal hyperbilirubinemia, leading to both faster reductions in bilirubin levels and shorter phototherapy times [22].

5. Limitation of the Study

The study's limitations include a relatively small sample size of 130 neonates, which may affect the generalizability of the findings. The short duration of the study, which was conducted over one year, limits the long-term assessment of UDCA's effectiveness and safety. Additionally, the study only included term and late preterm neonates, excluding those with more severe conditions like sepsis or requiring exchange transfusion, which may lead to a selection bias. Furthermore, the assessment of bilirubin levels was limited to specific time points, potentially missing other fluctuations.

6. Conclusion & Recommendation

This study found that the addition of UDCA to standard phototherapy in neonates with unconjugated hyperbilirubinemia significantly reduced the duration of phototherapy compared to phototherapy alone, without increasing the incidence of rebound hyperbilirubinemia. Despite no significant differences in baseline characteristics, such as gestational age, birth weight, and initial bilirubin levels between the groups, the UDCA-treated group experienced a faster decline in bilirubin levels and a shorter hospital stay. These findings suggest that UDCA may be an effective adjunct therapy in managing neonatal jaundice.

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