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A Comparative Study of Phototherapy Versus Phototherapy Plus Ursodeoxycholic Acid in the Treatment of Indirect Hyperbilirubinemia in Neonate

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Abstract

Background: Hyperbilirubinemia is a common neonatal problem. Phototherapy and exchange transfusion is the conventional treatment for indirect hyperbilirubinemia. In the treatment of cholestatic liver disorders, Ursodeoxycholic acid (UDCA) is a bile acid widely used. Few studies have been conducted using UDCA in indirect hyperbilirubinemia. Aim of the study: This study was planned to assess the additive effect of UDCA on reducing indirect hyperbilirubinemia in neonates receiving phototherapy. **Material & Methods:** This prospective randomized controlled trial was conducted among neonates with indirect hyperbilirubinemia in the neonatal wards of Bangladesh Shishu Hospital and Institute, Dhaka, Bangladesh from June 2018 to July 2020. Finally, 140 neonates were included in the study. Eligible cases were randomized into two groups by the lottery method. Group A (n=70) received phototherapy and Group B (n=70) received UDCA at a dose of 10 mg/kg/day orally twice daily in addition to phototherapy. Total serum bilirubin levels were measured every 12 hours until serum bilirubin level falls below 10 mg/dl and then phototherapy was stopped. Demographic data, clinical features, laboratory parameters, outcome variables, and complications were recorded in a pre-format sheet. CBC with PBF, Total and indirect bilirubin, Blood grouping and Rh and typing, CRP, Reticulocyte count, and Coombs test were obtained at enrolment. Comparison of parameters among themselves was done by unpaired t-test and chi-square test. Analyzed outcomes were: time for resolution of jaundice, total duration of phototherapy, length of hospital stays, and adverse effects of the drug. The two groups did not differ statistically in age, sex or weight. The mean total serum bilirubin level measured at 12, 24, 36, 48, and 60 hours of treatment in group A was 16.10±1.43, 14.76±1.45, 13.34±1.68, 11.84±1.35, and, 10.57±0.74 respectively, and in the group, B was,15.18±1.63, 13.18±2.25, 11.39±1.56, 9.84±0.81 and, 9.44±0.46 respectively ($p<0.001$). The mean duration of phototherapy (64.11±10.8 vs. 47.18±7.51 hours, $p<0.001$) and length of hospital stay (2.80 ±0.40 vs. 2.19±0.39 days, p=<0.001). **Conclusion:** The inclusion of UDCA as an adjuvant to phototherapy is more effective in reducing indirect hyperbilirubinemia in neonates.

Keywords:-Hyperbilirubinemia, Phototherapy, Exchange transfusion, Ursodeoxycholic acid (UDCA)

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INTRODUCTION

Hyperbilirubinemia is a common problem during the neonatal period.[1] It affects half of the full-term and almost all of the preterm infants.[2] Jaundice is the yellow discoloration of the baby's skin, eyes, and other tissues due to the deposition of bilirubin. A newborn baby cannot get rid of the bilirubin easily and it can accumulate in the blood, tissues, and other fluids of the baby's body giving rise to hyperbilirubinemia.[3] Hyperbilirubinemia in neonates is defined as total serum bilirubin (TSB) >95th percentile on the hour-specific Bhutani nomogram.[4] Bilirubin is conjugated in the liver but some portions of it remain unconjugated. If the level of unconjugated bilirubin is high and remains untreated, it can cross the blood-brain barrier and cause bilirubin-induced neurologic dysfunction The risk of neurodevelopmental damage correlates with the increase in the level of unconjugated bilirubin.[3] Bilirubin toxicity was rarely seen in term infants when serum bilirubin concentrations did not exceed 20 mg/dl.[5] In circumstances like asphyxia, acidosis, hypoxia, hypo perfusion, sepsis, and hyperosmolarity, neurological damage can happen even at lower values.[6] Thus, every case requires prompt review and the institution of adequate management. Conventional treatment for severe indirect hyperbilirubinemia consists of phototherapy and exchange transfusion. Phototherapy can disrupt mother-child bonding.[7] It can also lead to several potential complications like retinal degenerative changes, bronze baby syndrome, and thermal instability.[8] Exchange transfusion is associated with significant morbidity and even mortality. Therefore, using adjuvant therapies, which can decrease the duration of phototherapy and hyperbilirubinemia can be highly effective.[9] Up to now, several drugs, like metalloporphyrins, D-penicillamine, phenobarbital, activated charcoal, clofibrate, and bile salts have been used for the treatment of neonatal indirect hyperbilirubinemia, but none of them has yet been evaluated adequately to allow routine application.[10] Several studies have shown phenobarbital is effective in lowering the level of indirect hyperbilirubinemia and decreasing the duration of phototherapy. It has several complications, including an increase in drowsiness, reduction of breastfeeding, dehydration, and neurological disorders.[7] Thus, performing studies on medications with lower complications seems necessary. Ursodeoxycholic acid (UDCA) is a bile acid that is widely used in the treatment of cholestatic liver disorders.[11] It protects the liver against oxidative stress, prevents hepatic cellular apoptosis, stimulates the flow of bile, and suppresses the immunological confounding factors.[10]UDCA is more hydrophilic in comparison to bile acids. When it is administered orally, it gradually displaces the more hydrophobic ones in the bile that accumulate during cholestasis. Thus, it improves the flow of bile and reduces intestinal reabsorption of biliary acids. UDCA is metabolized to an insoluble form by intestinal bacteria that are then excreted in feces. It has a potential role to protect the newborn brain and liver cells from the damaging effect of high unconjugated bilirubin levels. It can also inhibit the apoptotic effects of unconjugated bilirubin on both hepatocyte and neuronal cells.[3] UDCA is well tolerated in children and has limited complications in pediatrics.[10]The usual dose in

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neonates is 10-20 mg/kg/day.[8]A study was conducted to see the effect of UDCA and phototherapy on unconjugated bilirubin (UCB) in rats, which showed that UDCA increased the turnover of UCB through its fecal disposal.[12]Adding UDCA as adjuvant therapy in the management of neonatal jaundice may not only protect the brain from the damaging effect of high bilirubin levels but may also decrease the duration of phototherapy. So, the present study aimed to investigate the effect of UDCA on reducing indirect hyperbilirubinemia in neonates receiving phototherapy, with the hope to reduce the lengths of phototherapy and hospital stay.

Objectives

General objective:

To observe the rapidity of fall of serum bilirubin in neonates with indirect hyperbilirubinemia receiving phototherapy versus those receiving phototherapy with ursodeoxycholic acid.

Specific objectives:

- Estimation of serum bilirubin level
- To assess the duration of phototherapy in the phototherapy group
- To assess the length of the hospital stays in the phototherapy group.
- To assess the duration of phototherapy in phototherapy plus ursodeoxycholic acid group.
- To assess the length of the hospital stay in phototherapy plus ursodeoxycholic acid group.

MATERIAL AND METHODS

It was a randomized controlled study, from June 2018 to July 2020 on the Neonates from 24 hours to 14 days of age with indirect hyperbilirubinemia. The total sample size was 140 patients, 70 in each group, at the Bangladesh Shishu Hospital and Institute, Dhaka. Bangladesh.

Inclusion criteria:

- Premature neonates
- Term neonates from 24 hours up to 14 days of age
- Birth weight of 2500 to 4000gm
- Exclusively breast-fed
- Total bilirubin level 14 to 20 mg/dl and direct bilirubin < 20% of total

Exclusion criteria:

- Premature neonates
- Neonatal sepsis
- ABO and Rh incompatibility
- Infants with the need for or having exchange transfusion
- Infants who have been previously exposed to phototherapy

After approval from the ethical review committee and after proper informed written consent from the parents or local guardians, an initial evaluation of each patient by history and clinical examination was done. CBC with PBF, total and indirect bilirubin, blood grouping & Rh typing, reticulocyte count, Coombs test, and C-reactive protein was obtained at enrolment. Serum bilirubin level estimation was done in Dimension Siemens EXL machine by auto analyzer method. Indirect bilirubin was calculated by subtracting the direct bilirubin

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from the total bilirubin. Patients were randomized into two groups by lottery method. One group named as phototherapy group (group A) was given only blue light phototherapy. Another group named phototherapy plus ursodeoxycholic acid group (group B) was given blue light phototherapy plus ursodeoxycholic acid. All the patients received blue light fluorescent bulb single surface phototherapy continuously by an infant blue light phototherapy machine. The distance between the phototherapy lamp and the baby was 30 cm. During this procedure, the eyes were covered by eye patches and the genitalia was covered with a small nappy. Phototherapy was interrupted only during breastfeeding and nappy change. Ursodeoxycholic acid was given orally as syrup form at a dose of 10 mg/kg/day twice daily. Total serum bilirubin level was measured every 12 hours until total bilirubin level reached <10 mg/dl. Thereafter phototherapy was discontinued. Patients were clinically evaluated daily during their hospitalization. They were also evaluated specifically about any adverse effects related to study medications in both groups. Data were analyzed by SPSS version 26.0. Data were expressed as numbers and percentages for categorical variables or as means and ranges for quantitative variables. To compare categorical variables between groups of patients, the chi-square ($\chi 2$) test was used. Unpaired t-test was used to compare clinical efficacy in both groups and for continuous variables. Results of the statistical analysis were presented on tables and charts. For all statistical tests, the p-value of less than 0.05 was considered statistically significant. Ethical approval had been taken from the Ethical Review Committee (ERC) of Bangladesh Shishu Hospital & Institute.

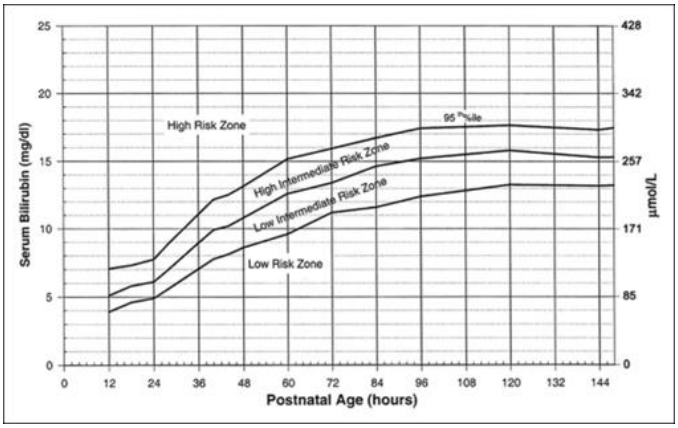

Figure 1: Risk designation of term and near-term well newborns based on their hour-specific serum bilirubin values.[4]

RESULTS

In this study total of 140 neonates were analyzed based on their basic demographic features, total serum bilirubin in different time periods, duration of phototherapy, length of hospital stays, and development of adverse effects. There were no dropout cases during the study period.

[Table 1] showed the mean age of studied subjects is 4.76±1.30 days in Group A and Group B 4.60±1.23. The mean difference was not statistically significant (p=0.464) between the groups. There was no statistically significant difference in gender between the two groups (p=0.127). The mean weight is 2910±220 grams and 2870±190 grams in Group A and Group B respectively, with no significant difference found between them (p=0.248). There was no statistically significant difference between the two groups regarding gestational age (p=0.508).

[Table 2] showed the mean total serum bilirubin at the time of hospitalization in Group A and Group B were 17.64±1.30 and 17.60±1.23

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respectively, without statistically significant difference (p=0.843).

[Table 3] showed the mean total serum bilirubin measured at 12, 24, 36, 48, and 60 hours of treatment in Group A was 16.10±1.43, 14.76±1.45, 13.34±1.68, 11.84±1.35, and 10.57±0.74 respectively. In Group B, it was 15.18±1.63 at 12 hours, 13.18±2.25 at 24 hours, 11.39±1.56 at 36 hours, 9.84±0.81 at 48 hours, and 9.44±0.46 at 60 hours. This result shows that the mean total serum bilirubin level was significantly decreased in Group B compared with Group A (p<0.001).

[Table 4] shows after taking 36 hours of phototherapy 56 patients were remaining in Group B and it was 67 in the case of Group A. After 48 hours only 13 patients were remaining in Group B while 56 patients were remaining in Group A. After 60 hours, all patients in Group B stopped phototherapy while 38 patients were still under phototherapy in Group A.

Table 1: Demographic characteristics of the study patients in two groups (N=140)

Demographic characteristics	Group A(n=70)	Group B(n=70)	p-value
Age (days) 2-5 6-8	 49(70.0%) 21(30.0%)	 53(75.7%) 17(24.3%)	
Mean ±SD	4.76±1.30	4.60±1.23	0.464
Gender Male Neonate Female Neonate	 37(52.9%) 33(47.1%)	 28(40.0%) 42(60.0%)	 0.127
Weight (g)	2910±220	2870±190	0.248
Gestational age (weeks)	38.51±1.18	38.64±1.14	0.508

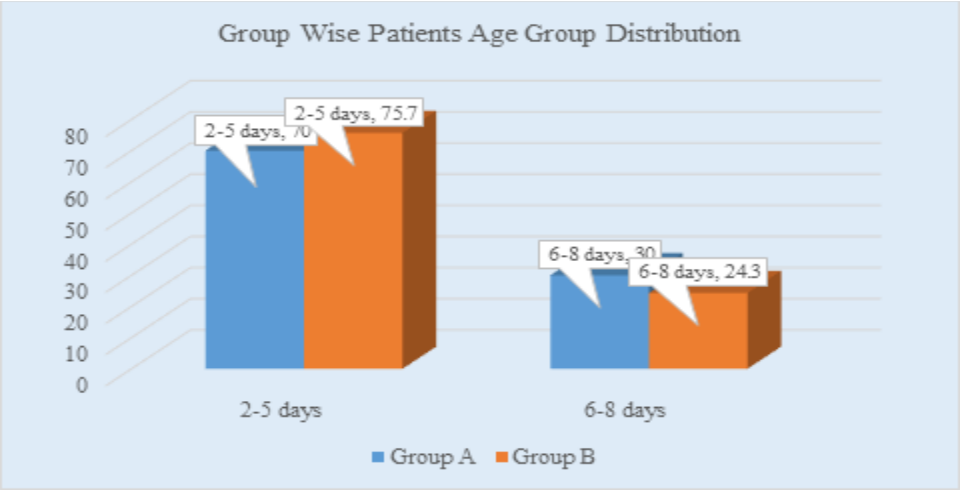

Figure 2: Group wise Patients Age Group Distribution

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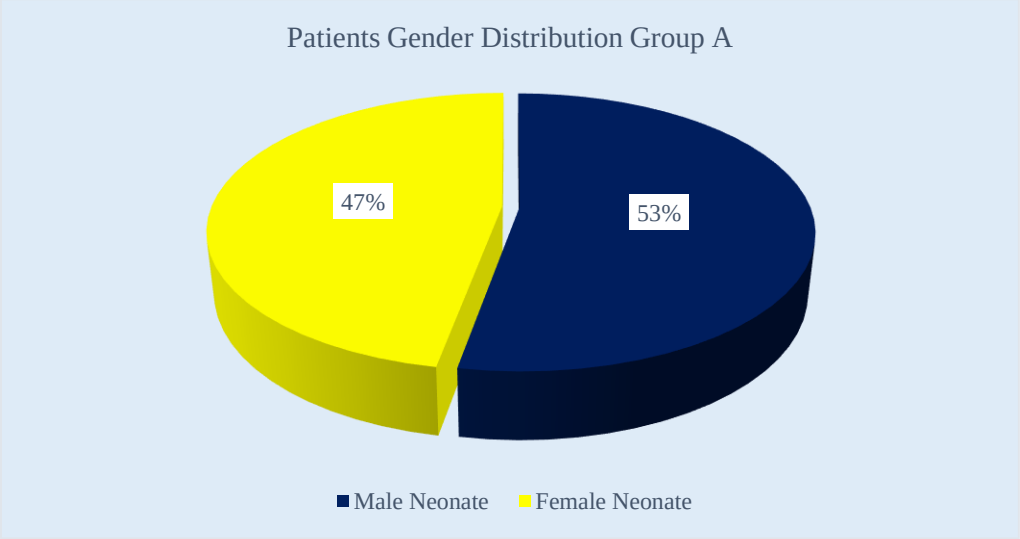

Figure 4: Patients Gender Distribution Group A

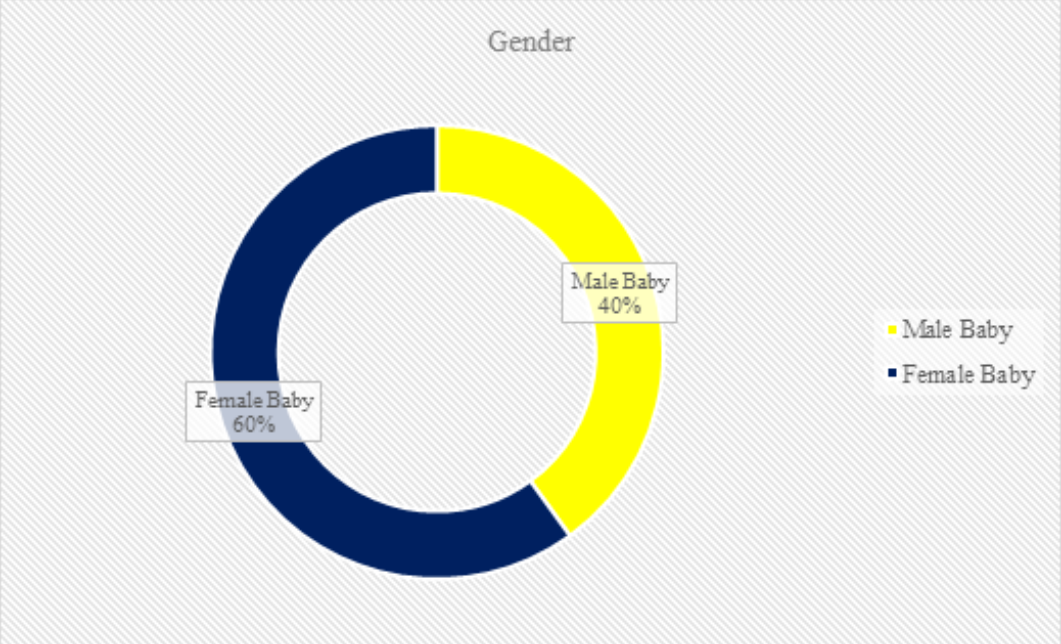

Figure 5: Patients Gender Distribution Group B

Table 2: Comparison of Group A and Group B regarding the mean of total serum bilirubin level at the time of hospitalization (N= 140)

Total serum bilirubin (mg/dl)	Group A(n=70)Mean ±SD	Group B(n=70)Mean ±SD	p-value
At the time of hospitalization	17.64±1.30	17.60±1.23	0.843

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Table 3: Comparison of Group A and Group B regarding the mean total serum bilirubin level at different time points (N=140)

Total serum bilirubin (mg/dl)	Group A(n=70)Mean ±SD	Group B(n=70)Mean ±SD	p-value
12 hours after hospitalization	16.10±1.43	15.18±1.63	<0.001s
24 hours after hospitalization	14.76±1.45	13.18±2.25	<0.001s
36 hours after hospitalization	13.34±1.68	11.39±1.56	<0.001s
48 hours after hospitalization	11.84±1.35	9.84±0.81	<0.001s
60 hours after hospitalization	10.57±0.74	9.44±0.46	<0.001s

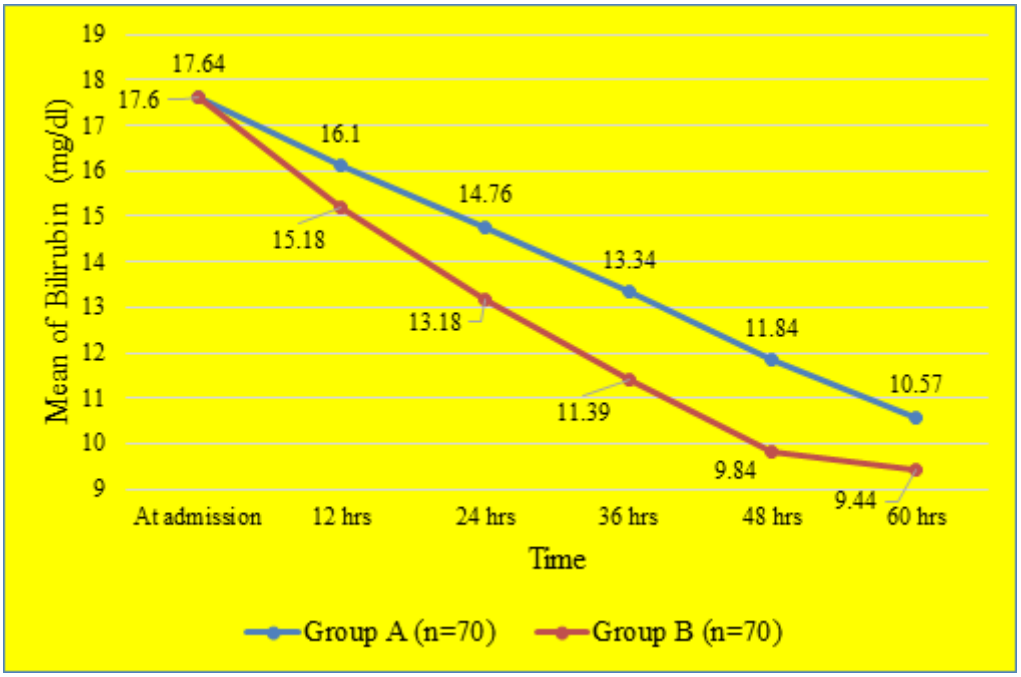

Figure 6: Line graph showing the mean total bilirubin levels in different time periods

Table 4: Comparison of Group A and Group B regarding the need of phototherapy at different time points (N=140)

Requirement of phototherapy	Group A(n=70)	Group B(n=70)	p-value
At the time of hospitalization	70(100%)	70(100%)	1.000
12 hours after hospitalization	70(100%)	70(100%)	1.000
24 hours after hospitalization	70(100%)	70(100%)	1.000
36 hours after hospitalization	67(95.7%)	56(80.0%)	0.004s
48 hours after hospitalization	56(80.0%)	13(18.6%)	<0.001s
60 hours after hospitalization	38(54.3%)	0(0.0%)	<0.001s

Table 5: Comparison of Group A and Group B regarding the total duration of phototherapy (N=140)

Variable	Group A(n=70)Mean ±SD	Group B(n=70)Mean ±SD	p-value
Duration of phototherapy (hours)	64.11±10.8	47.18±7.51	<0.001*

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Table 6: Comparison of Group A and Group B regarding the duration of hospital stay (N=140)

Variable	Group A(n=70)Mean ±SD	Group B(n=70)Mean ±SD	p-value
Duration of hospital stay (days)	2.80±0.40	2.19±0.39	<0.001*

Table 7: Distribution of the patients by adverse effects in two groups (N=140)

Adverse effects	Group A(n=70)	Group B(n=70)	p-value
Yes	2(2.9%)	3(4.3%)	0.648
No	68(97.1%)	67(95.7%)	
Total	70(100.0%)	70(100.0%)	

[Table 5] shows, that the duration of phototherapy in Group A was 64.11±10.8 hours and in Group B was 47.18±7.51 hours. This difference was statistically significant (p<0.001).

[Table 6] showed there is a significant difference present between Group A and Group B regarding the mean duration of hospital stay (p<0.001).

[Table 7] showed that two patients in Group A developed adverse effects in the form of loose stool. In Group B two patients developed a transient skin rash and another patient developed loose stool. There was no significant statistical difference (p=0.648).

DISCUSSION

In this study, there were no statistically significant differences observed between the two groups regarding the mean age, gender distribution, and mean weight of the newborn. Similar findings were also found in other studies.[13] In this study, the mean gestational age in Group A was 38.51±1.18 weeks and it was 38.64±1.14 in the case of Group B. There was no significant difference between the two groups regarding the mean gestational age of the neonates, which is similar to the study.[9]In this study, we found a significant reduction of TSB in the phototherapy plus ursodeoxycholic acid group in comparison to the phototherapy group. A randomized clinical trial upon 80 neonates, also found that there was a significant reduction of TSB in the phototherapy plus ursodeoxycholic acid group in comparison to the phototherapy group, which is similar to our study.[7] Several other studies also found a similar additive effect of UDCA in reducing indirect hyperbilirubinemia in neonates in their studies.[3,10]UDCA led to an ≥ 18hours reduction in the duration of phototherapy in neonates suffering from indirect hyperbilirubinemia most probably by increasing unconjugated bilirubin turnover through its fecal disposal.[10] This finding is similar to the present study, where there was a marked reduction in the duration of phototherapy in the phototherapy plus ursodeoxycholic acid group. In the study, there was at least 24 hours reduction in the duration of phototherapy.[14] Which is also similar to the present study. In this study, 36 hours after hospitalization 56 patients were remaining in group B while 67 patients were remaining in group A; 48 hours after hospitalization 13

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patients were remaining in group B but 56 patients remained in the case of Group A. After 60 hours all patients in group B stopped phototherapy, while 38 patients were still under phototherapy in group A. This is similar to the findings of a previous study.[10]The only study on the effect of UDCA on decreasing unconjugated bilirubin in rats showed that UDCA increased unconjugated bilirubin turnover through its fecal disposal.[12]A similar effect in rats is reported.[15,16] The reduction of unconjugated bilirubin in this study also seems to result from the same mechanism. The most common adverse effects of UDCA in children are nausea, diarrhea, constipation, and headache.[15] In this study, we found diarrhea in one patient and skin rash in two patients in phototherapy plus ursodeoxycholic acid group. There were no significant adverse effects of UDCA during the study period. Similar findings were also found in a previous study.[17]

CONCLUSIONS

This study showed that the inclusion of UDCA as an adjuvant to phototherapy is more effective than phototherapy alone in treating neonates with indirect hyperbilirubinemia.

Limitation of the study:

Single-centered study with a limited sample size. Neonatal jaundice having risk factors was not included in this study.

Recommendations

Hyperbilirubinemia is a major health problem among newborn babies. From this study, we can recommend UDCA can be used as an adjuvant to phototherapy in treating indirect hyperbilirubinemia in neonates. But a multicentered randomized control study is needed to obtain more reliable results.

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