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Research Article

Role of Ursodeoxycholic Acid in Lowering Indirect Hyperbilirubinemia in Neonates Under Phototherapy

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Abstract

Introduction: Hyperbilirubinemia is a common benign problem in neonates, however in some circumstances; it may cause bilirubin induced neurological dysfunction. Although phototherapy remains the mainstay of treatment for neonatal jaundice, it has some side effects.

Aim: The aim of this study was to assess the additive effect of Ursodeoxycholic Acid (UDCA) in reducing indirect hyperbilirubinemia in neonates under phototherapy.

Patients and Methods: This randomized controlled study was performed on 100 newborn with indirect hyperbilirubinemia divided into two groups. Group A: included 50 neonates, received Ursodeoxycholic Acid orally in addition to phototherapy. Group B: included 50 neonates, received phototherapy only. All patients were subjected to detailed history taking, thorough clinical examination and laboratory investigations. Total serum bilirubin (TSB) and direct bilirubin were measured on admission and followed up every 12 hours (h) till serum bilirubin became below 10 mg/dl.

Results: The sex, mean age and weight, onset of jaundice and total serum bilirubin at the time of admission were comparable in both groups ($P > 0.05$). The mean TSB measured at 12h, 24h, 36h and 48h of phototherapy in group A was 13.82 ± 1.11, 11.94 ± 1.60, 10.66 ± 1.52, 9.48 ± 1.33 mg/dl respectively and in group B was 15.15 ± 1.41 at 12h, 13.70 ± 1.25 at 24h, 12.49 ± 1.25 at 36h, 11.47 ± 1.13 at 48h. The TSB levels were significantly lower in the group who received UDCA and phototherapy ($P < 0.05$). The mean duration under phototherapy till reaching TSB < 10 mg/dl in group A (42.96h) were significantly lower than that in group B (71.52 h) ($P < 0.0001$).

Conclusion: UDCA is considered an effective and safe complementary therapeutic adjuvant in neonatal indirect hyperbilirubinemia.

Keywords: Hyperbilirubinemia; Jaundice; Neonates; Phototherapy; Ursodeoxycholic Acid

Abbreviations

UDCA: Ursodeoxycholic Acid; TSB: Total Serum Bilirubin; h: Hours; SPSS: Statistical Package of Social Science; SD: Standard Deviation

Introduction

Hyperbilirubinemia is a common and, in most cases, a benign problem in neonates. Jaundice is observed during the 1st week of life in nearly 60% of term infants and 80% of preterm infants [1]. In some circumstances, increased bilirubin levels may cause bilirubin induced neurological dysfunction and chronic bilirubin encephalopathy, known as kerincterus [2].

Conventional treatment for indirect hyperbilirubinemia is phototherapy and some severe cases require exchange transfusion [3].

Although phototherapy remains the mainstay of treatment for neonatal jaundice, it has some side effects [4]. Neonatal phototherapy separates neonates from their mothers, which might interfere with establishing adequate parent-child bonding. Other recorded complications were bronze baby syndrome, retinal degenerative changes, water and electrolyte disorders, and thermal instability [5]. These harmful effects indicate the need to develop alternative pharmacological treatment strategies for unconjugated hyperbilirubinemia or using adjuvant therapies, which reduce the duration of phototherapy and hyperbilirubinemia [6].

Pharmacologic agents including: Phenobarbital, Ursodeoxycholic Acid (UDCA) and Metalloporphyrins can be used to increase conjugation, increase bile flow and inhibit the formation of bilirubin respectively [7]. Unfortunately, Phenobarbital lead to drowsiness, nausea, vomiting, dehydration, reduction of breast-feeding, developing skin eruptions in addition to neurological disorders [8].

Ursodeoxycholic Acid is a bile extract that has been in use for treatment of cholestatic liver disorders [9]. The addition of UDCA was found to reduce the duration of phototherapy in the neonates suffering from indirect hyperbilirubinemia to at least 18 hours (h) reduction without side effect [10].

Aim of the Study

The aim of this study was to assess the additive effect of UDCA in reducing indirect hyperbilirubinemia in neonates under phototherapy.

Patients and Methods

This randomized controlled study was performed on 100 newborn with indirect hyperbilirubinemia attending the neonatal care unit in National Liver Institute, Menoufia University and Temi Alamdid hospital from January 2018 to June 2019. Patients were divided randomly into two groups. Group A: included 50 neonates, received UDCA orally 10 mg/kg/day divided 12 hourly in addition to phototherapy. Group B: included 50 neonates, received phototherapy only (served as control).

Our study included term newborns who developed indirect hyperbilirubinemia from the second day of life with level of total serum bilirubin (TSB), on admission, between 14 - 20 mg/dl. Infants with Rh or ABO incompatibility, infants with TSB more than 20 mg/dl, premature neonates and infants with neonatal sepsis were excluded from the study.

All patients were subjected to detailed history taking, thorough clinical examination and laboratory investigations including: complete blood count, blood group and Rh of mother and baby, reticulocytic count and C-reactive protein. TSB and direct bilirubin were measured on admission and followed up every 12h till serum bilirubin became below 10 mg/dl (using Cobas 6000 14j4-07, Tokyo Japan and Respons 920, 920699, Germany).

Phototherapy was received from the start of admission (using Lullaby Phototherapy system, SDW122202S43PA, India, 2014). The lamps of the devices were (BLUE LED, OSRAM DULUXL, 18W/71, Italy) with 35cm distance from the patient. Phototherapy was received according to charts of American Academy of Pediatrics [11]. Phototherapy was discontinued when the level of TSB reached < 10 mg/d.

Ursodeoxycholic Acid was given at dose of 10 mg/kg per day divided 12 hourly [12].

The two groups were compared regarding TSB level at different time points, the time duration in which bilirubin levels reached < 10 mg/dl and the duration of phototherapy.

Statistical analysis

Data were analyzed using the Statistical Package of Social Science (SPSS) program for Windows, version 18 (SPSS Inc., Chicago, Illinois, USA). The normality of data was first tested with one-sample Kolmogorov-Smirnov test. Qualitative data were described using number and percent. Association between categorical variables was tested using Chi-square test. Continuous variables were presented as mean ± SD (standard deviation) and the two groups were compared with Student t test. Pearson correlation was used to correlate continuous data. The results were considered significant when the probability of error is less than 5% ($P \leq 0.05$).

Results

Our study included a total of 100 full term infants who developed jaundice from the second day of life, weighted 2.5 to 4 kg with TSB between 14 and 20 mg/dl. There were no statistical significant difference observed between the two groups as regard the sex, mean age and weight, onset of jaundice and the mean TSB at the time of admission ($P > 0.05$). Group A included 30 (60%) males and 20 (40%) females while group B included 28 (56%) males and 22 (44%) females ($P = 0.685$). The mean age of the studied neonates was 5.48 ± 1.09 days and 5.01 ± 1.30 days in group A and group B

respectively (P = 0.09). The mean weight was 3.28 ± 0.36 Kg and 3.19 ± 0.37 Kg in group A and group B respectively (P = 0.215). The mean onset of jaundice in group A and group B was 3.22 ± 0.70 and 2.99 ± 0.83 days respectively (P = 0.141). The mean TSB at the time of admission in group A and group B was 17.20 ± 1.26 and 16.91 ± 1.35 mg/dl respectively (P = 0.266).

The TSB significantly decreased at different time points after admission in group A than group B with a significant P-value < 0.001. The mean TSB was 13.82 ± 1.11 in group A, while it was 15.15 ± 1.41 in group B after 12h of phototherapy. Also, TSB in group A was less than that in group B after 24, 36, 48 h with P- value < 0.001 (Table 1).

Total serum bilirubin (TSB)	Group A (N = 50) Mean ± SD	Group B (N = 50) Mean ± SD	P-value
TSB on admission	17.20 ± 1.26	16.91 ± 1.35	0.266
TSB after 12 hrs	13.82 ± 1.11	15.15 ± 1.41	<0.0001
TSB after 24 hrs	11.94 ± 1.60	13.70 ± 1.25	<0.0001
TSB after 36 hrs	10.66 ± 1.52	12.49 ± 1.25	<0.0001
TSB after 48 hrs	9.48 ± 1.33	11.47 ± 1.13	<0.0001

Table 1: Comparison between the studied groups as regards TSB at different time points after admission.

Our results revealed a highly statistically significant decrease in the duration under phototherapy in group A than group B, as Patients in group A needed to stay around 42.96 h under phototherapy to reach TSB < 10 mg/dl while those in group B needed about 71.52 h under phototherapy to reach that level (P < 0.0001).

After 24h of phototherapy 16% of cases in group A (8 cases) had TSB < 10 mg/dl and stopped phototherapy while no cases in group B reached that level. At 36h of phototherapy 28% of cases in group A (14 cases) had TSB < 10 mg/dl and stopped phototherapy while 6% in group B (3 cases) reached that level. At 48h of phototherapy 44% of cases in group A (22 cases) had TSB < 10 mg/dl and stopped phototherapy while 14% in group B (7 cases) reached that level. The number of cases who stopped phototherapy before 48h was significantly higher in group A than group B (Figure 1).

The TSB percentage decrease at different intervals in group A was more than that in group B especially in the first 12h. Also, within group A the percentage decrease of TSB was highest in the first 12h (Table 2).

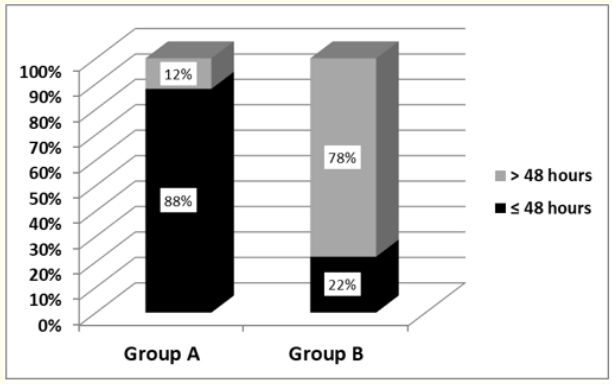

Figure 1: Percentage of cases who stopped phototherapy before and after 48 h of treatment in both groups.

Decrease percentage	Group A (N = 50)	Group B (N = 50)
Decrease % in 1st 12h	19.6%	10.4%
Decrease % 12-24 h	13.6%	9.5%
Decrease % 24-36 h	10.7%	8.8%
Decrease % 36-48 h	11.1%	8.1%

Table 2: TSB percentage decrease at different intervals in group A and group B.

No significant complications were recorded in both groups.

Discussion

Jaundiced baby usually makes the physicians anxious because bilirubin is potentially toxic to the central nervous system, although indirect hyperbilirubinemia is benign in most cases [2]. Despite that phototherapy is the standard therapy for neonatal hyperbilirubinemia, it has some disadvantages such as being expensive and preventing the relationship between the mother and the baby [11]. Therefore, using adjuvant therapies as pharmacological intervention is of outmost importance. Performing studies on medications with lower complications seems necessary. Among some drugs that can augment phototherapy is UDCA, a bile extract that is normally present in human bile in a low concentration [9].

The results of the present study showed the superior effect of adding the UDCA to phototherapy on neonatal indirect hyperbilirubinemia than treatment with phototherapy alone aiming to reduce the duration of phototherapy and hospitalization to avoid their complications.

The TSB levels in the present study decreased significantly in neonates who received UDCA and phototherapy compared to those who received phototherapy only (P < 0.001) without recorded complications. This synergistic effect of UDCA to phototherapy may be related to the protective effect of UDCA to cholangiocytes from cytotoxicity of hydrophobic BAs; stimulation of UDCA to hepatobiliary secretion; protection of hepatocytes from apoptosis caused by BAs and its immune modulatory properties [13]. In addition, it has been found that UDCA had the potential to protect the newborn brain cells from the damaging effects of unconjugated bilirubin [14].

Such additive effect of UDCA in reducing indirect hyperbilirubinemia in neonates was reported by Honar., *et al*. who concluded that, adding UDCA to phototherapy in neonates with indirect hyperbilirubinemia is more effective compared to treatment by phototherapy alone. Honar., *et al*. performed their study on 80 neonates. TSB level on admission was 15.9 ± 1.7, 16.3 ± 1.5 mg/dl in the case group and standard group respectively. TSB in the case group after 12h, 24h and 48h was 12 ± 1.6, 10 ± 1.1 and 9.8 ± 0.2 mg/dl respectively and in the standard group was 14.4 ± 1.3 at 12h, 12.5 ± 1.4 at 24h and 10.1 ± 1.1 at 48h with a highly statistically significant decrease in the group who received UDCA and phototherapy [10].

In the present study, the mean duration under phototherapy till reaching TSB < 10 mg/ dl was much reduced in neonates who received UDCA and phototherapy than those treated with phototherapy only. The addition of UDCA led to more than 24 h reduction in the duration under phototherapy in the neonates with indirect hyperbilirubinemia most probably by increasing unconjugated bilirubin turnover through its fecal disposal.

The previous finding was similar to that of Shahramian., *et al*. who found that, there was a difference between the 2 groups at least 24h to reach TSB level below 10 mg/dl [15]. Moreover, Hassan., *et al*. stated that, the addition of UDCA led to at least 18 h reduction in the duration of phototherapy in the neonates suffering from unconjugated hyperbilirubinemia [12].

The results in the present study revealed that, UDCA must be started early at the beginning of phototherapy especially in the first 12h as the percentage decrease of TSB in group A was highest in the first 12h and greater than the first 12 h decrease in group B. This finding was in agreement with Jafari., *et al*. who cleared that the effect of UDCA was more prominent in the first 8 hours [16].

A more hopeful finding in our study is that, there was an increase in the number of cases who stopped phototherapy before 48h in group A (44 cases) than in group B (11cases) which proved the efficacy of the addition of UDCA to phototherapy.

Conclusion

UDCA is considered an effective complementary therapeutic adjuvant in neonatal indirect hyperbilirubinemia, without side effects which renders this drug an excellent choice in neonatal indirect hyperbilirubinemia.

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Conflicts of Interest

None.

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