RESEARCH ARTICLE

Therapeutic Effects of Ursodeoxycholic Acid in Neonatal Indirect Hyperbilirubinemia; a Randomized Double-Blind Clinical Trial

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Background: Ursodeoxycholic acid (UDCA) is a safe drug used in the treatment of cholestatic liver disorders in children. The aim of this study was to investigate the synergistic effect of UDCA in combination with phototherapy in treating indirect neonatal hyperbilirubinemia.

Methods: Present double-blinded, randomized clinical trial was conducted among neonates with jaundice who were under treatment with phototherapy in the neonatal ward affiliated with the Zabol University of Medical Sciences in 2017. The patients (200 neonates) were randomly divided into intervention (phototherapy+ UDCA) and control (phototherapy alone) groups. The intervention group received 15 mg/kg UDCA daily.

Results: Total bilirubin levels at birth, 24, 48, and 72 hours after therapy were 16.89± 2.49, 14.28± 2.05, 11.62± 2.46, and 10.26± 1.92 mg/dl in controls and 15.79± 2.18, 12.77± 1.86, 10.08± 1.66, and 8.94± 1.38 mg/dl in intervention group respectively (P< 0.001). The ratio of neonates with total bilirubin< 10 mg/dl were 28% and 55% after 48 hours, and 64% and 90% after 72 hours of therapy initiation in phototherapy alone and phototherapy+ UDCA groups respectively (P< 0.001). The mean reduction of direct bilirubin was not significantly different between the groups.

Conclusion: UDCA was effective in accelerating reduction of total bilirubin level in neonates with unconjugated hyperbilirubinemia under phototherapy but had no effect on direct bilirubin levels.

Keywords: Unconjugated hyperbilirubinemia; Ursodeoxycholic acid; Phototherapy

Neonatal jaundice is a common physiological problem affecting over half of all full term and the majority of preterm infants. Thus, newborn infants must be monitored for signs of hyperbilirubinemia to prevent acute bilirubin encephalopathy or kernicterus [1-2]. Physiologic mechanisms of neonatal jaundice include increased bilirubin burden on liver cells, decreased hepatic uptake of bilirubin from plasma, decreased bilirubin conjugation, and defective bilirubin excretion [3]. G6PD deficiency, ABO incompatibility, low birth weight and sepsis are common causes of non-physiological neonatal jaundice [2].

Hyperbilirubinemia can be treated through either blood exchange transfusion or phototherapy to convert bilirubin to its derivatives that can bypass the liver conjugating system and be excreted directly into the bile or urine. Due to the high risk of transfusion associated complications, especially in ill infants, exchange transfusion should be spared to those at risk of bilirubin encephalopathy [4]. Phototherapy is standard therapy for neonatal hyperbilirubinemia [5] and plays a significant role in the treatment and prevention of hyperbilirubinemia in the newborn [6]. However, this treatment can result in the development of hypocalcemia and serious complications such as convulsion [7].

Another therapeutic approach in neonatal indirect hyperbilirubinemia is pharmacological intervention [8]. Pharmacologic agents such as phenobarbital and ursodeoxycholic acid (UDCA) can improve bile flow and help reducing bilirubin concentrations. UDCA is a hydrophilic bile acid that is prescribed for treatment of various cholestatic disorders. It is normally present in human bile, albeit in a low concentration. It is the major bile acid in black bear's bile, which has been used in Chinese traditional medicine for treatment of liver diseases [9]. Oral administration of UDCA has been shown to substantially improve clinical and biochemical indices in a wide variety of liver diseases [10]. The mechanisms underlying the beneficial effects of UDCA in cholestatic disorders have been partly unraveled. The effects of UDCA on improving indirect hyperbilirubinemia in infants is unknown. This study was conducted to explore the synergistic effects of

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UDCA with phototherapy on total and direct bilirubin level in infantile hyperbilirubinemia and compare the effects to those of phototherapy alone.

Methods

The present double-blind, randomized clinical trial was conducted among neonates with jaundice who were under treatment with phototherapy in the neonatal ward affiliated with the Zabol University of Medical Sciences in 2017. The patients (200 neonates) were selected using convenience method and were randomly (https://www.randomizer.org) divided into intervention (100 neonates who were treated with phototherapy+ UDCA) and control groups (100 neonates who were treated with phototherapy alone). The phototherapy treatment was carried out by an educated nurse blinded to the UDCA intervention. One trained physician was aware of neonates who received UDCA and did not have any contact with either the parents or the medical team (including the nurses). The neonates entered the study after obtaining written informed consents from their parents. The study was approved by the Ethics Committee of Zabol University of Medical Sciences, Zabol, Iran (ID: Zbmu.1.REC.1396.64). The study was also registered in the Iranian Registry of Clinical Trials (IRCT20171124037615N1).

Inclusion criteria

Inclusion criteria were birth weight of 2.5 to 4 kg, being exclusively breast-fed, gestational age of 38 to 41 weeks, age of 3-5 days old, total bilirubin level of 12 to 22 mg/dL, and direct bilirubin level< 2 mg/dL.

Exclusion criteria

Infants with ABO and Rh incompatibility, glucose-6-phosphate dehydrogenase (G6PD) deficiency, direct hyperbilirubinemia, septicemia, and diseases leading to hyperbilirubinemia (Crigler-Najjar syndrome, Gilbert syndrome, hypothyroidism/hyperthyroidism, liver diseases), premature neonates, and the infants with diabetic mothers were excluded from the study.

Interventions

The intervention group, received 15 mg/kg UDCA daily divided q12 h (capsules of 300 mg; manufactured by Dr Abidi Company, Tehran, Iran). The drug was administrated orally dissolved into water and sucked up by the babies. The control group received just routine phototherapy. Phototherapy was performed continuously using daylight fluorescent bulbs (Westinghouse, Pittsburgh, PA) in an Air Shields unit. During phototherapy, genitalia and both eyes of infants were covered.

On the first day of hospitalization, history and physical examinations were conducted. As well, total and direct bilirubin levels were measured in both groups. Total bilirubin level was measured by Diazo method every 24 hours until the total bilirubin level reached< 10 mg/dL when phototherapy was discontinued.

Statistical analysis

Statistical methods were performed in SPSS 19 software. Normal distribution was checked by Kolmogorov–Smirnov test. The two groups were compared regarding total bilirubin levels at different time points using independent and paired samples student t-test. Mann Whitney U test was applied as non-parametric test. P value less than 0.05 was considered statistically significant.

Results

The age ranged from 3 to 5 days in the both groups. The frequencies of female infants in the intervention and control groups were 47% and 48%, respectively.

Total bilirubin levels at birth, 24, 48, and 72 hours after birth were 16.89± 2.49, 14.28± 2.05, 11.62± 2.46, and 10.26± 1.92 mg/dl in controls and 15.79± 2.18, 12.77± 1.86, 10.08± 1.66, and 8.94± 1.38 mg/dl in intervention group respectively (Figure 1).

After 24 hours of initiation of treatment, the mean total bilirubin in the intervention group was reduced by an average of 3.02±1.22 mg / dL, which was statistically significant (p< 0.001) from the baseline. Also, in the control group, an average reduction of 2.60±1.98 mg / dL was observed at 24 hours which was also statistically significant from the baseline (p< 0.001, Table 1).

Although the ratio of neonates with total bilirubin levels less than 10 mg/dl was not significantly different between the two groups at 24 hours from therapy initiation, significantly higher ratios of the patients in the phototherapy+ UDCA group had total bilirubin levels< 10 mg/dl at 48 and 72 hours (P< 0.0001, Table 2).

Direct bilirubin levels showed no significant changes during 72 hours in neither of phototherapy of phototherapy+ UDCA groups (Figure 2). After 24 hours of onset of treatment, the mean concentration of direct bilirubin increased in the intervention group as 0.07± 0.32 mg/dl while the value increased by an average of 0.10±0.30 mg / dL in the control group which was statistically significant (p=0.02). However, there was no significant difference in direct bilirubin changes between the groups after 72 hours of treatment (Table 3).

Table 1- Changes of total bilirubin levels in neonates with hyperbilirubinemia who received either phototherapy or phototherapy+ UCDA

Changes in total bilirubin levels	Phototherapy N=100	Phototherapy + UDCA N=100	P
Mean difference at 24 hours (mg/dl)	2.60± 1.98	3.02± 1.22	0.076
Mean difference at 48 hours (mg/dl)	5.30± 2.71 *	6.01± 1.74*	0.035
Mean difference at 72 hours (mg/dl)	7.18± 2.61*	8.08± 1.54*	0.035

*; P< 0.001 compared to 24-hour levels.

Table 2- Ratios of neonates reaching total bilirubin levels< 10 mg/dl at 24, 48, and 72 hours from birth two study groups

Total bilirubin levels < 10 mg/dl		Phototherapy N=100 n (%)	Phototherapy + UDCA N=100 n (%)	P
At 24 hours†	Yes	99 (99)	94 (94)	0.05*
	No	1 (1)	6 (6)	
At 48 hours	Yes	72 (72)	45 (45)	<0.0001*
	No	28 (28)	55 (55)	
At 72 hours	Yes	36 (36)	10 (10)	<0.0001*
	No	64 (64)	90 (90)	

*; Fisher's exact test
†; time points from the birth

Table 3- Changes of direct bilirubin levels in neonates with hyperbilirubinemia who received either phototherapy or phototherapy+ UCDA

Changes in total bilirubin levels	Phototherapy N=100	Phototherapy + UDCA N=100	P*
Mean difference at 24 hours	- 0.10±0.30 †	- 0.07± 0.32	0.02
Mean difference at 48 hours	- 0.05 ± 0.36	- 0.07 ± 0.43	0.06
Mean at 72 hours	- 0.04 ± 0.58	- 0.01 ± 0.31	0.8

†; the "-" sign denotes higher levels of direct bilirubin at 24, 48, and 72 hours after birth respective to birth time.
*; Mann-Whitney U test

Figure 1- Total bilirubin changes in newborns in both intervention and control groups during treatment. *; P< 0.001 for comparison of total bilirubin levels between phototherapy and phototherapy + UDCA groups.

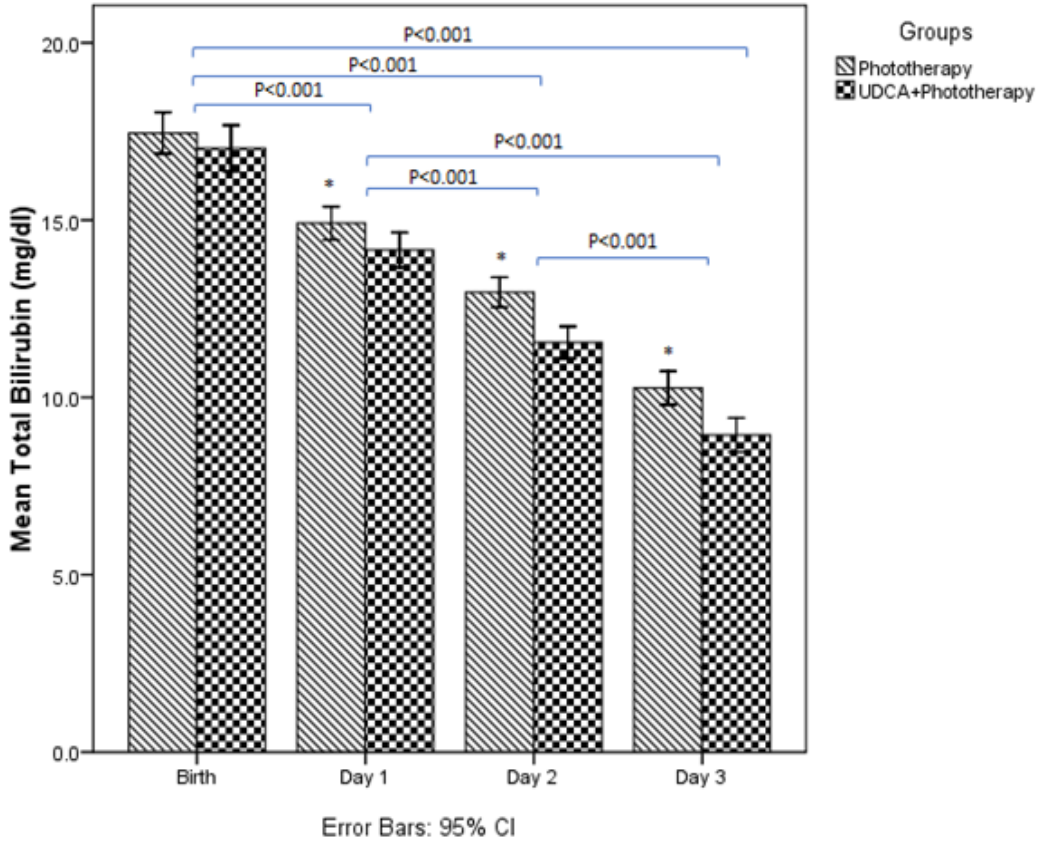
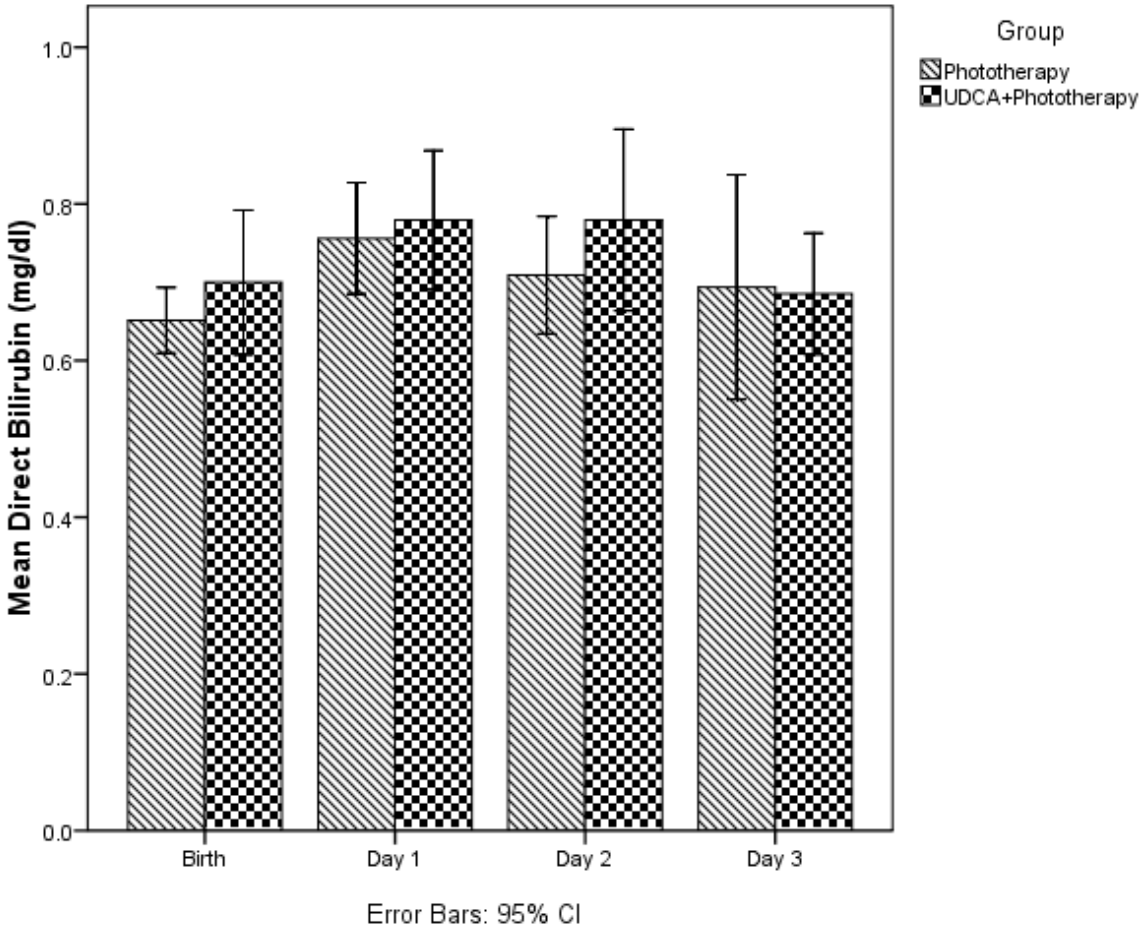


Figure 2- Direct bilirubin changes in newborns in both intervention and control groups during treatment



Discussion

UDCA has been a beneficial therapeutic in patients with cholestatic liver diseases [11]. Though, the efficiency of UDCA for resolving hyperbilirubinemia of different etiologies has not been appropriately evaluated in pediatrics. Especially, few data are available regarding UDCA potential effects in neonatal unconjugated hyperbilirubinemia. In present work, we enrolled 100 neonates with indirect hyperbilirubinemia receiving 15 mg/kg daily UDCA along with their routine phototherapy. We noticed that UDCA accelerated total bilirubin reduction in neonates with indirect hyperbilirubinemia. At 48 and 72 hours from therapy initiation, neonates within phototherapy+ UDCA experienced an average reduction in total bilirubin level of 6.01± 1.74 mg/dl and 8.08± 1.54 mg/dl which were significantly higher than the reductions in the neonates received phototherapy alone (5.30± 2.71 and 7.18± 2.61 mg/dl respectively, P=0.03). We found only two similar studies concerning with the effects of UDCA in neonatal indirect hyperbilirubinemia. In one study, Honar et al who enrolled 40 neonates with indirect hyperbilirubinemia treated with 10 mg/dl UDCA daily [12]. The researchers reported that UDCA in combination with phototherapy was more effective than phototherapy alone in lowering total bilirubin level at 12, 24, and 48 hours after therapy [12]. The time-lapses required to achieve total bilirubin level of< 10 mg/dl were 15.5± 6 and 44.6±13.3 hours for combination of phototherapy and UDCA and phototherapy alone respectively [12]. In another study, Hassan et al also described that total bilirubin levels were 7.6±0.9 mg/dl and 10.2±1.4 mg/dl in neonates with indirect hyperbilirubinemia who received combination of UDCA and phototherapy and phototherapy alone respectively [13]. These are in accordance with our study in which 55% and 90% of neonates received UDCA and phototherapy reached total bilirubin level< 10 mg/dl at 48 and 72 hours respectively. This while these ratios were 28% and 64% in phototherapy alone group respectively (P< 0.0001). We also noted that total bilirubin levels were 10.26± 1.92 mg/dl and 8.94±1.38 mg/dl in phototherapy and phototherapy+ UDCA groups respectively at 72 hours of therapy initiation. In a full term infant, UDCA was reported to reduce the total bilirubin level by 17.8 mg/dl in two days after initiation [14]. However, we observed an average reduction in total bilirubin level of 8.08± 1.54 mg/dl in neonates who received UDCA and phototherapy after 72 hours. These observations suggest administrating UDCA as a synergistic agent with phototherapy can accelerate improvements in bilirubin levels in neonates with physiologic indirect hyperbilirubinemia. Nevertheless, UDCA may also be effective in lowering hyperbilirubinemia of different etiologies such as liver diseases in pediatric populations [15]. Further studies are required to stablish a standardized dose-adjusted therapeutic protocol for neonates to achieve optimized results.

A number of mechanisms have been noted for UDCA

action in lowering bilirubin levels. Regarding cellular protective effects of UDCA [9, 16], it may be plausible to consider that UDCA can reduce turnover of erythroblasts and therefore production of indirect bilirubin [14]. An increment in bilirubin fecal secretion and turnover has also been suggested to be involved in UDCA bilirubin lowering properties [17-19]. On the other hand, the effects of UDCA have been noted to be dose-dependent as 600 mg/dl UDCA was able to resolve hyperbilirubinemia in all, but the dose of 150 mg/dl was effective in only half of patients with cholestatic hyperbilirubinemia [11]. Furthermore, UDCA has protected cholangiocytes against cytotoxicity of hydrophobic bile acids and hepatocytes against bile acid–induced apoptosis [12]. UDCA can also inhibit beta glucuronidase and therefore reduce bilirubin levels in newborns [3]. One or all of these mechanisms may be of relevance in individual with different cholestatic disorders or at different clinical stages. No side effects of UDCA have been reported in children or pregnant women [9, 12-13]. We also encountered no unwanted reaction or complaint during UDCA administration in our study. The excellent safety profile of UDCA render this drug as an excellent choice in pediatrics.

Conclusion

Our study showed that UDCA in combination with phototherapy can reduce the total bilirubin among neonates with unconjugated hyperbilirubinemia. Therefore, it is advisable to consider UDCA as an effective agent and complementary therapeutic in neonatal indirect hyperbilirubinemia.

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