

Original Research Article

Effect of Oral Ursodeoxycholic Acid on Indirect Hyperbilirubinemia In Neonates Treated With Phototherapy At Tertiary Care Centre, Jaipur.

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Abstract

Background: Jaundice is defined as yellowish discoloration of skin, sclera and mucous membrane. Neonatal hyperbilirubinemia is a common problem in the neonatal period occurring in nearly 5-25% neonates. **Objective:** To investigate the effect of Ursodeoxycholic acid in reducing unconjugated bilirubin levels of infants undergoing phototherapy for Neonatal hyperbilirubinemia. **Methods:** This study was a double blind, placebo controlled, randomized clinical trial conducted in the Department of Paediatrics, Santokba Durlabhji Memorial Hospital, Jaipur in active collaboration with Department of Ophthalmology, OBG and Pathology from January 2016 to June 2016. The 100 enrolled neonates were subdivided into two groups. **Study Group:** Patients in this group were administered oral Udcament suspension in a dose of 10mg/kg/day every 12 hourly till the serum bilirubin levels fell below 10mg/dl. **Control Group:** Patient in this group received placebo syrup in the form of sucrose solution in similar amounts 12 hourly till the serum bilirubin levels fell below 10 mg/dl. **Results:** The differences of mean STB between the two groups at admission, 12, 24, 36 and 48 hours was 0.72, 0.84, 0.69, 0.56, and 0.51 respectively with a 95% CI of -0.16 to 1.12, 0.22 to 1.47, -1.27 to -0.1, -0.99 to -0.14 and -0.9 to 0.11 with the p value being 0.11, 0.008, 0.02, 0.01 and 0.01. This indicates a positive effect of oral udcamentin reducing the levels of unconjugated bilirubin along with phototherapy. 70 newborns were evaluated by fundus examination at the age of 6 month & 12 months. None of them was found any kind of ophthalmological abnormality. **Conclusion:** Addition of oral Ursodeoxycholic acid to phototherapy in neonates with indirect hyperbilirubinemia is more effective as compared to phototherapy alone in reducing serum bilirubin levels.

Keywords: Newborn, Indirect Hyperbilirubinemia, Phototherapy, Ursodeoxycholic acid

Introduction

The word "Jaundice" is derived from the French word "Jaune" meaning yellow. Jaundice is defined as yellowish discoloration of skin, sclera and mucous membrane. Neonatal hyperbilirubinemia is a common problem in the neonatal period occurring in nearly 5-25% neonates¹. It is, in fact the most common condition that requires medical attention in newborns. Adults appear jaundiced when the serum bilirubin level is >2mg/dl, and newborns appear jaundiced when it is >7mg/dl. Approximately 85% of all term newborns and most premature infants develop clinical jaundice. A serum bilirubin level >15mg/dl is found in 3% of normal term babies². It is the most common cause of re-admissions to the hospital after

early hospital discharge of term neonates^{3,4}. It is more common in preterm infants than in term infants, mainly because of a delay in the expression of hepatic glucuronyltransferase, the enzyme that conjugates bilirubin⁵. Neonatal jaundice may be physiological or pathological. Immaturity of the hepatic function because of low concentrations of the binding ligandin in the hepatocytes and low activity of the conjugating enzyme glucuronyltransferase as well as elevated bilirubin production because of increased breakdown of fetal erythrocytes have been cited as the major cause of “physiological jaundice” in the newborn. Several lines of evidence suggest the importance of intestinal metabolism of unconjugated bilirubin (UCB) and enterohepatic circulation (EHC) in the pathogenesis of neonatal jaundice⁶⁻⁸. Condie, as early as 1859, commented that jaundice in the newborn was related to “The want of a free evacuation of the meconium”⁹. The existence of EHC of bilirubin was first described in early 1960’s when radio-labelled bilirubin became available^{10,11}. The absence of an intestinal flora for the reduction of conjugated bilirubin to urobilinoids, high levels of intestinal glucuronidase, preponderance of bilirubin monoglucuronide rather than diglucuronide, decreased gut motility and limited nutrient intake thus prolonging intestinal transit time with poor evacuation of bilirubin laden meconium during neonatal life increases the enterohepatic circulation whereby bilirubin diglucuronide secreted into the intestine is hydrolysed and the resulting bilirubin reabsorbed. Studies have suggested that in a neonate, the postulated enterohepatic cycling is of a magnitude that could be significant in the overall body economy of bilirubin. Interestingly, only one third of bilirubin reabsorbed from the intestine is cleared by the liver during the first pass^{12,13} metabolism, the remainder may enter the systemic circulation. To block the process of enhanced enterohepatic circulation, various strategies have been used to bind the bilirubin in the intestinal lumen to substances that resist resorption, products such as activated charcoal, oral agar & calcium phosphate have been used but with inconsistent results and adverse effects^{7,14}. Under certain circumstances unconjugated bilirubin can be toxic to the central nervous system, resulting in encephalopathy and neurological impairment¹⁵. Currently the standard therapies for hyperbilirubinemia include phototherapy and exchange transfusion. However, these options are costly, time consuming and potentially risky. For instance side effects associated with phototherapy include dehydration, rashes, oxidative injury, thermal instability, electrolyte disturbances, bronze baby syndrome, irradiation and possibly DNA damage^{16,17}. Common problems with exchange transfusion include apnoea, bradycardia, cyanosis, vasospasm, hypothermia, coagulation and electrolyte abnormalities, thrombocytopenia, infection, arrhythmias, portal vein thrombosis and sudden death⁵. Uptill now, several drugs such as activated charcoal, D-penicillamine, phenobarbitone, metalloporphyrins, clofibrate and bile salts have been used in the treatment of indirect hyperbilirubinemia¹⁸⁻²⁰. Several studies have shown phenobarbital to be effective in reducing indirect hyperbilirubinemia and decreasing the duration of phototherapy²¹. Nevertheless it has complications, including increase in drowsiness, reduction of breastfeeding, dehydration and neurological disorders²⁰. Thus, performing studies on medications with lower complications seems necessary. On the contrary, ursodeoxycholic acid (UDCA) is a bile acid that is widely used in the treatment of cholestatic liver disease. It protects the liver against oxidative stress, prevents cell apoptosis, stimulates bile flow and suppresses the confounding factors in immunological mechanisms^(22,23). UDCA is well tolerated and has limited complications in paediatrics²⁴. Proposed mechanism of action of ursodeoxycholic acid are changes in the composition of mixed phospholipid rich micelle, reduction of bile acid cytotoxicity of bile and may be reduction of hydrophobic bile acid concentration in the cholangiocytes²⁵, stimulation of hepatobiliary secretion via calcium dependant mechanism and protein kinase C dependant mechanism may cause insertion of transporter molecules into the hepatocyte canalicular membrane²⁵, hepatocyte protection against bile acid induced apoptosis²⁵, UDCA increases

unconjugated bilirubin turnover through increasing its faecal disposal²⁶, UDCA protects human blood brain barrier endothelial cells from disruption by unconjugated bilirubin.²⁷ Owing to the lack of sufficient data about the effect of UDCA on neonatal unconjugated hyperbilirubinemia, the present study is aimed to investigate the effect of UDCA on reducing the unconjugated bilirubin levels of infants undergoing phototherapy.

Aims and Objectives

To investigate the effect of Ursodeoxycholic acid in reducing unconjugated bilirubin levels of infants undergoing phototherapy for Neonatal hyperbilirubinemia.

Material and Methods

The present study was a double blind, placebo controlled, randomized clinical trial conducted in the Department of Paediatrics, SantokbaDurlabhji Memorial Hospital, Jaipur in active collaboration with Department of Ophthalmology, OBG and Pathology from January 2016 to June 2016.

Study Design:

This is a hospital based, prospective study.

Study type:

Interventional study (Randomized controlled trial).

Study area:

The present study was conducted in the Department of Pediatrics, in active collaboration with the Department of Ophthalmology, OBG and Pathology, SantokbaDurlabhji Memorial Hospital, Jaipur.

Study duration:

The study was conducted on neonates (inborn + outborns) admitted to Neonatal ICU falling in inclusion criteria at SantokbaDurlabhji Memorial Hospital, Jaipur from January 2016 to June 2016.

Sample size with Justification:

This study was carried out from January 2016 to June 2016. A total of 400 neonates were delivered in the Department of Obstetrics and Gynaecology, SantokbhaDurlabhji Memorial Hospital, Jaipur during the study period. Out of these neonates, those born alive at ≥ 37 weeks of gestation were 180. Neonates eligible for screening were 115, after excluding the neonates meeting any of the mentioned exclusion criteria. Out of these, a total of 94 neonates could be screened. 29 out of these 94 neonates were either lost to follow up or withdrew from the study after enrolment. Newborns which were admitted to the nursery (delivered outside) and who met the inclusion criteria after screening were 53. 18 out of these 53 neonates were lost to follow up. Hence, in actuality, a total of 100 neonates were analysed. The 100 enrolled neonates were subdivided into two groups according to the therapeutic modalities received. The study group contained 50 neonates who received oral ursodeoxycholic acid suspension therapy along with phototherapy while the control group contained 50 neonates who received placebo along with phototherapy. All the data was recorded on predesigned and pretested proforma and was analysed statistically.

Data Analysis:

The data was coded and entered into Microsoft Excel spreadsheet. Analysis was done using SPSS version 20 (IBM SPSS Statistics Inc., Chicago, Illinois, USA) Windows software program. The variables were assessed for normality using the Kolmogorov Smirnov test. Descriptive statistics included computation of percentages, means and standard deviations. The Unpaired t test (for quantitative data within two groups) and analysis of variance (ANOVA) [for quantitative data within three groups] were used for comparison of all clinical indicators. Chi-square test and Fisher exact test were used for qualitative data whenever two or more than two groups were compared. Level of significance was set at $P=0.05$. ($p<0.05$ – significant, $p<0.01$ – highly significant, $p<0.0001$ – very highly significant)

Selection criteria:**Inclusion Criteria:**

1. Full term babies (gestational age of 38 to 41 weeks).
2. Total Bilirubin levels of 13 to 20 mg/dl.
3. Birth weight of more than 2000 grams.
4. More than 1 day (≥ 24 hours) old.
5. Direct bilirubin levels of less than 2 mg/dl.

Exclusion Criteria:

1. Rh incompatibility (mothers with Rh negative blood group).
2. Babies requiring exchange transfusion / phototherapy within 24 hrs of age.
3. Major gross congenital anomalies
4. Systemic sepsis (requiring intravenous antibiotics).
5. Infant of diabetic mother
6. Hypo/hyperthyroidism
7. Liver diseases
8. Preterm neonates

Method of Collection of Data

Neonates falling into the inclusion criteria were enrolled in the study after taking an informed consent from the parents after explaining them about the study. At anytime parents were free to withdraw from the study. The enrolled newborns were subdivided into two groups depending on the treatment received according to the following plan – **Study Group:** Patients in this group were administered oral Udcament suspension in a dose of 10mg/kg/day every 12 hourly till the serum bilirubin levels fell below 10mg/dl. **Control Group:** Patient in this group received placebo syrup in the form of sucrose solution in similar amounts 12 hourly till the serum bilirubin levels fell below 10 mg/dl.

Randomization and blinding

The patients who were meeting the inclusion criteria were selected with simple random sampling. Before the start of the study a random sequence of numbers were generated (initially from 1 to 150, expecting at least 75 cases and 75 controls but later number fell down to 100) using a table of random numbers by using graph pad software. This Random sequence of numbers from 1 to 150 were then divided into 2 groups of 75 each. One group received the drug Udcament and the other placebo in similar dose and amount. The drug and the placebo were administered by a first year resident who used to note the number (code) of the patient and outcome on a sheet, but she herself did not know what she was giving as

the drug and the placebo were of the same colour and were packed into similar looking bottles and were labelled with a code. Only one second year resident (who was posted in the wards and not in the NICU for the period of study) knew the codes of the neonates who received the drug Udcament and had no contact with either the parents or the medical team till the end of the study.

Intervention

The intervention group which included 50 neonates with unconjugated hyperbilirubinemia received oral Ursodeoxycholic acid in the form of Udcament suspension. It comes in a 100 ml bottle with a composition of 125mg/5ml, manufactured by Delcure Lifesciences limited. It was given in a dose of 10mg/kg /dose with a dropper that is available with the bottle, every 12 hourly till the bilirubin levels fell below 10 mg/dl along with phototherapy whereas the control group (n=50) received placebo in similar amounts along with phototherapy. In our Neonatal Intensive care unit we have Phoenix LED (Light Emitting Diode) phototherapy units which delivers blue light with peak intensity of 455 nm and maintains it for 20,000 hours. These Phototherapy units have ten LED bulbs and the height of these phototherapy units can be adjusted. The distance between the phototherapy units and baby was kept 30 cms. We maintained a "flux" or the minimum spectral irradiance of 15 microwatt/cm²/nm for each phototherapy unit. We used to measure the flux using a flux meter (Phoenix irradiance meter) twice weekly. We had planned to change the lights once the flux falls below 15 microwatt/cm²/nm but it did not fall below this level as our phototherapy units were quite new. During phototherapy, genitalia and both eyes of infants were covered. A detailed clinical history and Physical examination were done.

Investigations:

Following investigations were carried out in all icteric neonates:

- a. Serum bilirubin (total, direct and indirect) levels after day 1 and then 12 hrly till it fell below 10mg/dl.
- b. Mother's blood group and Rh typing.
- c. Baby's blood group and Rh typing
- d. Complete hemogram.
- e. Septic screen.
- f. Thyroid function tests.
- g. Slit lamp and Fundus Examination.

Estimation of serum bilirubin

Venous whole blood was taken in microcapillaries and centrifuged at 10000 rpm for 10 minutes and serum thus obtained was assessed immediately for total, direct and indirect serum bilirubin levels. STB estimation was done spectrophotometrically using diazo reagent by Malloy and Evelyn method.

Results

There were 31 males and 19 females in the study group while in the control group there were 33 males and 17 females. Difference in the gender distribution between the study and control group were found to be non-significant ($X^2=0.89$; $p=0.34$). The mean birth weight of neonates in the study group receiving Ursodeoxycholic acid therapy was 2.73 ± 0.23 kg while in the control group receiving placebo treatment it was 2.69 ± 0.41 kg which was almost similar and the difference between the two groups was not found to be statistically significant ($p=0.51$). The distribution of cases in study and control group according to the mode of delivery in our study. It is shown that amongst the study group 30% deliveries were assisted

by LSCS and 70% were vaginal deliveries whereas amongst control group 26% deliveries were through LSCS and 74% were vaginal deliveries. The difference between the two groups was found to be non-significant ($X^2 = 0.59$; $p=0.43$).

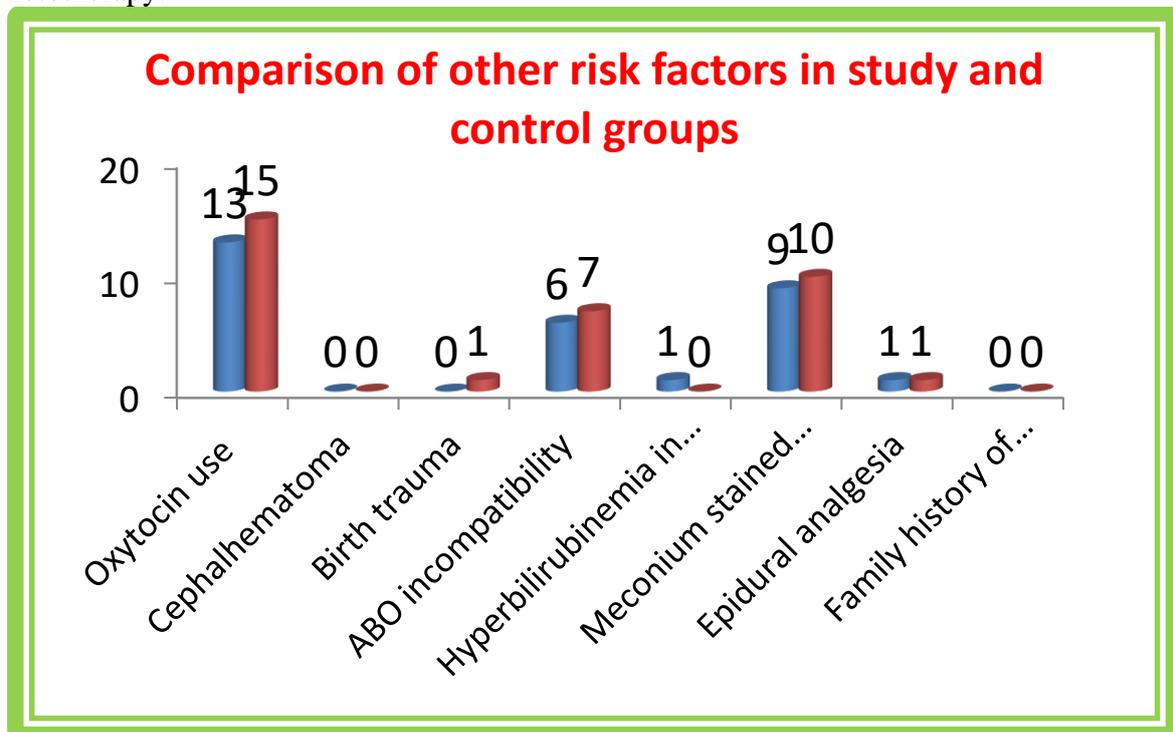
Table 1: Comparison of bilirubin level at various time interval

Bilirubin	Groups	N	Mean	Std. Deviation	Mean difference	CI	P value
On admission	Case	50	16.33	1.58	0.72	-0.16 to 1.62	0.11
	Control	50	15.6	2.78			
12 HR	Case	50	14.308	1.56	0.84	0.22 to 1.47	0.008 (S)
	Control	50	13.46	1.58			
24 HR	Case	50	11.78	1.407	0.69	-1.27 to -0.1	0.02 (S)
	Control	50	12.47	1.55			
36 HR	Case	46	10.46	0.89	0.56	-0.99 to -0.14	0.01 (S)
	Control	42	11.03	1.11			
48 HR	Case	21	9.48	0.68	0.51	-0.9 to 0.11	0.01 (S)
	Control	28	9.99	0.66			

Test applied: Unpaired t test

S=Significant

Table 01 reflects the comparison of mean levels of total serum bilirubin on admission, 12, 24, 36 and 48 hours respectively between the case and control groups. According to this, mean STB levels on admission are comparable in both the groups (p 0.11). The mean difference between the two groups at admission, 12, 24, 36 and 48 hours was 0.72, 0.84, 0.69, 0.56, and 0.51 respectively with a 95% CI of -0.16 to 1.12, 0.22 to 1.47, -1.27 to -0.1, -0.99 to -0.14 and -0.9 to 0.11 with the p value being 0.11, 0.008, 0.02, 0.01 and 0.01. This indicates a positive effect of oral udcamentin reducing the levels of unconjugated bilirubin along with phototherapy.



Above graph depicts the distribution of other risk factors or other baseline characteristics of the enrolled neonates in the study and control groups. According to this, the two groups were similar in all baseline variables or risk factors for neonatal jaundice such as presence of cephalhematoma, birth trauma, oxytocin use, epidural analgesia given to mothers, history of jaundice in sibling or family history of jaundice. All the newborns, which were given phototherapy with or without syrup udcament were evaluated on follow up at the age of 6 month & 12 months of age for ophthalmological examination. Out of 100 newborns, 30 lost during follow up and remaining 70 newborn from both groups were evaluated by slit lamp and Fundus Examination. None of them was found any kind of ophthalmological abnormality at the age of 6 & 12 months.

Discussion

Jaundice is an important problem in the first week of life. It is a cause of concern for the physician and a source of anxiety for the parents. High bilirubin levels may be toxic to the developing central nervous system and may cause neurological damage even in term newborns. Reducing the Unconjugated bilirubin of infants undergoing phototherapy using a drug is an exciting approach for prevention of neonatal hyperbilirubinemia. Among compounds having this potential, ursodeoxycholic acid was demonstrated to be promising in both in-vitro and some in-vivo studies. The aim of this study was to assess the additive effect of Ursodeoxycholic Acid on reducing indirect hyperbilirubinemia in neonates receiving phototherapy. In our study a total no. of 100 neonates of either sex born at ≥ 37 weeks of gestation with total serum bilirubin levels falling between 13-20mg/dl at 2-6 days of age, not meeting the pre-defined exclusion criteria were enrolled in the study. These were further subdivided into two groups - the study group (50 neonates) and the control group (50 neonates) who were to receive either oral udcament suspension and phototherapy or placebo and phototherapy respectively and serum bilirubin levels were taken every 12 hourly till the levels fell below 10mg/dl. There was no significant difference between the two groups regarding the mean age, mean weight and gender distribution, and these findings were similar to the study done by **Honar et al²⁹** and **Hasan et al²⁸**. There was also no significant difference between the Mean serum Bilirubin levels at admission in our study which is similar to study done by **Honar et al²⁹** and **Hasan et al²⁸**.

AT Admission

Table 2:

STUDY	Case group	Control group	P value
Hasan et al	16.3 \pm 1.7	16.5 \pm 2.9	0.852
Honar et al	15.9 \pm 1.7	16.3 \pm 1.5	–
Our study	16.3 \pm 1.58	15.6 \pm 2.78	0.11

Once, after starting the drug Ursodeoxycholic acid and phototherapy in the study group and phototherapy and placebo in the control group the levels of Mean serum Bilirubin fell at a faster rate in the study group and the results were statistically significant. This finding in our study was comparable to findings of **Honar et al²⁹** and **Hasan et al²⁸**.

Tables comparing the mean bilirubin levels at 12, 24, 36 and 48 hours in our study and the study done by Honar et al²⁹ and Hasan et al²⁸

AT 12 hours

STUDY BY	Study group	Control group	P- value
Hasan et al	11.7±1.5	14.6±1.6	<0.001
Honar et al	12±1.6	14.4±1.3	<0.001
Our study	14.3±1.56	13.46±1.58	0.11

At 24 hrs

STUDY	Case group	Control group	P- value
Hasan et al	8.8±1.1	13.2±5.8	.001
Honar et al	10±1.1	12.5±1.4	.001
Our study	11.78±1.4	12.47±1.55	.02

At 36 hours

STUDY	Case group	Control group	P-value
Hasan et al	7.6±0.9	10.2±1.4	0.001
Our study	10.46±0.89	11.03±1.11	0.01

At 48 hrs

STUDY	Case group	Control group	P-value
Hasan et al	NA	9.1±0.8	NA
Honar et al	9.8±0.2	10.1±1.1	<0.001
Our study	9.48±0.68	9.99±0.66	0.01

From the above tables it is clearly seen that the Bilirubin levels fell at a faster rate in study group as compared to the control group, and the values are statistically significant. It can also be seen from the above tables that the Mean levels of Bilirubin in our study were decreasing at a low rate as compared to the two other studies. The possible explanation for this can be the interruption of phototherapy in some patients as the mother insisted on giving breast milk to the child. So for the duration of breast feeding these babies did not receive phototherapy. The study group was also examined regarding udcament complication, such as diarrhoea and vomiting, however, no such complications were detected in any of our patients neither did **Honar et al²⁹** and **Hasan et al²⁸**. Because of the lack of studies on this topic we could compare our results with these two studies only. Few studies have been done on animals. One such study was done by **Cuperus et al³⁰** which investigated the effect of oral UDCA in lowering unconjugated bilirubin (UCB) in Gunn rats, and showed that UDCA increased UCB turnover through increasing its fecal disposal. **Mendez et al³¹** reported a similar effect in rodents probably by causing bile salt malabsorption and concluded that dietary UDCA and cholesterol induce enterohepatic cycling of bilirubin. So, the results of the present study

showed that 12 and 24 hours after hospitalisation mean total bilirubin level decreased significantly in patients receiving UDCA and phototherapy compared to those who received placebo and phototherapy. The highest effect of UDCA accompanied with phototherapy occurred within first 48 hours of admission.

Conclusion

From the present study, we conclude that Adding Ursodeoxycholic acid to phototherapy in neonates with indirect hyperbilirubinemia is more effective as compared to phototherapy alone in reducing serum bilirubin levels.

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