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# THERAPEUTIC ROLE OF URSODEOXYCHOLIC ACID IN MANAGEMENT OF NEONATES WITH INDIRECT HYPERBILIRUBINEMIA

**Pediatrics**

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## ABSTRACT

**Objectives:** This study was undertaken to investigate the therapeutic effect of Ursodeoxycholic acid (UDCA) in reducing the indirect hyperbilirubinemia of the infants undergoing phototherapy and reduction of the duration of phototherapy.

**Methods:** This study was an open labelled randomized controlled trial on neonates with indirect hyperbilirubinemia who required phototherapy; admitted to Rajkiya Mahila Chiktsayla Ajmer affiliated to JLN Medical College Ajmer from June 2018 to May 2019. Total 100 neonates were registered for this study were randomly divided into two groups, group A (n=50) received UDCA 15 mg/kg/day orally divided 12 hourly in addition to phototherapy, while group B (n=50) received only phototherapy.

**Results:** The mean total serum bilirubin at 24, 48, 72, and 96 h of treatment in group A which was given UDCA with phototherapy was 13.67± 0.513, 10.590 ± 0.388, 9.49 ± 0.41, and 7.566 ± 0.456, respectively, and in group B given only phototherapy was 14.5 ± 1.93 at 24 h, 12.7 ± 0.503 at 48 h, 10.49 ± 0.263 at 72 h, and 9.322 ± 0.234 at 96 h. Significant $P<0.05$ after 24 hr and highly significant $P< 0.001$ after 48,72 and 96 hr of phototherapy. Duration of phototherapy in group A was 65.2 ± 10.19 h and in group B was 84.90 ± 13.85 h, with statistically significant difference ($P < 0.001$).

**Conclusions:** Addition of UDCA at 15 mg/kg/day to phototherapy in neonate with indirect hyperbilirubinemia is more effective than phototherapy alone in reducing unconjugated bilirubin and duration of phototherapy

## KEYWORDS

Indirect hyperbilirubinemia, Phototherapy, UDCA

## INTRODUCTION

Neonatal jaundice (Hyperbilirubinemia) is a common problem in neonates, being noticed during the first week of life in 60% of term infants and 80% of preterm infants[1]. Pathological jaundice is mainly caused by different clinical conditions resulting in indirect hyperbilirubinemia. Indirect Hyperbilirubinemia can be treated through either phototherapy or blood exchange transfusion. Phototherapy, however, has several known disadvantages while exchange transfusion associated with serious complications, especially in ill infants so exchange transfusion should be spared to those at risk of bilirubin encephalopathy[2]. Therefore, using adjuvant therapies, which reduces the duration of phototherapy and hyperbilirubinemia, can be highly effective. Till now, several drugs, such as activated charcoal, D-penicillamine, phenobarbital, metalloporphyrin, clofibrate and bile salts, have been used for the treatment of indirect hyperbilirubinemia but none of them has yet been evaluated sufficiently to allow routine application[3,4].

Ursodeoxycholic Acid (UDCA) is a hydrophilic bile acid which is regularly used in treatment of cholestatic liver disorders. UDCA can improve bile flow and help reducing bilirubin concentration[5]. It protects the liver against oxidative stress, prevents cell apoptosis, stimulates the bile flow, most probably by increasing unconjugated bilirubin turnover through its faecal disposal and suppresses the confounding factors in immunological mechanisms[6]. Owing to the lack of sufficient data about the effect of UDCA on neonatal unconjugated hyperbilirubinemia, the present study was undertaken to investigate the therapeutic effect of UDCA on reducing the unconjugated bilirubin of the infants undergoing phototherapy.

## METHODS

This study was an open labelled randomized controlled trial study conducted on newborns with indirect hyperbilirubinemia who were admitted in Rajkiya Mahila Chiktsayla Ajmer affiliated to JLN Medical College Ajmer from June 2018 to May 2019.

**Inclusion Criteria:**

A. Neonates with birth weight 2.5 to 4 kg and gestation age from 38 to 41 week from 24 hours up to 14 days with total serum bilirubin (TSB) levels in phototherapy range and direct bilirubin <20% of total.
B. Patient's attendants willing to give written informed consent.

**Exclusion Criteria:**

A. Preterm < 37-week gestation age.
B. Neonate with direct hyperbilirubinemia > 2mg/dl or > 20 % of TSB.
C. Neonate who is hemodynamically unstable. (because of shock, severe haemolysis, sepsis, any congenital anomaly etc.)
D. Neonates in whom oral feeding or oral medication is contraindicated.
E. Infants who have been previously exposed to phototherapy.
F. Infants with needing exchange transfusion.

A total of 100 eligible neonates based on above inclusion and exclusion criteria were enrolled in this study after taking informed consent from their parents; and randomly divided into two groups. Group A (n=50) received UDCA orally 15 mg/kg/day divided 12 hourly in addition to phototherapy, while group B (n=50) received only phototherapy. As cases of direct hyperbilirubinemia were excluded from the study, hence change in TSB was considered reflective of alteration in indirect hyperbilirubinemia so the efficacy of UDCA was measured by comparing the two groups group A and group B by levels of mean TSB at different time points of 24 hrs,48 hrs,72 hrs. and 96 hr and comparison of total duration of phototherapy needed by group A and group B was done.

All the 100 new-born babies included in the study were subjected to further evaluation by detailed history and physical examination. Baseline serum indirect and direct bilirubin determination was done by DMSO calorimetric method. Other investigations done were complete blood count, peripheral blood smear for RBC morphology, Blood grouping (ABO and Rh) of mother and baby. Cases having blood group incompatibility either ABO or RH were subjected to additional investigation like PBF, reticulocyte count, direct comb test. other investigation like TLC, DLC, CRP CSF, urine, blood culture, LFT, x ray chest, USG cranium, abdomen was done if indicated.

All data analysis was done using SPSS version 20 (IBM SPSS Statistics Inc., Chicago, Illinois, USA) Windows software program. The two groups were compared regarding total serum bilirubin at different time point of 24 hrs. ,48 hrs.,72 hrs. and 96 hrs using Student t-test for comparison of means and Chi-square test for contingency tables. With confidence interval set at 95% and P-value <0.05 was considered statistically significant.

The institutional approval was taken from ethical committee of JLN Medical College, Ajmer. Signed informed consent was taken from parents of newborns.

## RESULTS

Both groups i.e. group A- cases (UDCA given) and group B- control (UDCA not given) were statistically matched as far as age, gender and birth weight is concerned. (Table No. 1)

**Table No 1: Age, Gender And Weight Wise Distribution Of Cases And Control**

| | UDCA given ( Group A) | UDCA not given(Group B) | P Value |
|---|---|---|---|
| **Age, Mean (SD)** | 2.6800 (2.62890) | 2.6400(2.87036) | 0.75 |
| **Gender Percentage(%) Male** | 32(64%) | 29(58.0%) | 61(61%) P value 0.53 |
| **Female** | 18(36.0%) | 21(42.0%) | 39(39%) P value 0.53 |
| **Total** | 50 | 50 | 100 |
| **Weight, Mean (SD)** | 3.0020 (0.27441) | 2.9940 (0.25747) | 0.88 |

The mean TSB at the time of admission was 18.39 ± 1.49 (range: 14.5–20 mg/dl) and 18.38 ± 1.57 (range: 14–20 mg/dl) in the intervention group A and the control group B, respectively so both groups were statistically matched as regards TSB at the time of admission. (Table No .2)

The mean TSB measured at 24, 48, 72, and 96 h of treatment in group A was 13.67± 0.513, 10.590 ± 0.388, 9.49 ± 0.41, and 7.566 ± 0.456, respectively, and in group B was 14.5 ± 1.93 at 24 h, 12.7 ± 0.503 at 48 h, 10.49 ± 0.263 at 72 h, and 9.322 ± 0.234 at 96 h. There was significant reduction in mean TSB in patients receiving UDCA and phototherapy compared with those only treated with phototherapy ($P < 0.05$) after 24 h of treatment. After 48 hr, 72 hr and 96 hr of treatment there was a high significant reduction in the level of TSB in group A than that in group B ($P < 0.001$). (Table No. 2)

Duration of phototherapy in group A was 65.2 ± 10.19 h and in group B was 84.90 ± 13.85 h, with statistically significant difference ($P < 0.001$). (Table No. 3).

No short term side effect of UDCA reported in intervention group during the treatment period.

**Table No 2 :TSB (mg/dl) At Admission , After 24, 48, 72 And 96 Hour Of Phototherapy**

| S.No | Time | | UDCA given (Group A) (N=50) | UDCA not given (Group B) (N=50) | P value |
|---|---|---|---|---|---|
| **1.** | At admission | Mean | 18.3980 | 18.3820 | 0.93 |
| | | Std. Deviation (SD) | 1.49744 | 1.57055 | |
| **2.** | 24 hours | Mean | 13.7180 | 14.5140 | 0.007 (S) |
| | | Std. Deviation (SD) | .51377 | 1.93392 | |
| **3.** | 48 hours | Mean | 10.5900 | 12.7000 | 0.001 (S) |
| | | Std. Deviation (SD) | .38874 | .50386 | |
| **4.** | 72 hours | Mean | 9.4980 | 10.4960 | 0.001 (S) |
| | | Std. Deviation (SD) | .41082 | .26338 | |
| **5.** | 96 hours | Mean | 7.5660 | 9.3220 | 0.001 (S) |
| | | Std. Deviation (SD) | .45607 | .23499 | |

**Table No 3:Duration Of Phototherapy Mean (hours) Among Studied Groups**

| | Mean | Std. Deviation | P value |
|---|---|---|---|
| **UDCA given( Group A)** | 64.6320 | 10.19000 | 0.001 (S) |
| **UDCA not given( Group B)** | 84.9000 | 13.85439 | |

## DISCUSSION

In present study, we enrolled 100 neonates with indirect hyperbilirubinemia eligible for study based on inclusion / exclusion criteria. The study group received UDCA at dose of 15 mg/kg/day BD for 3days along with their routine phototherapy while control group was given only phototherapy. Two groups having no significant difference between the sex, mean age, mean weight of the new-born, or TSB level at the beginning of the study were taken.

The mean TSB revealed at 24, 48, 72 and 96 hr of treatment in group A was 13.67± 0.513, 10.590 ± 0.388, 9.49 ± 0.41 and 7.566 ± 0.456 respectively, and in group B was 14.5 ± 1.93 at 24 h, 12.7 ± 0.503 at 48 h, 10.49 ± 0.263 at 72 h and 9.322 ± 0.234 at 96 h. These results showed that the mean TSB level had significantly decreased in patients receiving UDCA and phototherapy compared with those only treated with phototherapy ($P < 0.05$) after 24 h of treatment. After 48 h ,72h and 96 h of treatment, there was a high significant reduction in the level of total bilirubin in group A than that in group B ($P < 0.001$)1. similarly, Honar N et al 2015[7], Hassan et al 2015[8], Jafari s et al.2018 [9], El gandy et al 2019 [10] showed that 12, 24, and 48 hours after hospitalization the rate of fall was higher and the mean total bilirubin had significantly reduced in patients receiving ursodeoxycholic acid (UDCA) and phototherapy both compared to those who underwent phototherapy alone.

The addition of UDCA in our study lead to at least 20 hours' reduction in the duration of phototherapy in the neonates suffering from indirect hyperbilirubinemia, Similarly, Honar et al. (2015) and Hassan et al (2015) concluded that UDCA led to ~24-h and 18 hrs. reduction in the duration of phototherapy respectively in the neonates having indirect hyperbilirubinemia. No short side effect was reported in intervention group during the treatment period. Similarly, Hassan et al[8] and Honar[7] also did not report any adverse effect of UDCA.

## CONCLUSION

To conclude, addition of UDCA at 15 mg/kg/day to phototherapy in neonate with indirect hyperbilirubinemia was found to be more effective than phototherapy alone in reducing the levels of TSB as well as in reducing the duration of phototherapy. Therefore, it may be prudent to recommend that incorporation of UDCA in therapeutic armamentarium would be effective and safe, thus reducing burden in NICU/SNCUs specially in resource poor settings in management of neonatal indirect hyperbilirubinemia.

## DECLARATIONS

*Funding: Nil*
*Conflict of interest: Nil*
*Ethical approval: This research study was approved by institute ethical committee*

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