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Ursodeoxycholic acid and phototherapy versus phototherapy and placebo on neonatal indirect hyperbilirubinemia

Masood Zadkarami[1], Foroozan Rahimpour[1], Amir Kamal Hardani[1], Hazhir Javaherizadeh[2,3*]

[1]Department of Neonatology, Children's Medical Center, Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran
[2]Alimentary Tract Research Center, Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran
[3]Department of Pediatric Gastroenterology, Children's Medical Center, Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran

***Correspondence to**
Hazhir Javaherizadeh, Email: Hazhirja@yahoo.com, Hazhirja@ajums.ac.ir

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Abstract

Introduction: Recently ursodeoxycholic acid was recommended for the treatment of neonatal hyperbilirubinemia in a few studies.
Objectives: This study aimed to compare ursodeoxycholic acid and phototherapy versus phototherapy in lowering the level of bilirubin in neonates who was admitted due to hyperbilirubinemia.
Patients and Methods: This randomized double-blind study was carried out in the department of neonatology at the children's medical center of Ahvaz Jundishapur of the University of Medical Sciences. Inclusion criteria were weight 2500-4200 g and exclusive breastfeeding. Gestational age between 38-41 weeks and age between 3-7 days were included. Total bilirubin between 14-20 according to Bhutani nomogram and direct bilirubin was less than 2 mg/dl was included. Exclusion criteria were ABO incompatibility, Rh incompatibility, G6PD (glucose-6-phosphate dehydrogenase) deficiency, sepsis, hypothyroidism, liver problem, prematurity and newborn of diabetic mothers. A dose of 5 mg/kg per dose of ursodeoxycholic acid (UDCA) was prescribed for neonates every 12 hours. Placebo is also prescribed for other neonates. Unconjugated bilirubin was measured after 4 hours and every 12 hours till total bilirubin=12 mg/dL. The primary outcome measures were total bilirubin level four hours and every 12 hours after admission till reached 12 mg/dL. The secondary outcome measure was total bilirubin=12 mg/dL at 12-24 hours after admission and diarrhea, vomiting, skin rash or any adverse effect in the neonates who received UDCA. Neonates who underwent phototherapy and UDCA were the case group. Neonates who received phototherapy and placebo were allocated in the control group. Data were analyzed using SPSS version 16.0. Kolmogorov-Smirnov test was conducted to evaluate data distribution. Intention-to-treat analysis was used. Mann-Whitney U test was conducted for data analysis.
Results: In the current study, 30 cases and 30 control were included. Discharged neonates were 96% among the UDCA group and 87% among the control group in the 1st 24 hours after admission. Among the UDCA group, 100% were discharged at the 2nd 24 hours of admission and 96% among the control. The duration of phototherapy was shorter in the case group than in the control group, however this difference had no statistical difference.
Conclusion: No significant difference between neonates who underwent phototherapy and phototherapy+ UDCA in terms of duration of phototherapy and bilirubin reduction was found.
Trial Registration: The trial protocol was approved by the Iranian Registry of Clinical Trials (identifier: IRCT20181003041225N1; https://en.irct.ir/trial/34272, ethical code; IR.AJUMS.REC.1397.899).

Introduction

Neonatal hyperbilirubinemia is common during infancy (1). If the portion of unconjugated bilirubin is very high, untreated unconjugated hyperbilirubinemia can cause bilirubin-induced neurological dysfunction (2). This neurological dysfunction is permanent or even may lead to death (3). Phototherapy is the mainstay of therapy (4). Several drugs in addition to phototherapy are recommended in the literature.

Recently, ursodeoxycholic acid (UDCA) is recommended in the literature for the treatment of indirect hyperbilirubinemia (5,6). UDCA had a role in the treatment of neonatal cholestasis (7). UDCA induces biliary flow and reduces intestinal absorption of biliary acid (8). Moreover, UDCA inhibits the apoptotic effect of unconjugated bilirubin on hepatocytes and neuronal cells (9). Studies about the effect of UDCA on indirect hyperbilirubinemia are limited following the search of Medline and Scopus.

Objectives

This study aimed to compare conventional phototherapy and conventional phototherapy and UDCA in the treatment of unconjugated hyperbilirubinemia in healthy appearance term neonates.

Key point

Recently ursodeoxycholic acid was recommended for the treatment of neonatal indirect hyperbilirubinemia according to the some published papers. This randomized clinical trial was conducted to compare ursodeoxycholic acid+ phototherapy versus placebo+phototherapy on lowering bilirubin among healthy term neonates. This study showed, no statistically significant difference between two methods regarding indirect bilirubin level and discharge of neonates.

Patients and Methods

Study design

This randomized double-blind study was carried out in the department of neonatology at the children's medical center of Ahvaz Jundishapur of the University of Medical Sciences. Inclusion criteria were weight 2500-4200 g and exclusive breastfeeding. Gestational age between 38-41 weeks and age between 3-7 days also were included. Total bilirubin between 14-20 mg/dL according to the Bhutani curve and direct bilirubin was less than 2 mg/dL was included.

Exclusion criteria were ABO incompatibility, Rh incompatibility, glucose-6-phosphate dehydrogenase (G6PD) deficiency, sepsis, hypothyroidism, liver problem, prematurity and newborn of diabetic mother. A dose of 5 mg/kg per dose of UDCA was prescribed for neonates every 12 hours. Placebo is also prescribed for other neonates. Unconjugated bilirubin was measured after 4 hours and every 12 hours till total bilirubin = 12 mg/dL. Neonates in case group received treatment with UDCA and phototherapy. Neonates who received phototherapy and placebo were allocated in the control group.

Statistical analysis

Data were analyzed using SPSS version 16.0. Kolmogorov-Smirnov test was conducted to evaluate data distribution. Intention-to-treat analysis was employed. Mann-Whitney U test was conducted for data analysis. The flow chart of the study was seen in Figure 1.

Results

In the current study 30 case and 30 control were included. The age of the case and control according to hours were shown in Table 1. Total bilirubin among case and control before starting treatment was shown in Table 1. As seen in Table 2, the duration of phototherapy was shorter in the case group than in the control group; however, there was no significant between the two groups in terms of duration of phototherapy ($P=0.198$). A comparison between total bilirubin levels between the control and case group in terms of 4, 12, and 24 hours following treatment was shown in Table 3.

Discharged neonates were 96% among cases and 87% among the control group in the 1st 24 hours after admission. Among the case group, 100% were discharged at the 2nd 24 hours of admission, and 96% were among the control (Table 4).

Discussion

In the current study, the duration of admission in the case

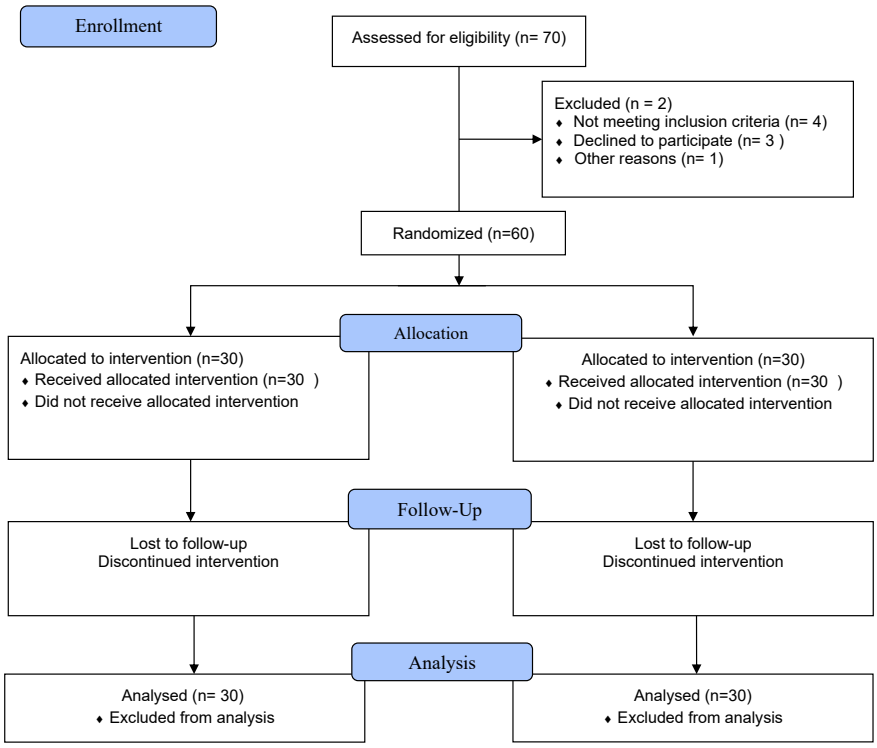

Figure 1. CONSORT flow diagram of the study.

Table 1. Age, weight and head circumference among case and control

	Case (n=30)	Control (n=30)
Age (h)	118.10±34.94	119.43±38.00
Body weight (g)	2500±419.527	2450±395.244
Height (cm)	50.26±2.08	49.73±1.26
Head circumference (cm)	34.13±1.15	34.45±0.99
Total bilirubin(admission) (mg/dL)	16.74±1.86	16.99±1.81

Table 2. Duration of phototherapy among case and control group

Phototherapy duration (h)	N	Minimum	Maximum	Mean ± SD
Case	30	8.00	36.00	14.73±6.03
Control	30	6.00	60.00	18.20±10.72

group was shorter than in the control group, however this difference was not statistically significant. In the study by Ughasoro et al, UDCA accentuates the effect of phototherapy in reducing total serum bilirubin and reducing the duration of treatment (10). The sample size of the study by Ughasoro et al (10) was less than the current study.

In the study by El-Gendy et al, duration of phototherapy was significantly shorter among neonates who received UDCA treatment (6).

In another study, UDCA has a beneficial effect in reducing bilirubin levels and duration of hospital admission in neonatal indirect hyperbilirubinemia. In a recent study on mice, UDCA reduces both plasma and brain bilirubin (5). It should remember that no adverse effect of this drug was seen in our study. The result of these studies differs from our studies. It may be due to different sample sizes or genetic backgrounds. In a previous meta-analysis by Kuitunen et al (11), they found low-quality evidence that UDCA as an adjuvant to phototherapy decreases the indirect bilirubin. Furthermore, the dose of UDCA was different between studies (11). Most of the studies published were conducted in Middle East region (6, 11), therefore larger studies from different geographical region and more sample size are recommended.

Conclusion

In this study, we did not find statistical significance to recommend UDCA as an adjunct therapy for neonates with physiologic hyperbilirubinemia; however, another large multi-centric study is recommended.

Limitations of the study

Limitations of this study include a single-center study and a lack of longer follow-up to check rebound hyperbilirubinemia in two groups.

Availability of data and material

Data was available with the corresponding author.

Acknowledgments

This study was approved by the research affair of Ahvaz Jundishapur University of Medical Sciences.

Authors' contribution

Methodology: HJ
Validation: MZ.
Formal analysis: FR and HJ.
Investigation: MZ and HJ
Resources: MZ and AH.
Data curation: FR.
Writing–original draft: MZ and FR.
Writing–review and editing: HJ.
Visualization: FR.
Supervision: MZ and AH.
Project administration: MZ.

Conflicts of interest

The authors declare that they have no competing interests.

Ethical issues

The research conducted in accordance with the tents of the Declaration of Helsinki. The Ethics Committee of Ahvaz Jundishapur University of Medical Sciences approved this study. The institutional ethical committee at Ahvaz Jundishapur University of Medical Sciences accepted all study protocols. Accordingly, written informed consent was taken from all participants before any intervention. This study was part of pediatric residential thesis of Forouzan Rahimpour at this university (thesis#U-97221). The trial protocol was approved by the Iranian registry of clinical trial (identifier: IRCT20181003041225N1; https://en.irct.ir/trial/34272). Ethical issues (including plagiarism and data fabrication double

Table 3. Comparison between total bilirubin level between undischarged control and case group in terms of 4, 12, and 24 hours following treatment

Total bilirubin (mg/dL)	Case (n = 30)	Control (n = 30)	*P* value
4 hours after phototherapy	14.96 ± 2.52 (n=30)	15.04 ± 2.44(n=30)	>0.05
12 hours after phototherapy	11.41 ± 2.73 (n=28)	12.00 ± 2.56 (n=29)	> 0.05
24 hours after phototherapy	11.55 ± 2.40 (n=6)	11.52 ± 2.78 (n=10)	>0.05

Table 4. Discharged neonates after 1st and 2nd hour between case and control group

Case	Discharged neonates (%)		Significance level
	1st 24 hour	2nd 24 hour	
Case (n=30)	96%	100%	0.165 (Mann-Whitney U)
Control (n=30)	87%	97%	

publication) have been completely observed by the authors.

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