Original Research Article

Role of ursodeoxycholic acid in neonates with indirect hyperbilirubinemia-an open labelled randomised control trial

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Received: 04 December 2017

Accepted: 30 December 2017

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ABSTRACT

Background: Ursodeoxycholic Acid (UDCA) is a bile acid widely used in the treatment of cholestatic liver disorders. Few studies have been conducted using UDCA in indirect hyperbilirubinemia. We planned this study to know the role of Ursodeoxycholic acid on indirect hyperbilirubinemia in neonates

Methods: The study was conducted in Department of Paediatrics and Neonatology at Eras Lucknow Medical College and Hospital from November 2015 to September 2017 in 96 term neonates with total bilirubin levels in phototherapy range. They were randomized into 3 Groups receiving either phototherapy only or UDCA at 10mg/kg/day or 20mg/kg/day along with phototherapy.

Results: Present study showed that there was a higher rate of fall and less duration of phototherapy required in children receiving UDCA. However, there was no difference in the group receiving 10mg vs 20 mg /kg/day

Conclusions: We conclude that by giving UDCA at 10mg/kg/day along with phototherapy in neonate with indirect hyperbilirubinemia leads to faster resolution of hyperbilirubinemia.

Keywords: Indirect hyperbilirubinemia, Phototherapy, UDCA

INTRODUCTION

Hyperbilirubinemia is a common problem in infants. According to some population based studies from developing nations, it is responsible for nearly 15-35% of neonatal intensive care unit (NICU) admissions.¹⁻³

Typically, phototherapy has been used to reduce the amount of bilirubin in neonates. However, it is expensive and disrupts mother child bonding.⁴ Can also lead to potential complications like retinal degenerative changes, bronze baby syndrome, and thermal instability.¹

Therefore, adjuvant therapies like phenobarbital, metalloporphyrin, clofibrate and bile salts that decrease the duration of phototherapy are being looked into.¹

Ursodeoxycholic acid is a bile acid widely used in the treatment of cholestatic liver disorders.⁴ Few studies have been conducted using UDCA in indirect hyperbilirubinemia. The usual dose in neonates is 10-20 mg /kg day.⁵ It prevents the liver against oxidative stress, prevents cellular apoptosis and stimulates bile flow.⁴ Therefore, we planned this study to know the role of Ursodeoxycholic acid on indirect hyperbilirubinemia in neonates

The aims and objectives of this study were to study the rate of fall of serum bilirubin in neonates with indirect hyperbilirubinemia receiving phototherapy versus those receiving phototherapy and ursodeoxycholic acid, to compare the duration of phototherapy required in infants with indirect hyperbilirubinemia receiving ursodeoxycholic acid versus those receiving phototherapy

only and to compare doses 10 mg/kg/day versus 20 mg/kg/day of Ursodeoxycholic acid in treating indirect hyperbilirubinemia along with phototherapy.

METHODS

The study was conducted in Department of Paediatrics and Neonatology at Eras Lucknow Medical College and Hospital from November 2015 to September 2017.

Inclusions criteria

Term neonates from 24 hours up to 14 days with total bilirubin levels in phototherapy range and direct bilirubin <20% of total.

Exclusion criteria

- Infants with need for or having undergone exchange transfusion
- Those with signs of sepsis, Rh or Abo incompatibility, any congenital anomalies
- Infants who have been previously exposed to phototherapy.

Sample size was calculated with power of 90% which came out to be 96 with 32 in each group. They were randomized into 3 groups Group A, treated with phototherapy alone, Group B, was treated with phototherapy and 10 mg/kg/day of Ursodeoxycholic acid,

Group C, was treated with phototherapy and 20 mg/kg day of Ursodeoxycholic acid.

Ursodeoxycholic acid was orally administered 12 hourly along with phototherapy in groups B and C. Serum bilirubin levels were measured after 8, 16, 24, 36 and 48 hrs and 12 hourly thereafter till the serum bilirubin was normalised. VITROS chemistry products BuBc slides were used to measure unconjugated serum bilirubin (Bu) and conjugated serum bilirubin (Bc). The Vitros BuBc slide method was performed using the VITROS BuBc slides and the VITROS chemistry products. Ethical clearance was taken by the hospital ethical committee.

RESULTS

96 children with indirect hyperbilirubinemia were recruited randomly to receive the predefined treatment modality. Baseline characteristic of all were comparable. None of the children reported any significant adverse events during the course of treatment.

Table 1 shows that at the start of therapy serum bilirubin was comparable in all 3 groups, while after 8 hours there is significant difference between Group A and B and Group A and C

The Table 2 demonstrates that the rate of fall of bilirubin is significant after 8 hours of therapy in Group A versus Group B and Group A versus Group C but no significant difference between Group B and Group C.

Table 1: Intergroup comparison of Serum Bilirubin at different time periods.

Period of Observation	Group A			Group B			Group C			ANOVA	
	n	Mn	SD	n	Mn	SD	n	Mn	SD	F	'p'
Admission	32	16.47	1.65	32	16.22	1.67	32	16.64	1.72	0.492	0.613
8 hours	32	15.78	1.94	32	14.28	2.69	32	13.90	2.55	5.432	0.006
16 hours	27	14.66	2.57	12	14.18	2.12	8	14.61	2.29	0.174	0.841
24 hours	14	15.32	1.72	1	13.00	.	0	.	.	1.696	0.215
36 hours	9	12.58	2.25								
Final Visit	32	13.44	2.66	32	13.54	2.53	32	13.46	2.33	0.013	0.987

Table 2: Comparison between Group of S. Bilirubin at different time periods.

	Group A versus Group B			Group A versus Group C			Group B versus Group C		
	Mn diff	SE	p	Mn diff	SE	p	Mn diff	SE	p
Admission	0.25	0.42	0.824	-0.16	0.42	0.919	-0.41	0.42	0.588
8 hours	1.50	0.60	0.039	1.88	0.60	0.007	0.38	0.60	0.804
16 hours	0.49	0.84	0.830	0.06	0.97	0.998	-0.43	1.10	0.920
24 hours									
36 hours									
Final visit	-0.10	0.63	0.987	-0.02	0.63	1.000	0.08	0.63	0.992

Table 3: Intergroup comparison of visit at S. bilirubin level returned to normal.

Gender	Total	Group A		Group B		Group C	
		No.	%	No.	%	No.	%
8 hours	49	5	15.63	20	62.50	24	75.00
16 hours	32	13	40.63	11	34.38	8	25.00
24 hours	6	5	15.63	1	3.13	0	0.00
36 hours	9	9	28.13	0	0.00	0	0.00
		$\chi^2=38.473(df=6); p<0.001$ A Vs B $\chi^2=20.833(df=3); p<0.001$ A Vs C $\chi^2=27.639(df=3); p<0.001$ B Vs C $\chi^2=1.837(df=2); p=0.399$					

The Table 3 shows that phototherapy could be stopped in only 56 % of Group A neonates at 16 hours as compared to 97% and 100% in group B and group C respectively.

DISCUSSION

Ursodeoxycholic acid (UDCA), a bile acid that is widely used in the treatment of cholestatic liver disorders has emerged as a ray of hope. UDCA has benefit of protecting the liver against oxidative stress, preventing cell apoptosis, stimulating the bile flow, and suppressing the confounding factors in immunological mechanisms.⁶ In Pediatric practice too, UDCA has been shown to be well tolerable without any major complications.⁷ The goal of an RCT performed is generally to show that a new drug is superior to an existing standard treatment or placebo with regard to an endpoint that has been defined a priori - frequently a "hard" endpoint such as survival. The proof of superiority is consciously and intentionally obtained under conditions that do not necessarily reflect everyday clinical practice. An ideal RCT should have similar sampling frame (inclusion and exclusion criteria), study condition and patient characteristics in order to rule out any selection bias to be cause of difference in outcome.⁸

The results of the present study showed that 8, 12, 24, 36 and 48 hours after hospitalisation the rate of fall was higher (Table 2) and the mean total bilirubin had significantly reduced in patients receiving ursodeoxycholic acid (UDCA) and phototherapy alone compared to those who underwent phototherapy alone (Table 1). This effect was more prominent in the first 8 hours. UDCA led to reduction in the duration of phototherapy in neonates suffering from indirect hyperbilirubinemia most probably by increasing unconjugated bilirubin (UCB) turnover through its fecal disposal. The only study on the effect of UDCA on decreasing UCB is the one conducted by Cuperus FJ et al on rats in 2009, the findings of that study showed that UDCA had increased UCB turnover through increasing its fecal disposal.⁹ Reduction of UCB in the present study also seems to result from the same mechanism. Nonetheless, Mandez-Sandez et al investigated the effect

of UDCA in rats and mice showed the increase of enterohepatic UCB after the oral consumption of UDCA.⁶

The safety and efficacy of UDCA has been reported in both adult and pediatric age groups. Owing to a cytoprotective and stabilizing effect of UDCA it has not been reported to accompany any side effect and hence is a safe treatment modality as observed in previous study.^{10,11} Similar to present study, Hassan et al and Honar also did not report any side effect of UDCA treatment.^{12,4}

However, there was some limitation in the present study as we were not able to predict all the variables which have a role in indirect hyperbilirubinemia. Further studies need to evaluate the efficacy of UDCA in the treatment of UCB of neonates. Also, we could not evaluate the long term side effects if any of UDCA so we recommend further investigation with larger sample size and long term follow up.

CONCLUSION

It can be concluded that by adding UDCA at 10 mg/kg/day to phototherapy in neonate with indirect hyperbilirubinemia is more effective than phototherapy alone. Other than being highly effective in reducing the levels of total bilirubin the administration of UDCA immediately after or during the first 48 hours after hospitalisation will also decrease the time period required for phototherapy.

Funding: No funding sources

Conflict of interest: None declared

Ethical approval: The study was approved by the Institutional Ethics Committee

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Cite this article as: Jafari S, Khan KA, Bhatnagar S, Srivastava G, Nanda C, Chandra A. Role of ursodeoxycholic acid in neonates with indirect hyperbilirubinemia-an open labelled randomised control trial. *Int J Contemp Pediatr* 2018;5:432-5.