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Original Research Article

Effect of Ursodeoxycholic Acid in Lowering Neonatal Indirect Hyperbilirubinemia: A Randomized controlled trial

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Abstract

Hyperbilirubinemia is a common and, in most cases, a benign problem in neonates. Conventional treatment for severe indirect hyperbilirubinemia consists of phototherapy and exchange transfusion. Several drugs like Metalloporphyrins, D-pencillamine, phenobarbital, activated charcoal, 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. To assess the additive effect of Ursodeoxycholic Acid on reducing indirect hyperbilirubinemia in neonates under phototherapy. This study is a randomized controlled trial on neonates with indirect hyperbilirubinemia who required phototherapy; admitted to neonatal care unit of Sulaimani Pediatric Teaching Hospital during the period of February 2014 to February 2015. 200 neonates were enrolled in this study and randomly divided into two groups, group A (n=100) received Ursodiol 10 mg/kg/day orally divided 12 hourly in addition to phototherapy, while group B (n=100) received only phototherapy. Total serum bilirubin levels were measured every 12 hours until reaching to below 10mg/dl and then phototherapy was stopped. The two groups were compared regarding total serum bilirubin at different time points using t-test for comparison of means and Chi-square test for contingency tables, and ($p<0.05$) was considered statistically significant. The mean total serum bilirubin in group A was 11.7±1.5, 8.8±1.1, and 7.6±0.9 mg/dl at 12, 24 and 36 hours respectively, after the beginning of Ursodiol and phototherapy, while these measures were 14.6±1.6, 13.2±5.8, 10.2±1.4 and 9.1±0.8 mg/dl at 12, 24, 36 and 48 hours respectively in group B ($p < 0.001$), and the duration of phototherapy in both group A and group B were 23.2±5.6 and 41.1±7.2 hours respectively ($p< 0.001$). Ursodeoxycholic Acid has an additive effect if used with phototherapy in the neonate with indirect hyperbilirubinemia and reduces the time needed for phototherapy.

Keywords: Indirect hyperbiliruninemia, phototherapy and neonatal jaundice, Ursodeoxycholic acid

INTRODUCTION

Hyperbilirubinemia in neonates is defined as a total serum bilirubin (TSB) >95th percentile on the hour-specific Bhutani nomogram (Bhutani et al., 1999). Hyperbilirubinemia is a common and, in most cases, benign problem in neonates. Jaundice is observed during the first week of life in approximately 60% of term infants and 80% of preterm infants (Amabalavanan and Carlo, 2011). Conventional treatment for severe indirect hyperbilirubinemia consists of phototherapy and exchange transfusion. Phototherapy, however, has

Table 1. Gender, mean age and weight of the studied groups

Characteristics	**Group A** Mean ± SD	**Group B** Mean ± SD	P value
Age(day)	5.4±1.4	5.3±1.5	0.886
Wt (kg)	3.2±0.4	3.1±0.4	0.287
Gender			
Male	56	51	0.471
Female	44	49	
Total	100	100	

several known disadvantages while exchange transfusion is associated with a significant morbidity, and even mortality. These harmful effects indicate the need to develop alternative pharmacological treatment strategies for unconjugated hyperbilirubinemia. Up till now, several drugs like metalloporphyrins, D-pencillamine, phenobarbital, activated charcoal, 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 (Dennery et al., 2001; Dennery, 2002). Ursodeoxycholic Acid (UDCA) is a bile acid which is widely used in treatment of cholestatic liver disorders. It protects the liver against oxidative stress, prevents cell apoptosis, stimulates the bile flow, and suppresses the confounding factors in immunological mechanisms (Copaci et al., 2005). UDCA is well tolerated and has limited complications in pediatric (Balistreri, 1997).

The aim of this study was to assess the additive effect of Ursodeoxycholic Acid on reducing indirect hyperbilirubinemia in neonates receiving phototherapy.

Patients and method

This randomized controlled study was done on newborns with indirect hyperbilirubinemia who were admitted to the neonatal care unit in Sulaimani Pediatric Teaching Hospital from February 2014 to February 2015. A total of 200 neonates were enrolled in this study after taking informed consent from their parents; and randomly divided into two groups. Group A (n=100) with received Ursodiol (made in Italy number 00040 Pomezia Rome company) orally 10 mg/kg/day divided 12 hourly in addition to phototherapy, while group B (n=100) received only phototherapy. Total serum bilirubin (TSB) levels were measured every 12 hours until reaching below 10mg/dl and then phototherapy was stopped. Included neonates were term, with weight appropriate for gestational age, 3-7 days old, exclusive breast-fed, having total serum bilirubin level of 14-20 mg/dl and direct bilirubin level < 2mg/dl. Exclusion criteria were; Rh or ABO incompatibility, premature neonates, sepsis and infants of diabetic mothers.

On the first day of admission, history including birth weight, the onset of hyperbilirubinemia, the family history of jaundice and their cause in other siblings were taken from all mothers. Complete neonatal examination was performed. Laboratory data included the followings: complete blood count, blood group and Rh, direct bilirubin and total serum bilirubin were done for both groups. For follow up TSB estimation; micro method was used by taking micro blood samples from the heel of the babies. The lamps of the phototherapy devices were LED type and they were at a standard distance from the patient, and their half lives were not more than 250 hours. All data analyzed using SPSS (version 20) software computer program. The two groups were compared regarding total serum bilirubin at different time points using t-test for comparison of means and Chi-square test for contingency tables. P-value <0.05 was considered statistically significant.

RESULTS

The mean age of the studied neonates was 5.4±1.4 days and 5.3±1.5 days in group A and group B respectively. No significant difference was found between the two groups (p = 0.886). The mean weight was 3.2 ± 0.4 Kg. and 3.1 ± 0.4 Kg. in group A and group B respectively, without statistically significant difference (P = 0.287). There was no statistically significant difference across gender between the two groups (P = 0.471), table 1.

The mean total serum bilirubin at the time of hospitalization in group A and group B were 16.3±1.7 and 16.5±2.9 mg/dl respectively, without statistically significant difference (p = 0.852). The mean total serum bilirubin estimation in both studied group at 12, 24 and 36 hours after hospitalization is presented in Table 2. The difference between the mean total serum bilirubin in the two groups was statistically significant at 12, 24 and 36 hours after hospitalization (P=0.001).

Thirty six hours after hospitalization only 8 patients were remaining in group A while 93 patients were remaining in group B; 48 hours after hospitalization, all patient in group A stopped phototherapy; while 49 cases were still under phototherapy in group B, table 2.

There was a statistically significant difference between the two groups regarding the time of phototherapy

Table 2. Mean TSB in both groups

Mean of TSB(mg/dl)	Group A	Group B	P value
On admission	16.3±1.7	16.5±2.9	0.852
After 12 hours	11.7±1.5	14.6±1.6	0.001
After 24 hours	8.8±1.1	13.2±5.8	0.001
After 36 hours	7.6±0.9	10.2±1.4	0.001
After 48 hours	NA	9.1±0.8	

Table 3. Duration of phototherapy in both groups

Duration	Group A	Group B	P.value
Time in hours	23.2±5.6	41.1±7.2	0.001

needed (P = 0.001), table 3.

Regarding acute adverse effects of Ursodiol, the patients were followed up during staying in hospital; no complications were reported in group A.

DISCUSSION

There was no significant difference between the two groups regarding the mean age, mean weight and gender distribution; these findings were similar to other studies elsewhere (Schwartz et al., 2011). The results of this study showed statistically significant reduction in TSB in group A, at 12, 24 and 48 hours after starting Ursodiol and phototherapy, in comparison with group B who was on phototherapy alone. Such additive effect of Ursodiol in reducing indirect hyperbilirubinemia in neonates was reported by Honar et al. from Shiraz (Honar et al., 2015). Earlier reports investigated the effect of oral UDCA in lowering unconjugated bilirubin (UCB) in Gunn rats, showed that UDCA increased UCB turnover through increasing its fecal disposal (Cuperus et al., 2009). Mendez et al reported a similar effect in rodents probably by causing bile salt malabsorption and concluded that dietary UDCA and cholesterol induce enterohepatic cycling of bilirubin (Méndez-Sánchez et al., 1998).

The addition of Ursodiol lead to at least 18 - hours reduction in the duration of phototherapy in the neonates suffering from indirect hyperbilirubinemia most probably by increasing unconjugated bilirubin turnover through its fecal disposal; this finding was similar to that of Honar et al. (2015). Furthermore; Palmela et al in an in-vitro study found that UDCA protect human blood-brain barrier endothelial cells from disruption by UCB (Palmela et al., 2015).

There were no adverse effects of UDCA during the study period; other studies also confirmed the safety of UDCA in children (Balistreri, 1997). However for long term adverse effects of UDCA further studies are needed.

CONCLUSION

In conclusion, the addition of oral UDCA to phototherapy in the treatment of neonatal indirect hyperbilirubinemia will be highly effective in reduction of hyperbilirubinemia as well as the time period required for phototherapy.

REFERENCES

Amabalavanan N, Carlo WA (2011). Jaundice and hyperbilirubinemia in newborn. In: Kliegman, Stanton, St.Geme, Schor, Behrman(Eds). Nelson's Text book of Pediatrics;19th edition; Philadelphia. Elsevier Saunders.603-607

Balistreri WF (1997). Bile acid therapy in pediatric hepatobiliary disease: the role of ursodeoxycholic acid. J Pediatr Gastroenterol Nutr. May;24(5):573-89

Bhutani VK, Johnson L, Sivieri EM (1999). Predictive ability of a predischarge hour-specific serum bilirubin for subsequent significant hyperbilirubinemia in healthy term and near-term newborns. Pediatrics; 103:6.

Copaci I, Micu L, Iliescu L, Voiculescu M (2005). New Therapeutical Indications of Ursodeoxycholic Acid. Romanian Journal of Gastroenterology.September Vol.14 No.3, 259-266

Cuperus FJ, Hafkamp AM, Havinga R, Vitek L, Zelenka J, Tiribelli C, Ostrow JD, Verkade HJ (2009). Effective treatment of unconjugated hyperbilirubinemia with oral bile salts in Gunn rats. Gastroenterology. Feb;136(2):673-82.e1.

Dennery PA (2002). Pharmacological interventions for the treatment of neonatal. Semin Neonatol. Apr;7(2):111-9.

Dennery PA, Seidman DS, Stevenson DK (2001). Neonatal hyperbilirubinemia. N Engl J Med; 344:581.

Honar N; Saadi E G; Saki F; Pishva N; Shakibazad N; Teshnizi SH (2015). Effect of Ursodeoxycholic Acid on Indirect Hyperbilirubinemia in Neonates Treated With Phototherapy: A Randomized Trial. J Pediatr Gastroenterol Nutr May 25. Epub 2015 May 25. http://dx.doi.org/10.1097/MPG.0000000000000874.

Méndez-Sánchez N, Brink MA, Paigen B, Carey MC (1998). Ursodeoxycholic acid and cholesterol induce enterohepatic cycling of bilirubin in rodents. Gastroenterology. Sep;115(3):722-32.

Palmela I, Correia L, Silva R, Sasaki H, Kim K, Brites D, Maria A. Brito (2015). Hydrophilic bile acids protect human blood-brain barrier endothelial cells from disruption by unconjugated bilirubin: an in vitro study. Front Neurosci.; 9: 80.

Schwartz HP, Haberman BE, Ruddy RM (2011). Hyperbilirubinemia: current guidelines and emerging therapies. Pediatr Emerg Care. Sep;27(9): 884-9.