Effect of Ursodeoxycholic Acid on Indirect Hyperbilirubinemia in Neonates Treated With Phototherapy: A Randomized Trial

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Effect of Ursodeoxycholic Acid on Indirect Hyperbilirubinemia in Neonates Treated With Phototherapy

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ABSTRACT

Background: Hyperbilirubinemia is a common neonatal problem. The present study aimed to investigate the effect of ursodeoxycholic acid in reducing indirect hyperbilirubinemia of infants under phototherapy.

Methods: This double-blind randomized clinical trial was conducted on neonates with jaundice, who had received phototherapy in the hospitals affiliated with the Shiraz University of Medical Sciences in 2013. A total of 80 neonates were enrolled in the study and were randomly divided into 2 groups. The intervention group (n = 40) with indirect hyperbilirubinemia received 10 mg · kg⁻¹ · day⁻¹ divided every 12 hours Ursobil (capsule 300 mg) in addition to phototherapy, whereas the control group (n = 40) received only phototherapy. Total bilirubin levels were measured every 12 hours until reaching <10 mg/dL, and then phototherapy was disrupted. The duration of phototherapy was measured. The 2 groups were compared regarding total bilirubin levels at different time points and duration of phototherapy using the generalized estimating equation (GEE) test.

Results: The mean of total bilirubin in the intervention group was 12 ± 1.6, 10 ± 1.1, and 9.8 ± 0.2 mg/dL 12, 24, and 48 hours after the beginning of phototherapy, respectively. On the contrary, these measures were 14.4 ± 1.3, 12.5 ± 1.4, and 10.1 ± 1.1 mg/dL in the control group, respectively, (P < 0.05). The mean time required for phototherapy to decrease the bilirubin level to <10 mg/dL was 15.5 ± 6 and 44.6 ± 13.3 hours in the case and control group, respectively, (P = 0.001).

Conclusions: Ursodeoxycholic acid had additive effect with phototherapy in neonates with indirect hyperbilirubinemia. This drug also reduced the time period needed for phototherapy and, consequently, decreased the hospitalization period.

What Is Known

- Unconjugated hyperbilirubinemia affects half of the full term and almost all of the preterm infants.
- Phototherapy is used for unconjugated hyperbilirubinemia treatment; however, it disrupts mother-child bonding and has potential complications.
- Ursodeoxycholic acid is a safe drug used in the treatment of cholestatic liver disorders in children, but it has not yet been studied in neonates.

What Is New

- Adding ursodeoxycholic acid to phototherapy in unconjugated hyperbilirubinemia neonates is more effective than phototherapy alone in reducing serum bilirubin.
- Ursodeoxycholic acid therapy during the first 48 hours of hospitalization decreases the duration of phototherapy needed for controlling neonatal unconjugated hyperbilirubinemia.

Key Words: neonatal indirect hyperbilirubinemia, neonatal jaundice, ursodeoxycholic acid

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dehydration, and neurological disorders (7). 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 disorders. It protects the liver against oxidative stress, prevents cell apoptosis, stimulates the bile flow, and suppresses the confounding factors in immunological mechanisms (9). UDCA is well tolerated and has limited complications in pediatrics (10).

One study, which was conducted on the effect of UDCA and phototherapy on unconjugated bilirubin (UCB) in rats, showed that UDCA increased the turnover of UCB by its fecal disposal (11).

Owing to the lack of sufficient data about the effect of UDCA on neonatal unconjugated hyperbilirubinemia, the present study aimed to investigate the effect of UDCA on reducing the UCB of the infants undergoing phototherapy, with the hope to reduce the lengths of phototherapy and hospitalization.

**METHODS**

The present double-blind, randomized clinical trial was conducted on neonates with jaundice who were treated through phototherapy in the neonatal wards affiliated with the Shiraz University of Medical Sciences in 2013. Shiraz is the capital city of Fars Province, located in the south of Iran. The patients were selected with simple random sampling and were also blindly divided in groups of case (who were treated with phototherapy + UDCA) and control (who were treated with phototherapy + placebo) by a single observer (a nurse who blindly treated the neonates with UDCA or placebo and observed the outcome).

Only 1 physician knew the code of neonates who received the UDCA and did not have any contact with either the parents or the medical team (including the nurses). Neither the nurse nor the parents knew which neonate received the UDCA. One statistics specialist calculated the sample size using a sample size formula for comparing 2 independent groups (α = 0.05, β = 0.2, d = μ1 – μ2 = 0.95, s1 = 1.5, and s2 = 1.5); sample size was calculated as 40 patients for each group.

Thus, 40 neonates for the case and 40 neonates for the control group were enrolled. Statistical power analysis at the end of the study was calculated as 92%, which was greater than power (1-β = 80%). Neonates entered the study after obtaining written informed consents from their parents.

The inclusion criteria of the study were birth weights of 2500 to 4000 g, being exclusively breast-fed, gestational age of 38 to 41 weeks, being >3 days old, total bilirubin level of 14 to 20 mg/dL, and direct bilirubin level <2 mg/dL. Infants with ABO and RH incompatibility, glucose-6-phosphate dehydrogenase (G6PD) deficiency, direct hyperbilirubinemia, septicemia, and diseases leading to hyperbilirubinemia (Criagler-Najjar syndrome, Gilbert syndrome, hypothyroidism/hyperthyroidism, liver diseases, etc), premature neonates, and the infants of diabetic mothers were excluded from the study.

The intervention group, which included 40 infants with unconjugated hyperbilirubinemia, received 10 mg · kg⁻¹ · day⁻¹ divided q12 h Ursobil (UDCA, capsule 300 mg; provided by Dr Abidi Company, Tehran, Iran) that was diluted with water (and was sucked by the babies) according to weight by pharmacist in addition to phototherapy, whereas the control group (n = 40) received placebo (which was water) and phototherapy. Phototherapy was performed continuously using daylight fluorescent bulbs (Westinghouse, Pittsburgh, PA) in an Air Shields unit (Drager, London, UK). The distance between the lamp and the baby was 30 to 35 cm. The duration of phototherapy was measured using a timer. It should be noted that the lamps of the phototherapy device were at a standard distance from the patients and were changed after 250 hours. During phototherapy, genitalia and both eyes of infants were covered.

On the first day of hospitalization, complete history and physical examination, total and direct bilirubin, reticulocyte count, Coombs test, G6PD level, complete blood count, Rh, and blood group experiments were performed for both groups. In addition, total bilirubin levels were measured by diazo method, every 12 hours until the total bilirubin level reached <10 mg/dL, and phototherapy was disrupted thereafter total bilirubin levels were not checked. (Table 1). All of the information was recorded on a data collection form, and the 2 groups were compared regarding total bilirubin levels at different time points, the time duration in which bilirubin levels reached <10, and the duration of phototherapy.

The study was approved by the ethics committee of the Shiraz University of Medical Sciences, Shiraz, Iran, and was registered in the Iranian Registry of Clinical Trials (ID: IRCT2013020512370N1). The parents signed written informed consent forms.

**Data Analysis**

All of the data analyses were performed using the SPSS statistical software (SPSS18, IBM SPSS Software, Armonk, NY). Data were mentioned as mean ± SD. Normality of data distribution was evaluated by Kolmogorov-Smirnov test. Independent sample t test was used to compare the mean of bilirubin in the 2 groups. Owing to some missing data (those bilirubin which were not checked when the neonate had 1 bilirubin test <10 mg/dL during phototherapy), the association between changes of bilirubin over time in each group were checked by the generalized estimating equation (GEE) method with linear link function and unstructured working correlation matrix. P <0.05 was considered as statistically significant.

**RESULTS**

The mean age of the studied subjects was 3.7 ± 1 (3–6 days) and 3.6 ± 1 days (3–7 days) in the intervention and the control groups, respectively, and no significant difference was found between the 2 groups in this regard (P = 0.44). Considering sex distributions in the intervention group, 21 subjects (52.5%) were female, and 19 (47.5%) were male. In the control group, in contrast, 22 (55%) subjects were female. Table 1 summarized the general characteristics.

<table>
<thead>
<tr>
<th>Variables</th>
<th>Intervention group</th>
<th>Control group</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>3.7 ± 1</td>
<td>3.6 ± 1</td>
<td>0.44</td>
</tr>
<tr>
<td>Sex (female, male) (%)</td>
<td>21 (52.5), 19 (47.5)</td>
<td>22 (55), 18 (45)</td>
<td>0.78</td>
</tr>
<tr>
<td>Mean total bilirubin on admission, mg/dL</td>
<td>15.9 ± 1.7</td>
<td>16.3 ± 1.5</td>
<td>0.44</td>
</tr>
<tr>
<td>Weight on admission, g</td>
<td>2970 ± 292</td>
<td>2985 ± 312</td>
<td>0.651</td>
</tr>
</tbody>
</table>
Ursobil’s Effect on Neonatal Hyperbilirubinemia

TABLE 2. Comparison of the case and control groups regarding the mean of total bilirubin at different time points after admission

<table>
<thead>
<tr>
<th>Time after hospitalization</th>
<th>Case group, mg/dL</th>
<th>Standard, mg/dL</th>
<th>P</th>
<th>95% Confidence interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>At the time of admission</td>
<td>15.9 ± 1.7</td>
<td>16.3 ± 1.5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>12 h after admission</td>
<td>12 ± 1.6</td>
<td>14.4 ± 1.3</td>
<td>&lt;0.001</td>
<td>-2.15 to -1.5</td>
</tr>
<tr>
<td>24 h after admission</td>
<td>10 ± 1.1</td>
<td>12.5 ± 1.4</td>
<td>&lt;0.001</td>
<td>-4.21 to -3.42</td>
</tr>
<tr>
<td>48 h after admission</td>
<td>9.8 ± 0.2</td>
<td>10.1 ± 1.1</td>
<td>&lt;0.001</td>
<td>-6.89 to -5.84</td>
</tr>
</tbody>
</table>

*Total bilirubin was checked and recorded till 10 mg/dL.

The mean of total bilirubin was 16.1 ± 1.6 mg/dL at the time of hospitalization. It was 15.9 ± 1.7 (range 13.2–20 mg/dL) and 16.3 ± 1.5 mg/dL (range 14–20 mg/dL) in the intervention and the control groups, respectively, (P = 0.44). The mean of total bilirubin in the 2 study groups at the time of hospitalization and 12, 24, 48, 60, and 72 hours after hospitalization is presented in Table 2. The results of GEE showed that the bilirubin levels over time within each group were significantly different (P = 0.008) (Fig. 1). Generally, the mean of bilirubin levels over time was significantly less than the control group (P < 0.001). In the intervention group, the bilirubin levels had decreased 1.65, 3.82, and 6.37 mg/dL, after 12, 24, and 48 hours, respectively. There was no significant association with age and sex in this regard.

The mean duration of time required for phototherapy for decreasing the bilirubin level to <10 mg/dL was 15.5 ± 6 and 44.6 ± 13.3 hours in the case and the control groups, respectively, and the difference was statistically significant (P = 0.001) (Fig. 2).

The intervention group was also examined regarding Ursobil complications, such as diarrhea and vomiting; however, no complications were detected in any of our patients.

DISCUSSION

The results of the present study showed that 12 and 24 hours after hospitalization, the mean total bilirubin level had significantly decreased in patients receiving Ursobil and phototherapy compared with those who had only undergone phototherapy (P < 0.05). It seems that the combination of Ursobil and phototherapy leads to a much more reduction in the total bilirubin levels in comparison with phototherapy alone. No significant difference was found between the 2 groups regarding the total bilirubin levels, however, 48 hours after hospitalization, which shows that the highest effect of phototherapy accompanied by Ursobil occurs in the first 48 hours of hospitalization. Moreover, the mean duration of phototherapy significantly decreased in the neonates receiving phototherapy and Ursobil compared with those who only underwent phototherapy (P < 0.05). In this study, no significant difference was observed between the 2 groups regarding the sex. Most of the study patients were 3 days old (52% in the case and 70% in the control groups). This is consistent with other studies conducted on this issue (12).

UDCA is commonly used for the treatment of cholestatic liver diseases. Previous studies revealed that there were 3 major mechanisms of action for UDCA: first, changes in the composition of mixed phospholipid-rich micelles, reduction of bile acid cytotoxicity of bile, and, maybe, reduction of the hydrophobic bile acid concentration in the cholangiocytes could protect cholangiocytes against cytotoxicity of hydrophobic bile acids; second, stimulation of hepatobiliary secretion, via Ca²⁺-dependent mechanisms and protein kinase C-α-dependent mechanisms may caused insertion of transporter molecules into the hepatocyte canalicular membrane and, maybe, activation of inserted carriers; third, hepatocytes’ protection against bile acid–induced apoptosis (13). According to the present study results, Ursobil led to an ≥24-hour reduction in the duration of phototherapy in the neonates suffering from indirect hyperbilirubinemia most probably by increasing unconjugated bilirubin turnover through its fecal disposal (14). The only study on the effect of UDCA on decreasing UCB is the one conducted by Cuperus et al (11) on rats in 2009; the findings of that study, showed that UDCA increased UCB turnover through increasing its fecal disposal. Reduction of UCB in the present study also seems to result from the same mechanism. Nonetheless, Ménendez-Sánchez et al (9) investigated the effect of UDCA in rats and mice and showed the increase of enterohepatic UCB after the oral consumption of UDCA.

The findings of the present study showed no short-term complication resulting from Ursobil. Long-term follow-up should

FIGURE 1. Results of GEE analysis of the total bilirubin levels in the case and control groups during therapy. GEE = generalized estimating equation.

FIGURE 2. Duration of phototherapy for the treatment of hyperbilirubinemia in both groups (the mean time in the case group was 15.5 ± 6 hours and in the control group it was 44.6 ± 13.3 hours). The difference was statistically significant (P = 0.001).
be done, however, to confirm the safety of this drug in neonates. Some studies have confirmed the safety and tolerability of this medication for children (10). During this study, none of the neonates developed adverse effects of UDCA.

The present study was the first one that investigated the effect of UDCA on reducing the UCB of the infants undergoing phototherapy; with the hope to reduce the lengths of phototherapy and hospitalization, there was some limitation in our study. Small sample size of this study limit us to compare different doses of UDCA to evaluate the best effective dose in the treatment of unconjugated hyperbilirubinemia of neonates, we could not predict all of the variables that had important effect in this regard; so further studies need to evaluate the efficacy of UDCA in the treatment of unconjugated hyperbilirubinemia of neonates. Also, to evaluate the long-term adverse effects of UDCA in the next step, we should design a 10-year follow-up study in our patients. Further investigation with larger sample size and long-term follow-up is suggested to use UDCA safely in improving the treatment of neonatal hyperbilirubinemia.

CONCLUSIONS

It can be concluded that adding UDCA to phototherapy in neonates with indirect hyperbilirubinemia is more effective compared with the treatment by 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 of hospitalization will also decrease the time period required for phototherapy.

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REFERENCES