Prophylactic effect of clofibrate on hyperbilirubinemia in very low birth weight twins

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ABSTRACT

**Aims:** To determine the prophylactic effects of clofibrate on hyperbilirubinemia in very low birth weight twins.

**Study design:** A randomized double blind clinical trial

**Place and Duration of Study:** Department of Neonatal Research Center, Imam Reza Hospital, Faculty of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran, between Oct 2010- Sep 2011.

**Methodology:** Forty neonates with very low birth weight (20 pairs of twins) having same blood group and sex were elected. Infants with congenital anomalies, metabolic diseases, hemolytic disease, and infections were excluded. Case group received a single dose of clofibrate 100 mg/kg and control group received sterile water. Both clofibrate and sterile water were administrated through orogastric tube and were the same volume. Serum bilirubin levels were measured before administration, 24, 48, 72 and 96 hours after the administration. Data was analyzed with repeated measurement ANOVAs.

**Results:** Total serum bilirubin after clofibrate administration was lower than control the group (F= 6.48, P=0.02); however, the duration of phototherapy and hospitalization were not significantly different between the two groups (P=0.39 and 0.91 respectively). Based on the physical exam and liver function tests, no side effects of drug were observed.

**Conclusion:** These findings suggest that clofibrate maintained total serum bilirubin lower in very low birth weight neonates but without effect on duration of phototherapy and hospitalization.

**Keywords:** clofibrate, hyperbilirubinemia, very low birth weight twins, newborn.
1. INTRODUCTION

Hyperbilirubinemia occurs in 80% of preterm infants. In these babies hyperbilirubinemia is higher, more persistent, longer and more likely to be associated with neurological injury than term neonates. The increased intensity and duration of hyperbilirubinemia in preterm infants as well as the immaturity of the blood – brain barrier have led to concern about greater risk of bilirubin encephalopathy in preterm infants [1,2,3]. Deficient uridin glucuronyl transferase (UDPG-T) activity that results bilirubin conjugation impairment has long been considered a major cause leading physiologic jaundice. In the first 10 days of life the UDPG-T activity in full term and premature neonates is usually less than 1% of adult values [3, 4].

There are three methods for the treatment of hyperbilirubinemia such as: Exchange transfusion for mechanical removal of bilirubin, phototherapy for bilirubin excretion in stool or urine and pharmacologic way which accelerates normal metabolic pathway for bilirubin excretion. Exchange transfusion is an invasive procedure with many complications and one percent mortality. The most common approach for treatment and prevention of neonatal hyperbilirubinemia is phototherapy, which reduces the incidence of exchange transfusion. This method has some disadvantages including anxiety of parents for baby hospitalization, high expenses and disrupted mother-infant bonding.

In neonates and especially very low birth weight infant UDPG-T activity is very low; therefore any inducer of UDPG-T activity will prevent hyperbilirubinemia. Several pharmacologic agents are capable to stimulate the hepatic glucuronyl conjugating system and some have even been used to reduce the concentration of serum bilirubin in newborn infants.

Phenobarbital is the most widely used drug in human studies. It is a potent inducer of microsomal enzymes that increase bilirubin conjugation. Clofibrate is also a glucuronyl transferase inducer and can increase bilirubin conjugation and excretion [5-6]. We have
performed two studies about therapeutic effects of clofibrate on jaundiced term and preterm newborn [7, 8]. Results of these two studies have showed that clofibrate has significant therapeutic effects on term newborns but it does not show a full therapeutic effect on preterm ones. The other research has also been conducted to study the prophylactic effects of clofibrate on very low birth weight neonates. According to this study, clofibrate has prophylactic effects only 24 hours after administration of clofibrate, and also the duration of phototherapy was reduced [9]. In present study, our aim was to assess prophylactic effect of clofibrate on hyperbilirubinemia in very low birth weight twins with the same blood group and sex.

Medical treatment is practical, economical and acceptable to parents, so studies about prophylactic and therapeutic effects of drugs on jaundice would be advantageous.

2. MATERIAL AND METHODS

In a randomized double blind clinical trial 40 very low birth weight neonates who were admitted to NICU of Imam Reza Hospital of Mashhad university of medical sciences, Iran were studied. Babies with congenital anomalies, metabolic diseases, hemolytic disease and infections were excluded. These neonates were healthy, breastfed twins with birth weight equal or less than 1500 grams with the same blood group and sex. Each pairs of twins were boy or girl and blood groups of them were the same. Laboratory investigations included complete blood count, red blood cell morphology, newborn's blood group and their mother's blood group, direct and indirect coomb's tests, reticulocyte count and erythrocyte G6PD level. The clinical examination, gestational age, birth weight, sex, serial total serum bilirubin (TSB), direct bilirubin, duration of phototherapy and hospitalization were recorded. TSB was measured by using a Unistat bilirubineometer (Reichert – Jung, Germany).

For measurement of direct bilirubin the colorimetric method of Lathe and Ruthven were used [10]. As all neonates were healthy preterm babies, phototherapy was started when total serum bilirubin concentration reached a threshold level based on AAP recommendation (TSB 5 grams/dl in babies with less than 750 grams birth weight, TSB 6 grams/dl in 751-
1000, TSB 7 grams/dl in 1001-1250 and TSB 8 grams/dl in more than 1250 grams birth weight)[3].

Phototherapy was discontinued when bilirubin decreased to 50% of Phototherapy level.

Each phototherapy unit contained six blue lamps. Energy output or irradiance of the phototherapy light was being maintained at 8-12 µw/Cm2/nm. **Level irradiance of phototherapy was checked routinely by fluoro-LITE meter 451, Minolta camera co. LTD, and maintain at 8 - 12 µW/Cm2/nm.**

The protocol of the study was approved by the local ethical committee of Mashhad University of medical science. The study was described to the parents of neonates before start of the research, and written informed consents were obtained. Babies were randomly divided in two groups. One groups received clofibrate 100mg/kg (clofibrate group n=20) and the other group received sterile water (control group n=20). Both clofibrate and sterile water were of the same volume. The clofibrate and placebo were coded, clofibrate with even number and placebo with odd number, each pair of twins received even number and the other one odd code. Nor physicians neither staff of laboratories knew about type of administration for each neonate. Cases were received clofibrate or placebo as a single dose by orogastric tube in the first 24 hours of age. Total serum bilirubin level was checked before, 24, 48, 72 and 96 hours after administration of drug. In order to check drug side effects, liver function tests (SGOT, SGPT) were performed finally. At the end of study, codes were opened. Data were analyzed with Statistical Package for Social Science (SPSS version 11.5). The used test was repeated measurement ANOVAs. P- Value less than 0.05 was considered statistically significant.

3. RESULTS

As the two groups were of the same blood groups and sex twins therefore, gestational age, demographic factors of mothers and newborns in both were the same. Mean gestational age was 31.95± 1.60 weeks and birth weight was 1396± 154 grams in clofibrate group and
Some pair of twins was boy and some girl. All type of blood groups were found in participants but each pair of twins had the same blood group. As table (1) shows laboratory results obtained from the two groups were nearly the same.

### Table 1: Laboratories workup of newborns

<table>
<thead>
<tr>
<th>Lab Tests</th>
<th>Clofibrate (No=20)</th>
<th>Control (No=20)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(Mean ± SD)</td>
<td>(Mean ± SD)</td>
<td></td>
</tr>
<tr>
<td>Hemoglobin g/dl</td>
<td>16.70 (5.30)</td>
<td>17.80 (4.55)</td>
<td>1.00</td>
</tr>
<tr>
<td>Hematocrit (%)</td>
<td>49.40(14.68)</td>
<td>52.20(13.60)</td>
<td>0.78</td>
</tr>
<tr>
<td>Reticulocyte (%)</td>
<td>5.34± 2.36</td>
<td>6.78± 2.45</td>
<td>0.19</td>
</tr>
</tbody>
</table>

Table (2) and figure (1) show total serum bilirubin levels of clofibrate group were lower than the control group in all days.

### Table 2: total serum bilirubin level in the two groups

<table>
<thead>
<tr>
<th>Test</th>
<th>clofibrate Mean±SD</th>
<th>Control group Mean±SD</th>
<th>difference Mean±SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>bilirubin before clofibrate mg/dl</td>
<td>4.79± 2.10</td>
<td>4.8 ± 1.62</td>
<td>0.01±1.7</td>
</tr>
<tr>
<td>Bilirubin 1 day after intervention mg/dl</td>
<td>6.42± 2.41</td>
<td>7.56 ± 2.00</td>
<td>1.14±2.3</td>
</tr>
<tr>
<td>Bilirubin 2 days after intervention mg/dl</td>
<td>7.67± 1.80</td>
<td>8.62 ± 2.07</td>
<td>0.95±2.26</td>
</tr>
<tr>
<td>Bilirubin 3 days after intervention mg/dl</td>
<td>7.64±2.31</td>
<td>8.15±2.25</td>
<td>0.5±3.05</td>
</tr>
<tr>
<td>Bilirubin 4 days after intervention mg/dl</td>
<td>5.10±2.32</td>
<td>6.72±3.11</td>
<td>1.62±3.6</td>
</tr>
</tbody>
</table>
Although in clofibrate group always TSB was lower than control group, there were significant difference between two groups after repeated measurement analysis (F= 6.48, P= 0.02). Changes of bilirubin based on the time also was significant different (F= 20.8, P<0.001).

Fig.1.

Table 3: phototherapy and hospitalization duration in two groups

<table>
<thead>
<tr>
<th></th>
<th>Clofibrate Mean±SD</th>
<th>Control group Mean±SD</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phototherapy duration days</td>
<td>5.89± 5.03</td>
<td>6.35± 6.01</td>
<td>0.39</td>
</tr>
<tr>
<td>hospitalization duration days</td>
<td>15.05± 14.28</td>
<td>16.86±20.34</td>
<td>0.91</td>
</tr>
</tbody>
</table>

Liver function tests (SGPT, SGOT) were normal in two groups at the end of study.

4. DISCUSSION
This study showed that total serum bilirubin maintained lower in clofibrate group after intervention compared to the control group. Effects of various reagents such as metalloporphyrins and depenicilamin have been identified on the metabolism bilirubin., This may inhibit heme oxygenase and agar and charcoal which lead to a decrease in the entrohepatic circulation. Clofibrate and phenobarbital are potent inducers of microsomal enzymes that increase bilirubin conjugation and excretion. The effect of phenobarbital on TSB levels begins within a few days of administration; in addition phenobarbital causes respiratory failure, drowsiness and also worsens bilirubin toxicity by alteration of bilirubin oxidation in brain. Clofibrate such as phenobarbital is a hepatic bilirubin metabolism inducer; in addition it can cause 100% increase in hepatic bilirubin clearance within six hours, with no drowsiness effect [6].

Gabilan found that clofibrate is a better glucuronyl transferase inducer than other drugs [11]. In this study it was recommended that clofibrate is the only pharmacological treatment of neonatal jaundice available at that time.

Bourget et al [6] suggested that a single oral dose of 50 mg/kg clofibrate may be a better treatment for jaundice compared to a single oral dose of 100 mg/kg.

Lindenbaum et al. [12] (1981) showed that after 16 hours of treatment mean plasma bilirubin levels are significantly lower in treated group compared to control group. Clofibrate also resulted in a shorter duration of jaundice and a restricted use of phototherapy.

In this study, we also found that the mean plasma total bilirubin levels 12, 24 and 48 hours after clofibrate administration were significantly lower in term jaundiced neonates compared to the control group (P < 0.0001, P < 0.0001 and P = 0.004, respectively). Nevertheless, treatment with clofibrate resulted in a shorter duration of phototherapy (P < 0.0001) [7].
Zahedpasha et al. [13] assessed the efficacy of clofibrate in full term G6PD deficient neonates affected with jaundice. Also it was shown that clofibrate induces a faster decline in total serum bilirubin level, decreases duration of phototherapy, and lowers the duration of hospitalization. No side effects were observed in these full-term G6PD deficient neonates.

Eghbalian et al. [14] performed a study to assess therapeutic effect of clofibrate in full term neonates who presented with nonhemolytic jaundice. Based on this study, a single dose of clofibrate (100 mg/Kg) accompanied with phototherapy is more effective than phototherapy alone for the treatment of non-hemolytic hyperbilirubinemia in term healthy newborn infants.

There is a little information available about effects of clofibrate on preterm infant. “Preterm infants are susceptible to bilirubin encephalopathy even at physiologic levels.” Lindenbaum et al studied the preventive effect of clofibrate in 46 premature neonates with gestational ages ranging between 31-36 weeks [15]. According to their study, the serum concentration of clofibrate equal or above 140 micrograms per deciliter which is the therapeutic level during the first 24 hours of treatment leads to a lesser intensity of jaundice 48 hours after treatment a lesser need for repeated bilirubin assay and the lesser use of phototherapy. In a study performed by Mohammadzadeh et al. therapeutic effect of clofibrate on low birth weight neonates affected with hyperbilirubinemia was assessed. Although therapeutic effect of clofibrate on treatment of jaundice wasn't significant, duration of phototherapy has been decreased significantly in the group who received clofibrate [8]. In another study performed by Mohammadzadeh et al which was the analysis of prophylactic effects of clofibrate on hyperbilirubinemia in very low birth weight neonates, it was shown that clofibrate had prophylactic effect on total serum bilirubin in the first 24 hours after drug administration and decreased duration of phototherapy in very low birth weight infants [9].
In the present research, we have studied the prophylactic effect of clofibrate on hyperbilirubinemia in very low birth weight twin infants which had the same blood group and sex. Although patients of the two groups had similar characteristics, we have observed a decrease in TSB after clofibrate administration. Duration of phototherapy and hospitalization was nearly the same in two groups. Results of our studies show that although clofibrate has therapeutic effects on term neonates affected with jaundice, the therapeutic effects on jaundiced preterm neonates were not significant. Immaturity of liver cells might be the reason for lack of effectiveness of clofibrate in preterm neonates, indeed glucuronyl transferase activity in immature liver cells could not be induced by clofibrate. Another reason for lack of effectiveness of clofibrate in preterm neonates could be the immature gastrointestinal system which was not able to absorb the drug properly.

Clofibrate has some side effects such as nausea, gastrointestinal disturbances, vomiting and loose stool in adults. Other possible side effects are muscle cramping, fatigue, pruritus, and alopecia. Chronic use of clofibrate has been reported as a hepatic carcinogen [16, 17, 18, and 19]. In neonatal studies which a single dose of clofibrate has been prescribed, no side effects have been reported. As long-term follow up studies has not been conducted, there are not sufficient data about the safety of clofibrate in neonates [6, 16]. We also did not find any side effects.

5. **CONCLUSION**

According to this study, clofibrate maintained total serum bilirubin level lower after its administration, but had no effect on duration of phototherapy and hospitalization. Further investigation should be conducted about drug metabolism and effects of frequent doses on preterm neonates in order to discover all its therapeutic and prophylactic properties and side effects.
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REFERENCES


