The Effect of Clofibrate on Neonatal Hyperbilirubinemia in Uncomplicated Jaundice

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Abstract

Objective: Clofibrate has been used for several years as a hypolipidemic drug. Our aim was to study the effect of Clofibrate on neonatal hyperbilirubinemia in uncomplicated jaundice.

Material & Methods: This clinical trial study has been conducted on 90 normal term neonates who were admitted for uncomplicated jaundice in 17th-Shahrivar Children's Hospital of Guilan University of Medical Sciences from September 2005 to January 2006. The data included: age, sex, total and direct serum bilirubin, weight and duration of hospitalization. All data were analyzed by using statistical methods.

Findings: All 90 infants enrolled in our study had received phototherapy. The infants were divided into Clofibrate group (G1) consisting of 26 boys (57.8%) and 19 girls (42.2%) and Control group with 24 boys (53.3%) and 21 girls (46.7%) (G2). There were no statistically overt differences between the two groups regarding sex distribution, age, weight and total serum bilirubin level at admission. Mean values for total bilirubin of serum in Clofibrate group 12, 24, 36, and 48 hours after admission were significantly lower than those for Control group ($P<0.001$). The mean time needed for phototherapy in Clofibrate group (38.8) (20-48h) was significantly shorter than that in control group (68.7) (36-96h) ($P<0.001$).

Conclusion: Clofibrate is effective and probably a safe drug for neonatal hyperbilirubinemia that can decrease the time needed for phototherapy and hospitalization, although further studies with a more precise and longer follow up is needed for proving its safety to be used routinely in the treatment of neonatal hyperbilirubinemia.

Key Words: Clofibrate, Neonate, Hyperbilirubinemia, Jaundice

Introduction

Bilirubin is one of the end products of Heme catabolism. Its clinical significance in the neonate relates to its propensity for deposition in the skin and mucous membranes and therefore producing jaundice. It may also deposit in the brain where it has been
implicated in causing transient dysfunction and, occasionally, permanent neuronal damage. "Kernicterus" refers to neurological consequences of the deposition of unconjugated bilirubin in brain tissue by damaging and scarring of the basal ganglia and brain stem nuclei[^1]. There are several nonpharmacological and pharmacological modalities for treating hyperbilirubinemia. Phototherapy has emerged as the most widely used nonpharmacological therapy for the treatment and prophylaxis of neonatal unconjugated hyperbilirubinemia[^2] but it has several untoward complications such as retinal damages, hyperthermia, loose stool and bronze baby syndrome.

Pharmacological agents introduced for treatment of unconjugated neonatal jaundice include Phenobarbital[^3], Metalloporphyrins[^4], agar, oral charcoal and D–penicillamine that more researches are necessary to prove their safety in clinical use[^5].

Clofibrate has been used for several years as a hypolipidemic drug[^6]. Clofibrate also increases bilirubin conjugation and excretion via induction of glucuronosyl transferase activity[^7], Its potency is three times more than Phenobarbital in induction of bilirubin conjugation[^8]. The effect of Clofibrate on uncomplicated hyperbilirubinemia was proposed in some studies[^9,10]. Mohammadzadeh and colleagues studied Clofibrate effect on reducing serum bilirubin level of neonates beyond the first week of life[^10]. The present study was designed to assess Clofibrate effect on uncomplicated hyperbilirubinemia of neonates during the first week of life.

**Material & Methods**

This clinical trial study was performed during September 2005 to January 2006, in 17th Shahrivar Children's Hospital affiliated to Guilan University of Medical Sciences in the north of Iran.

Patients of the study were admitted during the study period in this center for evaluation and treatment of jaundice. Infants with dehydration, infection, ABO or Rh incompatibility, G6PD deficiency, conjugated bilirubin above 2 mg/dl or exceeding 15% of total serum bilirubin (TSB) and congenital anomalies were excluded, and from the remainder 90 neonates were enrolled in this study. All selected neonates were born at term (with gestational age of 38 to 41 weeks), breastfed, had serum bilirubin (TSB) levels between 15 to 29.9 mg/dl and body weight 2500g to 4000g.

These neonates were randomly allocated to Clofibrate group (G1) and control group (G2) alternately; i.e. the first patient to group G1, the second one to G2, and so on, with the permission of their parents and the ethics committee of our university and the hospital. Both groups (G1 and G2) received phototherapy under standard conditions with 4 special white 420-480 nanometer lamps being used less than 240 hours and adjusted to about 30 centimeters above neonate. Group G1 received a single dose of 100 mg/kg Clofibrate. Immediately after admission and before starting any modalities, blood samples were withdrawn from both groups for routine jaundice laboratory tests such as complete blood count (CBC), total bilirubin (direct and indirect), reticulocyte count, Coomb's test, G6PD activity, blood group and Rh of neonates and their mothers. TSB and indirect bilirubin were measured every 12 hours till the end of phototherapy. All data were analyzed by using the statistical package for social sciences (SPSS v.11) software and were summarized and expressed as mean (and standard deviation). Statistical analysis of data was performed by chi-square test, Fisher exact test and independent t-test. Statistical significance was considered at a P value less than 0.05.

**Findings**

All 90 infants enrolled in our study received phototherapy. 45 infants include 26 boys (57.8%), and 19 girls (42.2%) belonged to Clofibrate (G1) and the rest 24 boys (53.3%),
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Table 1- Mean (and standard deviation) of age, weight and total serum bilirubin in two groups neonatal hyperbilirubinemia

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Clofibrate group G1</th>
<th>Control group G2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (day)</td>
<td>5.0 (1.5)</td>
<td>5.6 (2.1)</td>
</tr>
<tr>
<td>Weight (g)</td>
<td>3190 (268)</td>
<td>3151 (289)</td>
</tr>
<tr>
<td>TSB (mg/dl)</td>
<td>18.4 (1.4)</td>
<td>18.4 (1.8)</td>
</tr>
</tbody>
</table>

and 21 girls (46.7%) to control group (G2). There were no statistically overt differences between the two groups regarding sex, age, weight and TSB at the time of admission (Table 1).

No problems were detected in daily routine examinations during the hospitalization by neonatal ward physicians. There was no persistent hyperbilirubinemia. The mean values for TSB at 12th, 24th, 36th and 48th hours after admission in group G1 were statistically less than G2 group (Table 1).

All neonates in group G1 after 48 hours of starting the treatment did not need phototherapy, but in G2 38 of 45 neonates needed it for 72 hours and remainder for 96 hours. The mean (SD) and range duration of phototherapy in Clofibrate group (G1) was 38.8 (7.5) and 20-48 hours respectively, while in control group (G2) was 68.75 (15.40) and 36-96 hours, respectively (P<0.001). During hospitalization and 48 hours after discharge none of neonates demonstrated any complication. All neonates were followed for a period of a month and there was fortunately no complications found. Limitation of this study was inability to follow our patients with laboratory data on proceeding months.

Discussion

In the present study we compared the effect of combination therapy of single oral 100 mg/kg/dose of Clofibrate and phototherapy (group G1) with phototherapy alone (group G2) on TSB level of two groups of 45 neonates with marked hyperbilirubinemia.

TSB levels in group G1 at 12th, 24th, 36th and 48th hours after starting the treatment were significantly lower than those in group G2. Also, the mean time of phototherapy needed in group G1 was significantly lower than that in group G2.

Although unconjugated hyperbilirubinemia is a common neonatal disease, to date there are few drugs introduced to its treatment.

Table 2. Mean plasma bilirubin values during treatment in Clofibrate and Control group

<table>
<thead>
<tr>
<th>Time (hour)</th>
<th>Control group (G2)</th>
<th>Clofibrate group (G1)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Plasma bilirubin (mg/dl) (n = 45)</td>
<td>Plasma bilirubin (mg/dl) (n = 45)</td>
<td></td>
</tr>
<tr>
<td>12th</td>
<td>17.63 ± 1.06</td>
<td>15.82 ± 1.03</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>24th</td>
<td>16.61 ± 1.59</td>
<td>13.62 ± 1.57</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>36th</td>
<td>15.24 ± 1.65</td>
<td>11.95 ± 1.57</td>
<td>&lt;0.001</td>
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Some of these drugs such as Phenobarbital[2] and Chinese herbal remedies[12] act via similar way as induction of the conjugation of bilirubin, but they have some complications such as somnolence, stupor and respiratory insufficiency with Phenobarbital[5] and induced neurotoxicity in Chinese remedies such as Artemisia by displacement of bilirubin from albumin.

Although Clofibrate has several side effects in adults in longtime use such as nausea, loose stool, gastrointestinal upset, vomiting, muscle cramp, and pruritus[18], in the neonatal period with single high dose of Clofibrate such side effects have not been reported by researchers[9,18,11]. During our study and follow up of the patients no side effects could be detected too. In comparison to the recent similar study by Mohammadzadeh et al on the effect of Clofibrate in neonatal hyperbilirubinemia[10] we found similar significant decreasing effect of Clofibrate on TSB levels with proceeding times and shorter duration of phototherapy, but in Mohammadzadeh study the mean age of enrolled neonates was between 8-9 days (5.04 in their Clofibrate group)[10]. This is the time when in most term babies with hyperbilirubinemia the bilirubin level will be on receding trend[19]; in our study neonates were selected near to maximum level of bilirubin elevation in usual trend (5 days) for this treatment. In conformity with Mohammadzadeh et al[10], we did not find any side effects after a month of clinical follow up.

**Conclusion**

Clofibrate, a hypolipidemic drug, is an effective and probably safe drug also for neonatal hyperbilirubinemia and decreases the time needed for phototherapy. Although we didn’t find any side effects of Clofibrate after a course of one month of clinical evaluation, further studies with a more precise and longer follow up is needed for proving its safety to be used in the treatment of neonatal hyperbilirubinemia.

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**References**

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