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Original Article

# Effect of Clofibrate in Jaundiced Full-Term Infants: A Randomized Clinical Trial

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**Background:** **Hyperbilirubinemia is a common problem in newborn infants. It can progress to kernicterus in severe forms, unless an intervention is initiated. The objective of this study was to determine the therapeutic effect of clofibrate in full-term neonates with nonhemolytic jaundice.**

**Methods:** **A randomized clinical trial was performed on two groups of full-term jaundiced neonates: the clofibrate-treated group (n = 30) and the control group (n = 30). Infants in the clofibrate group received a single oral dose of 100 mg/kg clofibrate while the neonates in the control group received distilled water (same color and volume); both groups received phototherapy.**

**Serum total and direct bilirubin levels were measured at the beginning, 16, 24, 48, and 74 hours, after the start of the trial.**

**Results:** **The mean ± SD total serum bilirubin level of the control and clofibrate groups at enrollment was 17.5 ± 2.3 and 18.2 ± 1.9 mg/dL, respectively (*P* = 0.199). The mean ± SD total serum bilirubin in the control and clofibrate groups after 48 hours was 11.4 ± 2.4 and 10.1 ± 2.4 mg/dL, respectively (*P* = 0.047). After 72 hours of intervention, 25 (83%) neonates of the clofibrate group and 16 (53%) of the control group were discharged with a total serum bilirubin of <10 mg/dL (*P* = 0.026). No side-effect was observed on serial examination during hospitalization, and on the first and seventh day after discharge.**

**Conclusion:** **Clofibrate results in a faster decline in TSB, shorter duration of hospitalization and had no side effects in jaundiced full-term neonates.**

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**Keywords:** Bilirubin • clofibrate • jaundice • neonate



## Introduction

Neonatal jaundice is the most frequently encountered diagnostic and therapeutic problem in the newborn.[1] The incidence of severe neonatal hyperbilirubinemia is highest in Asians than in whites.[2] It can progress to kernicterus in severe circumstances unless an intervention is initiated.[3] Five to 10% of all newborns require intervention for pathologic jaundice.[4]

In the neonate, hyperbilirubinemia is usually due to either increased production, decreased elimination or increased enterohepatic circulation of bilirubin or a combination of them.[5, 6]

Neonatal jaundice is a frequent indication for phototherapy, exchange transfusion, or drug adminstration.[7]

Phototherapy is commonly used for the treatment of neonatal jaundice,[8] whereas exchange transfusion has an important role in the treatment of hyperbilirubinemia of newborns when the bilirubin level is high.[9]

Despite an understanding of the enzymatic pathways leading to bilirubin production and elimination, some pharmacologic agents such as D-penicillamine, phenobarbital, metalloporphyrins,

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and clofibrate may yet be proven to be useful in prevention or treatment of neonatal jaundice.[5] The safety and efficacy of this therapy, however, needs to be confirmed prior to widespread use.

Clofibrate is an activator of peroxisome-proliferated activated receptors (PPARs), and thus it affects lipid metabolism.[10, 11] This drug can also increase bilirubin conjugation and excretion (elimination of bilirubin).[12]

In a double-blind controlled study of infants without ABO incompatibility, 47 infants treated with a single oral dose of clofibrate demonstrated significantly lower bilirubin level after 16 hr of treatment as compared to 46 controls given corn oil alone.[13] Clofibrate treatment also resulted in a shorter duration of jaundice and a reduced use of phototherapy.[13, 14]

In the human neonatal study, no side-effects were observed.[12, 13] In the current study, we compared the effectiveness of oral clofibrate in the treatment of nonhemolytic jaundice in full-term neonates.

## Patients and Methods

Sixty full-term neonates with jaundice, admitted to the Neonatal Ward of Amirkola Children's Hospital, affiliated to Babol University of Medical Sciences, Babol, northern Iran from February 2003 through January 2004, were enrolled into this study. Regardless of their jaundice, these neonates were healthy, breast-fed, delivered between 38$^{th}$ and 41$^{st}$ weeks of gestational age after an uncomplicated pregnancy, and had a total serum bilirubin (TSB) between 15 and 25 mg/dL and a body weight of ≥2500 g. The clinical examination, birth weight, gender, age, and weight at enrollment, serial TSB, direct bilirubin, and duration of phototherapy were recorded. Laboratory tests included complete blood count, reticulocyte count, serum bilirubin level (total and direct), erythrocyte glucose-6-phosphate dehydrogenase (G6PD) level, $T_4$, and TSH. Total and direct serum bilirubin were estimated by Jendrassic Grof colorimetric method.

Exclusion criteria included presence of hemolytic disease, Rh or ABO incompatibility, a positive Coombs test, G6PD deficiency, conjugated bilirubin >1.5 mg/dL or 15% of TSB, dehydration, infection (congenital or acquired), and a history of phenobarbital intake either by mother or infant. The study was approved by the Ethics Committee of Babol University of Medical Sciences, Babol, northern Iran. After explaining the objectives of the study, written informed consents were taken from parents of all neonates. Sample size was calculated assuming a type one error of 5%, power of 80%, case group variance of 1.75, control group variance of 1.5, and an effect size (difference in mean bilirubin levels between the two groups) of 1.2 mg/dL.[2] Therefore, 60 neonates were randomized to either the clofibrate (n = 30) or control (n = 30) group.

All neonates in both groups received phototherapy. Each phototherapy unit had four special blue lamps (Philips Co., Germany) and adjusted to 25 cm above the infants' cots.

The infants in the colfibrate group received a single oral dose of clofibrate, 100 mg/kg, while the control group received distilled water in an equal amount and color as placebo.

Total and direct serum bilirubin levels were measured at the beginning, 16, 24, 48, and 72 hours after the start of phototherapy. Bilirubin evaluations continued until TSB declined to <10 mg/dL.

Blood exchange transfusion was performed for infants with TSB >25 mg/dL when phototherapy failed. All infants in this study were examined during hospital stay, on first and seventh days after discharge in the outpatient clinic for the evaluation of their icterus or any side-effects of the drug.

Data were analyzed with SPSS version 13. Numerical variables were compared between the control and clofibrate groups using the independent Student's *t*-test. The $\chi^2$ and Fisher exact tests were used to compare categorical variables between the two groups. *P* values of <0.05 were considered statistically significant.

## Results

From the total of 60 neonates, 30 (14 boys [47%], 16 girls [53%]) received clofibrate and 30 (14 boys [47%] and 16 girls [53%]) were in the control group. There was no significant demographic and TSB differences at enrollment between the two groups (Table 1).

No significant difference in the mean TSB was observed between the two groups at 16 and 24 hours after intervention. The mean TSB in the clofibrate group was significantly lower than the control group after 48 and 72 hours of treatment (Table 2).

**Table 1.** Baseline data in the control and clofibrate-treated groups.

| Demographic/ Plasma bilirubin level | Control group ($n$ = 30) Mean ± SD | Clofibrate group ($n$ = 30) Mean ± SD | $P$ value |
|---|---|---|---|
| Weight at enrollment (g) | 3183.3 ± 510.3 | 3083.3 ± 396.6 | 0.643 |
| Age at enrollment (day) | 6.37 ± 3.74 | 5.67 ± 1.84 | 0.362 |
| Sex | | | |
| Male | 14 (46.7%) | 14 (46.7 %) | 1 |
| Female | 16 (53.3%) | 16 (53.3%) | 1 |
| Bilirubin at enrollment | | | |
| Total | 17.50 ± 2.34 | 18.21 ± 1.85 | 0.199 |
| Direct | 0.76 ± 0.11 | 0.82 ± 0.12 | 0.158 |

After 72 hours of intervention, 25 (83%) neonates of the clofibrate group and 16 (53%) of the control group were discharged with a TSB of <10 mg/dL ($P$ = 0.026).

On serial examinations during hospitalization, on the first and seventh days after discharge in the outpatient clinic no drug side-effects were observed. None of the neonates in both groups needed exchange transfusion or re-hospitalization after discharge.

## Discussion

The present randomized clinical trial demonstrated that a single dose of clofibrate (100 mg/kg) in full-term newborns with significant jaundice (TSB >15 mg/dL) can significantly reduce the indirect bilirubin level after 48 hours of treatment and decrease the hospital stay.

Caballero-Noguez et al in a randomized clinical trial studied 30 neonates with unconjucted hyperbilirubinemia in their first week of life. They were divided into three random groups; group 1 received phenobarbital, group II received clofibrate, and group III received placebo. All received phototherapy and their total and indirect serum bilirubin levels were measured at the beginning of the treatment, 24, 48, and 72 hours later on. Clofibrate and phenobarbital significantly lowered bilirubin levels at the 48 and 72 hours in comparison to the group, which received the placebo.[14]

In another case-control study in 1985, Lindenbaum et al showed that a single oral dose of ethylclofibrate (100 mg/kg) significantly lowered the intensity of jaundice from 48$^{th}$ hour of treatment and reduced the need for repeated serum bilirubin assay or phototherapy.[15]

A double-blind controlled trial of the therapeutic effects of clofibrate, an inducer of bilirubin glucuronyl transferase, was performed on full-term neonates with nonhemolytic hyperbilirubinemia; 47 neonates were treated with a single oral dose of clofibrate which significantly lowered bilirubin level after 16 hours of treatment as compared with bilirubin level in 46 control neonates who were given only corn oil. Moreover, the duration of jaundice and need for phototherapy were also decreased in the clofibrate-treated group.[13]

In 2005, Mohammadzadeh et al in a controlled clinical trial treated 30 neonates with a single oral dose of clofibrate (100 mg/kg) plus phototherapy (clofibrate-treated group) while gave only phototherapy to another 30 neonates (control group). The mean plasma total bilirubin levels at 12$^{th}$, 24$^{th}$, and 48$^{th}$ hours of treatment were significantly lower in the clofibrate-treated group

**Table 2.** Plasma bilirubin level during treatment in the control and clofibrate-treated groups.

| Plasma bilirubin level (mg/dL) | Control group ($n$ = 30) Mean ± SD | Clofibrate group ($n$ = 30) Mean ± SD | $P$ value |
|---|---|---|---|
| 16$^{th}$ hr | | | |
| Total | 14.96 ± 2.03 | 14.26 ± 1.88 | 0.170 |
| Direct | 0.67± 0.10 | 0.68 ± 0.13 | 0.747 |
| 24$^{th}$ hr | | | |
| Total | 13.26 ± 2.24 | 12.56 ± 2.38 | 0.246 |
| Direct | 0.62 ± 0.09 | 0.57 ± 0.09 | 0.073 |
| 48$^{th}$ hr | | | |
| Total | 11.43 ± 2.38 | 10.09 ± 2.40 | 0.047 |
| Direct | 0.52 ± 0.05 | 0.55 ± 0.08 | 0.191 |
| 72$^{th}$ hr | | | |
| Total | 11.21± 1.93 | 9.56 ± 1.86 | 0.024 |
| Direct | 0.53 ± 0.08 | 0.53 ± 0.06 | 0.773 |

as compared with the control group, along with a shorter duration of jaundice and decreased need of phototherapy.[16] The results of these studies are in agreement with previous our studies, demonstrating that clofibrate can significantly reduce serum bilirubin level and the intensity and duration of jaundice and the need for phototherapy.

In the present study, administration of a single dose of clofibrate was well tolerated and no side-effects were observed; however, we followed the infants upto seven days after discharge. These data are also in agreement with previous studies which demonstrated that a single dose of 50 – 100 mg/kg of clofibrate was well tolerated with no side-effects.[11]

In adults, clofibrate has been used for many years as an antilipidemic agent that lowers serum lipids by reducing very low density lipoproteins rich in triglycerides and may lower PPARs.[10] Therefore, some side-effects such as nausea (common), gastrointestinal disturbances, vomiting, and loose stool were reported. Other possible complications are muscle cramping, fatigue, pruritis, and alopecia.[17]

Similar to phenobarbital, clofibrate increases bilirubin conjugation and excretion. It is even a better enhancer of glucuronyl transferase induction causing 100% increase of hepatic bilirubin clearance within six hours of administration.[18] Phenobarbital has a long half-life and its effects in severe jaundice are questionable.[5] The immediate side-effects of phenobarbital are somnolence and even stupor.[19]

In addition, phenobarbital may alter the oxidation of bilirubin in the brain leading to worsened bilirubin toxicity.[20] Some new pharmacologic agents are also utilized in the prevention and treatment of neonatal jaundice. Tin protoporphyrin and Sn MP are hemoxygenase inhibitors used successfully to treat jaundice in human neonates in two randomized-sequentially analyzed trials on full- and near-term infants. They are not yet employed outside research protocols.[21 – 22]

In conclusion, we believe that clofibrate results in a faster decline in serum total bilirubin and a shorter hospital stay with no side-effects. Clofibrate is actually the only available pharmacologic agent that can be used in neonatal jaundice simplifying the clinical treatment of these high-risk infants in an effective manner.



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