

## The Effect of Clofibrate on Decreasing Serum Bilirubin in Healthy Term Neonates under Home Phototherapy

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### Abstract

**Objective:** This study was designed to determine the effect of clofibrate on neonatal uncomplicated jaundice treated with home phototherapy.

**Methods:** This clinical trial study was performed on 60 newborns with jaundice that received home phototherapy. Inclusion criteria were body weight between 2500 to 4000 gr, breastfed, total serum bilirubin (TSB) between 14 to 20 mg/dl, aged over 72 hours. The neonates were randomly divided into two groups. All received home phototherapy. Group I received a single dose of 50 mg/kg clofibrate and the other group served as control group. Total serum bilirubin level was measured every 24 hours.

**Findings:** Two groups were matched regarding weight, sex, age and first TSB. At 24 and 48 hours of treatment, the mean values of TSB in the clofibrate group were 13.72 (1.56), 9.5 (0.56) and in the control group 15.30 (1.44), 12.6 (1.44). The results show that TSB was significantly decreased after 24 and 48 hours in clofibrate group ( $P < 0.001$ ). The mean duration of phototherapy in group I was 72(0.0) hours and in the control group 76.80 ( $\pm 9.76$ ) hours. The duration of phototherapy was significantly shorter in clofibrate group ( $P < 0.001$ ).

**Conclusion:** Clofibrate is effective for outpatients with neonatal hyperbilirubinemia who are under home phototherapy. Of course, further studies are needed for approved routine use of this drug in the treatment of neonatal jaundice.

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**Key Words:** Clofibrate; Phototherapy; Home Care; Neonatal Hyperbilirubinemia; Jaundice

### Introduction

In the first day of life, bilirubin production is increased to an estimated average of 8 to 10

mg/kg of body weight per day, an amount about two or three times greater than that of adults<sup>[1]</sup>. Approximately two thirds neonates become clinically jaundiced.

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Phototherapy is the most widely used form of therapy for the treatment and prophylaxis of neonatal hyperbilirubinemia<sup>[2]</sup>. Several potential complications may occur with the use of phototherapy<sup>[3]</sup>, such as retinal degeneration, fluid imbalance, and bronze baby syndrome.

Some reports have demonstrated that home phototherapy may be an effective and safe alternative to prolonged hospitalization for healthy full-term neonates with jaundice. Clear advantages of home-centered phototherapy include: (1) reduced cost; (2) avoidance of parent-infant separation; and (3) parental satisfaction<sup>[4]</sup>.

Although some pharmacological agents such as activated charcoal<sup>[5]</sup> or agar<sup>[6]</sup> are suggested to treat neonatal jaundice, further study of this type of therapy is needed before to their routine clinical use.

Glucuronyl transferase activity can be increased with administration of phenobarbital<sup>[7]</sup> or clofibrate<sup>[8]</sup>. Clofibrate decreases serum cholesterol and triglyceride levels in adults<sup>[9]</sup>. This drug has been proposed for treatment of neonatal hyperbilirubinemia<sup>[10]</sup>. Mohammadzadeh et al studied the effect of clofibrate on reducing serum bilirubin of neonates beyond the first week of life<sup>[11]</sup>. Badeli and colleagues determined the effect of clofibrate on uncomplicated hyperbilirubinemia of neonates during the first week of life<sup>[12]</sup>. Mohammadzadeh and Badeli studied the effect of 100mg/kg clofibrate.

The aim of the present study was determination the effect of 50 mg/kg of clofibrate on TSB of hyperbilirubinemia of neonates under home phototherapy.

## Subjects and Methods

From April 4, 2007 to June 20, 2008 60 neonates with uncomplicated hyperbilirubinemia who were under home phototherapy in Rasht, Iran, entered our study. The ethics committee of our university approved the study. Informed consent of the parents was obtained.

Inclusion criteria were body weight between 2500-4000 grams with gestational age 38 to 41

weeks, breastfed, and having total serum bilirubin (TSB) between 14 to 20 mg/dl, with postnatal age above 72 hours.

Infants with ABO or Rh incompatibility, G<sub>6</sub>PD deficiency, and conjugated hyperbilirubinemia or any concomitant disease were excluded. Portable phototherapy units consist of 4 special blue tubes placed 40 cm above the infant as home phototherapy. Patients were examined and a sample of serum bilirubin was taken daily.

The neonates (n=60) were randomly divided into two groups and they were matched regarding weight, sex, age and value of the first TSB. 30 neonates were allocated to clofibrate group (group I) and 30 neonates to control group (group II). All neonates in the two groups received home phototherapy.

The control group received no placebo. Clofibrate group (group I) was given a single dose of 50 mg/kg clofibrate before starting phototherapy. In the first day, laboratory tests included estimation of total bilirubin (direct and indirect), blood group including Rh of the mother and neonate, complete blood count (CBC), G<sub>6</sub>PD activity, Coombs test, reticulocyte count. Direct and indirect, as well as TSB were measured every 24 hours by the same laboratory till TSB dropped under 10 mg/dl. The duration of phototherapy was recorded with a timer.

Data were analyzed using SPSS 10; *t*-test and ANOVA were used for analyzing the data. *P*-value less than 0.05 was considered significant.

## Findings

Among 60 neonates, 30 infants consisting of 18 (60%) females and 12 (40%) males belonged to group I (clofibrate) and 17 (56.7%) females and 13 (43.3%) males to group II (control).

There were no statistically significant differences between the two groups regarding weight, age and first TSB value (Table 1). TBS values show significant difference between the two groups 24 and 48 hours after starting phototherapy at home. Group I showed lower value (Table 2). Mean ( $\pm$ SD) phototherapy time

**Table 1:** Mean ( $\pm$ SD) age, weight and first TSB-value in the two groups

Parameter	Group I	Group II
	Mean ( $\pm$ SD)	Mean ( $\pm$ SD)
Age (day)	6.80 (3.24)	6.6 (2.50)
Weight (g)	3107 (394.89)	3150 (469.40)
TSB (mg/dl)	17.24 (1.48)	17.42 (1.44)

SD: standard deviation

TSB: total serum bilirubin

in group I was 72( $\pm$ 0.0) hours and in group II 76.80 ( $\pm$ 9.76) hours.

The duration of phototherapy was significantly shorter in clofibrate group ( $P < 0.001$ ). All neonates in group I needed phototherapy still after 72 hours but in group II 24 (80%) neonates had to receive phototherapy for 72 and 6 (20%) for 96 hours. Serum bilirubin levels after physician's examining were measured at beginning and 24, 48 hours after phototherapy. Bilirubin of both groups was measured in the same laboratory.

On serial daily examination during phototherapy and up to 2 days after that no problems or side effects were observed. Also for a period of two months no complication was detected.

## Discussion

In this clinical trial study we determined the effect of lower dose (50 mg/kg) of clofibrate on neonatal hyperbilirubinemia in term neonates under home phototherapy.

In the present study we demonstrated that in clofibrate group there was lower TSB after 24 and 48 hours home phototherapy compared with control group. Also the neonates in group I needed to receive shorter phototherapy than those in group II.

The neonatal hyperbilirubinemia is the most common disease in neonatal period. Although there are advantages of home phototherapy, several potential complications may occur with its use. At present there is no safe drug for treatment of neonatal icterus and shortening of phototherapy time. The effect of numerous drugs on bilirubin metabolism and reducing hyperbilirubinemia has been identified. Metalloporphyrins and d-penicillamine act by inhibition of heme oxygenase, agar and charcoal by decreasing enterohepatic circulation. The clofibrate and phenobarbital are potent inducers of microsomal enzymes that increase bilirubin conjugation and excretion<sup>[13]</sup>. Clofibrate like phenobarbital is a hepatic bilirubin metabolism inducer, in addition causes 100% increase of hepatic bilirubin clearance within 6 hours with no drowsiness effect in contrast to the latter.

Clofibrate when used as an antilipidemic agent in adults, has some side effects such as nausea, gastrointestinal disturbance, vomiting and loose stools<sup>[14]</sup>. Other possible complications include cramps, fatigue, pruritus and alopecia<sup>[14]</sup>. None of these side effects were reported in neonates with a single dose of clofibrate<sup>[15,16]</sup>. Like phenobarbital, clofibrate increases bilirubin conjugation and excretion and is a better enhancer of glucuronosyl transferase induction causing 100% increase of hepatic bilirubin clearance within 6 hours<sup>[17]</sup>, sooner than phenobarbital<sup>[13]</sup>.

**Table 2:** Comparison of mean total serum bilirubin (mg/dl) after 24 and 48 hours of phototherapy in the two groups

Time (hour)	Group	No	Mean(SD) total bilirubin (mg/dl)	P- value
24	Clofibrate(I)	30	13.72 (1.56)	<0.001
	Control (II)	30	15.30 (1.44)	
48	Clofibrate(I)	30	9.5 (0.56)	<0.001
	Control (II)	30	12.6 (1.44)	

SD: Standard Deviation

Phenobarbital has a long half life and its effect on severe jaundice is questionable. Phenobarbital also causes drowsiness in neonates and may slow down the oxidation of bilirubin in the brain leading to worse bilirubin toxicity<sup>[18]</sup>.

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Although we detected in our studies no side effects in infants with a single dose of clofibrate, determination of minimum and effective dose would be important.

This study demonstrated that a single dose of clofibrate (50mg/kg) significantly reduces indirect hyperbilirubinemia in healthy breastfed term newborns with home-based phototherapy. This result is similar to the studies of Mohammadzadeh et al and Badeli et al, noting that they used 100 mg/kg of the drug in hospitalized patients. Our study demonstrated that lower dose of clofibrate is effective on neonatal hyperbili-rubinemia receiving home phototherapy as well.

Glabilan<sup>[17]</sup> used clofibrate in the treatment of early jaundice in full term neonates. He found significant reduction in bilirubinemia at 16 hours and decrease in the intensity and duration of jaundice and also phototherapy requirement.

Lindenbaum showed significant reduction 16 hours after treatment with clofibrate in TSB of 47 neonates<sup>[19]</sup>. Other studies in Iran and France confirmed the beneficial effect of clofibrate for reducing of TSB in babies with no risk factor for hemolysis<sup>[20]</sup>.

In conformity with those previous studies, we did not detect any untoward complications during therapy and after two months follow up.

Twenty mothers discontinued home phototherapy because of their own concern or others' comments; they were excluded of the study.

## Conclusion

This study suggests that a lower dose of clofibrate is effective in outpatients with

neonatal hyperbilirubinemia under home phototherapy. Similar to other studies we found no complications. Further studies are needed for approved routine use of this drug in non-hemolytic hyperbilirubinemia of healthy term newborns as outpatients.

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**Conflict of Interest:** None declared.

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