Original Article

Oral fenofibrate in neonatal hyperbilirubinemia: A randomized controlled trial

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Abstract

Objective: To evaluate the role of oral fenofibrate for lowering neonatal hyperbilirubinemia as compared to placebo. **Design:** Double-blind, randomized, placebo-controlled trial. **Setting:** NICU of tertiary care hospital of North India. **Subjects:** 50 neonates with neonatal hyperbilirubinemia. Neonates (≥35 weeks of gestation), birth weight (1.5-3.5 kg), jaundice beginning at day 3-11 after birth, total bilirubin level between 15 and 21 mg/dl, and clinically stable vital signs. **Intervention:** Neonates were assigned randomly to receive either single dose of oral fenofibrate at 10 mg/kg/dose on day 1 of admission and distilled water on the following next day or a single dose of oral glucose solution on day 1 and distilled water on the following next day. Malloy-Evelyn method was used to estimate the serum total bilirubin levels. All newborns enrolled in this study, received phototherapy. The cases were divided into two groups, i.e. study (fenofibrate) group and control group. **Measurement of Primary Outcome:** Duration of phototherapy. **Results:** Mean values for total serum bilirubin in fenofibrate group at 36 and 48 h after starting of phototherapy were significantly lower in the study group than those in the control group ($p<0.00001$). The mean time needed for phototherapy was also shorter in the study group than control group ($p<0.0002$). No side effects of fenofibrate were observed after a single dose administration. **Conclusion:** Fenofibrate appears to be an effective and safe drug for the treatment of neonatal hyperbilirubinemia. This decreases the duration of phototherapy and thus shortens the length of hospital stay.

Key words: *Fenofibrate, Neonatal hyperbilirubinemia, Phototherapy, Serum bilirubin*

Neonatal hyperbilirubinemia is a common problem in the neonatal period occurring in nearly 5-25% neonates [1]. There are several non-pharmacological and pharmacological modalities for treating hyperbilirubinemia. Nowadays, phototherapy and exchange transfusion are the standard therapies for unconjugated hyperbilirubinemia in neonates. However, both have their side effects and drawbacks [2,3]. Among all the modalities of treatment, phototherapy has emerged as the most widely used therapy for the treatment and prophylaxis of neonatal unconjugated hyperbilirubinemia, but it has several untoward complications such as deleterious effect to eyes, high temperature, loose stool, and bronze baby syndrome [4]. Pharmacological agents introduced for treatment of unconjugated neonatal jaundice include phenobarbitone, metalloporphyrins, and D-penicillamine [5]. Metalloporphyrins and D-penicillamine have not been proved very effective and safe in clinical use [5].

Fibrates have been used for several years as a hypolipidemic drug [6]. Fibrates also increase bilirubin conjugation and excretion via induction of glucuronyl transferase activity [7]. Its potency to induce bilirubin conjugation is many times more than phenobarbitone [8]. The effect of clofibrate on uncomplicated hyperbilirubinemia was proposed in some studies [9,10]. Mohammadzadeh et al. studied the effect of clofibrate on reducing serum bilirubin level of neonates beyond the first week of life [10]. Clofibrate, however, is no longer routinely used for hyperlipidemia in adults due to its adverse effect profile. Fenofibrate is now the most widely used fibrate in treating hyperlipidemia and has better safety profile than clofibrate [11]. The present study was designed to assess the effect of fenofibrate on neonatal hyperbilirubinemia in term and preterm neonates.

METHODS

This was a double-blind, randomized controlled trial conducted in the Department of Pediatrics, in active collaboration with the Department of Obstetrics and Gynaecology and Department of Pathology, of a tertiary care hospital of North India, from August 2013 to October 2014. The protocol was cleared by the Institutional Ethics Committee and written informed consent was taken from one of the parents before inclusion into the study.

Subjects

Neonates ≥35 weeks of gestation, weighing 1.5-3.5 kg, admitted to our NICU with stable vital signs and jaundice beginning at day 3-11 after birth and total bilirubin level between 15 and 21 mg/dl, were screened for inclusion in the study (Fig. 1). Exclusion criteria were direct hyperbilirubinemia, ABO incompatibility, Rh incompatibility, unstable vital signs, metabolic abnormalities, congenital defects, congenital infections, and physical abnormalities.

All potentially eligible neonates, not meeting the exclusion criteria, were screened for birth weight (1.5-3.5 kg) and serum bilirubin level at admission. Neonates with total serum bilirubin ≥15 mg/dl and ≤21 mg/dl were enrolled in the study after taking an informed consent from parents after explaining them about the study. At any time, parents were free to withdraw from the study.

Sample Size

Considering the admission of our NICU in previous years and time limit for study, a sample size with the total of 50 neonates was planned.

Interventions

The enrolled neonates were randomly assigned with computer-generated random number tables via software named random allocation software, to receive either oral fenofibrate (study group) or glucose solution (placebo group). Infants in both the groups were nursed on servo-controlled, open care bed, with skin temperature maintained at 36.5°C. Both groups received LED phototherapy under standard conditions, adjusted to about 30 cm above the neonate. The study group received a single dose of oral fenofibrate at 10 mg/kg/dose, whereas the control group received oral glucose solution.

Outcome Variables

Total, direct and indirect bilirubins were measured at admission, and after 24, 36, and 48 h of admission. Duration of phototherapy was also recorded in all cases.

Data Collection and Monitoring

Blood samples were withdrawn immediately after admission and before starting any treatment from both the groups for laboratory tests such as complete blood count (CBC), total bilirubin (direct and indirect), reticulocyte count, and blood group (ABO and Rh of neonates and their mothers). Serum bilirubin, total and differential, was recorded at the time of admission and after 24, 36, and 48 h duration of phototherapy in both groups.

Statistical Analysis

All the data were recorded on predesigned and pretested proforma and analyzed statistically. Continuous variables were

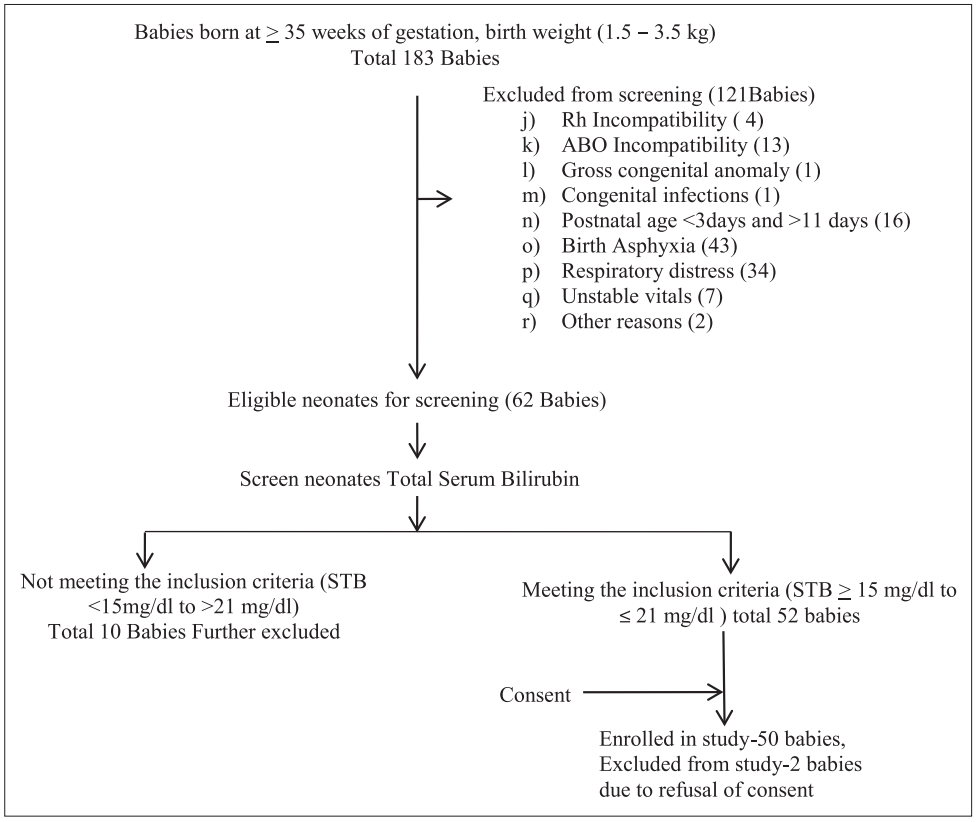

Figure 1: Screening for inclusion criteria

analyzed by Student's t-test, and categorical variables were analyzed by Chi-square test with Yates correction. Findings associated with a $p<0.05$ were considered significant.

Side Effects

There are some rare side effects reported in adults include nausea, vomiting, constipation, diarrhea, heartburn, stomach pain, pain in the back, arm, or legs, headache, weakness, muscle pain or tenderness, joint pain, fever, blistering or peeling skin, rash, redness, swelling, pain, tenderness, or warmth in one leg, shortness of breath, pain when breathing, coughing up blood [12], but these effects are difficult to monitor in neonates. We monitored side effects such as constipation, diarrhea, fever, blistering or peeling skin, rash, vomiting in our neonates.

RESULTS

All 50 neonates (25 each in fenofibrate and control group) received phototherapy. The fenofibrate (A) group included 16 males (64%) and 9 females (36%) while control (B) group comprised 15 males (60%) and 10 females (40%). There were no statistical overt differences between the two groups regarding age, sex, weight, and gestational age, mode of delivery, maternal age, and type of feeding, and other risks factors [Table 1].

The difference in mean total serum bilirubin levels in neonates between study and control groups at the time of admission was statistically non-significant (p=0.3597). However, the study group had significantly lower mean total bilirubin values after 24, 36, and 48 h as compared to placebo group. The mean serum bilirubin levels after 24, 36, and 48 h in study group and control group are given in Table 2. The difference in serum bilirubin levels between both the groups after 24 h was statistically non-significant (p=0.269); however, it became significant after 36 and 48 h of phototherapy ($p<0.0001$).

The mean duration of phototherapy in fenofibrate group was 38.40±11.02 h, which was lower than that of the control group (46.67±4 h) which was statistically significant (p=0.048). During hospitalization, 48 h after treatment and at the time of discharge, none of the neonates had any documented adverse effect (Fig. 2).

DISCUSSION

Although fibrates are hypolipidemic drug, it also increases bilirubin conjugation and excretion via induction of glucuronyl transferase activity. Thus, they decrease jaundice in neonates by influencing bilirubin metabolism. In the present study, the effect of combination therapy of single dose of fenofibrate (10 mg/kg) and phototherapy (study group) was compared with phototherapy alone (control group). In our study, 50 neonates, gestational age ≥35 weeks and birth weight between 1.5 and 3.5 kg, having total serum bilirubin at admission between 15 and 21 mg/dl were divided in the study and control group.

We observed that study group had significantly lower mean total bilirubin values after 24, 36, and 48 h as compared to control group. The mean duration of phototherapy in fenofibrate group was also lower than that of the control group. Kumar et al. [13]

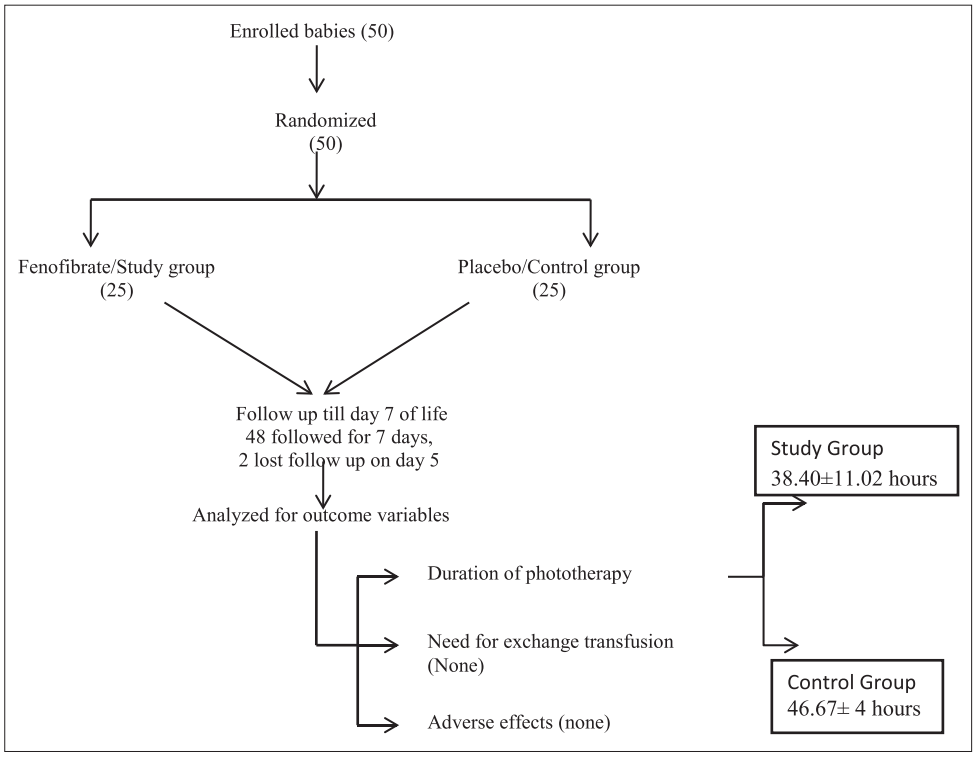

Figure 2: Trial flow of the study

Table 1: Comparison of other risk factors in the enrolled neonates in study and control groups

Risk factors	N (%)		χ^2	df	p
	Study	Control			
Polycythemia	2 (8)	1 (4)	1.39	3	0.710 statistically
Prematurity	9 (36)	8 (32)			not significant
Concealed hemorrhage	6 (24)	7 (28)			
Infection	8 (32)	9 (36)			

Table 2: Plasma total bilirubin values during treatment in fenofibrate and control group

Time in hours	TSB level in mg/dl		p value
	Fenofibrate group (A)	Control group (B)	
At admission (h)	18.54±1.50	18.91±1.32	0.36
24	15.86±1.44	16.36±1.56	0.27
36	13.23±1.43	15.12±1.50	<0.00001
48	11.11±1.41	13.76±1.50	<0.00001

TSB: Total serum bilirubin

and Alasy et al. [14] also reported almost similar findings from their study. In our study, there is a greater fall in the total serum bilirubin in the fenofibrate-treated group in 24, 36, and 48 h after admission in comparison to the fenofibrate-treated group in Alasy et al. 2013 and Kumar et al. in 2010. This may be attributed to the fact that we have used LED phototherapy in our study in comparison to conventional phototherapy in previous studies.

In 2009, Jaikrishan et al. [15] did a study on another hypolipidemic drug and gemfibrozil in late preterm and term neonates with moderate jaundice and concluded that gemfibrozil is effective in reducing the duration of phototherapy significantly. Similarly, clofibrate was also used by researchers for treatment and prophylaxis of hyperbilirubinemia of infancy at a dose of >100 mg/kg [10] but clofibrate has many side effects for which it is an obsolete drug nowadays.

Fenofibrate is very similar to clofibrate in its mechanism of action. It is easily available and has better safety profile and thus much safer to administer in pediatric age group than clofibrate. The present study clearly highlights the efficacy of oral fenofibrate in decreasing the level of serum bilirubin and duration of phototherapy in neonatal hyperbilirubinemia. Fenofibrate administration in neonates having hyperbilirubinemia can be a useful approach in decreasing serum bilirubin level in the present scenario, where the only treatment remains phototherapy and exchange transfusion.

The limitations of this study were small sample size, shorter duration of study, and difficulty in monitoring all possible side effects of fenofibrate in neonates. Although no side effects of fenofibrate were observed after a single dose, further studies with a more precise and longer follow-up are needed to prove its safety. It should not be used in clinical practice until safety evaluation is carried out in further large-scale studies.

CONCLUSIONS

The present study highlights the efficacy of oral fenofibrate in decreasing the level of serum bilirubin and duration of phototherapy in neonatal hyperbilirubinemia. During hospitalization, 48 h after treatment and at the time of discharge, none of the neonates documented any adverse effect. Thus, fenofibrate appears to be effective and probably safe drug for neonatal hyperbilirubinemia.

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