Efficacy and Safety of Fenofibrate in Uncomplicated Hyperbilirubinemia in Newborn: A Randomized Trial, with a 6-month Follow-up

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Authors’ contributions

This work was carried out in collaboration among all authors. Author JRG designed the study. Author VSR carried out the study and wrote the manuscript. Author JRG did the literature search and author BDR did statistics. All authors read and approved the final manuscript.

ABSTRACT

Objective: To study the effect and safety of Fenofibrate in uncomplicated hyperbilirubinemia in newborn with 6-month follow-up.

Materials and Methods: This is a randomized controlled clinical trial conducted in 60 normal term neonates admitted for uncomplicated hyperbilirubinemia in NICU at Sir T G Hospital, Bhavnagar from January 2012 to December 2012. The data included: age, sex, total serum bilirubin (TSB), weight and duration of phototherapy. All neonates enrolled in the study received phototherapy. They were divided in two groups of 30 each: control group A and group B receiving Fenofibrate (100 mg/kg single dose). There was statistically insignificant difference between the parameters of age, sex, weight and TSB between the two groups at hospitalization. Data was analyzed by using appropriate statistical methods.

Results: Mean values for total serum bilirubin in Fenofibrate group B at 24 and 48 hours after admission were significantly lower than those for control group A (p<0.0001,  p=0.0001). There was no significant difference in fall of TSB between 24 and 48 hours. The mean duration of phototherapy in Fenofibrate group (44.8h: 24-72h) was significantly shorter than that in control
group (55.2 h: 24-96 h) (P=0.02). There were no side effects of the drug observed during the study and during 6 months follow up period.

**Conclusion:** Fenofibrate as a single 100 mg/kg dose in healthy full term neonates, is effective and a safe drug (till six-month follow-up) for neonatal hyperbilirubinemia, that can decrease the time needed for phototherapy and hence hospitalization. Effect of a single dose seems to wane after 24 hours.

**Keywords:** Fenofibrate; neonatal hyperbilirubinemia; bilirubin; neonate; jaundice.

**ABBREVIATIONS**

NICU : Neonatal Intensive care unit  
TSB : Total serum bilirubin  
LED : Light emitting diode  
LFT : Liver function test  
LDH : Lactate dehydrogenase  
AST : Aspartate aminotransferase  
ALT : Alanine aminotransferase

**1. INTRODUCTION**

Bilirubin is one of the end products of Heme catabolism. It has propensity for deposition in the skin and mucous membranes and producing jaundice. It may also deposit in the basal ganglia and brain stem nuclei in brain where it causes transient dysfunction and, occasionally, permanent neuronal damage or Kernicterus [1].

Phototherapy is the most widely used treatment for unconjugated neonatal hyperbilirubinemia but it has several complications such as probable retinal damage (animal studies only), hyperthermia, loose stool, dehydration and bronze baby syndrome. The effect of LED radiations on human retinal pigment epithelial cells (HRPEpiC) when exposed to three light–darkness (12 h/12 h) cycles affect *in vitro* HRPEpiC in form of decrease in cellular viability and increasing cellular apoptosis [2]. Drugs introduced for the same like Phenoobarbital, Metalloporphyrins, agar, oral charcoal, artemisinin derivatives and D–penicillamine, are yet to prove their safety and efficacy in clinical use [3].

Fenofibrate has been used for several years as a hypolipidemic drug. It is a fibric acid derivative. Fenofibrate acts by activation of peroxisome proliferator activated receptor α (PPARα). This increases lipolysis and elimination of triglyceride-rich particles from plasma by activating lipoprotein lipase and reducing production of apoprotein C-III. It has a half life of 18-20 hours. It is well absorbed from the gastrointestinal tract and mainly excreted in the urine primarily as fenofibric acid and fenofibric acid glucuronide. Fenofibrate also increases bilirubin conjugation and excretion via induction of glucuronosyl transferase activity [4]. Its potency is three times more than Phenobarbital in induction of bilirubin conjugation [5].

Adverse drug reaction observed in adult clinical trials as well as post marketing surveillance, when used in daily dosage of 100 mg three times daily for 8 weeks (Goldberg) [6] and 24 weeks (Brown) [7], includes allergic reaction, pancreatitis, jaundice, liver fatty deposit, anorexia, cholecystitis, cholelithiasis, arthralgias, myalgia, skin rash, gynecomastia, venous thromboembolic events, blood dyscrasias and elevation of AST, ALT, LDH, S Creatinine. Reversible elevation of LFT and LDH can occur after few weeks of treatment but for other serious side effects it requires weeks to several years of exposure. In mice, Fenofibrate increased pancreatic acinar adenomas in both sexes and testicular interstitial cell tumors in males, according to two trials in mice, when used for 6 times the maximum recommended human dose, ie 1200 mg/kg /day for 24 month duration [8].

Clofibrate is a prototype drug amongst the fibric acid derivatives which was widely used for hypercholesterolemia until 2002 when it was discontinued because of the risk of increased mortality related to cardiac conditions like coronary artery disease as well as leucopenia, myotoxicity and thrombocytopenia. Fenofibrate has substituted clofibrate as hypolipidemic agent because of less adverse effect profile.

Mohammadzadeh [9] studied single dose Clofibrate (100 mg/kg) effect on reducing serum bilirubin level of neonates beyond the first week of life whereas, R Fallah [10] studied single dose Clofibrate (50 mg/kg) in first week of life. B Kumar studied the role of Fenofibrate (non micronised10 mg/kg) in reducing TSB in first week of life [11]. The present study was designed to assess single dose Fenofibrate
effect on uncomplicated hyperbilirubinemia of neonates during the first week of life.

2. MATERIALS AND METHODS

The study, which was a randomized control trial, was conducted in NICU in Sir T hospital during August 2016 to July 2017. Ethical committee approval was taken and trial was registered at www.ctri.in(CTRI/2016/07/007069 [11/Jul/2016]). A total of 60 term normal neonates were enrolled in this study after excluding jaundiced newborns with criterion mentioned in exclusion criteria. 

**Inclusion Criteria:** Neonates born at term (with gestational age of 38 to 41 weeks), exclusively breastfed, with total serum bilirubin (TSB) levels between 18.1 to 31.2 mg/dl and birth weight between 2500gm to 4600gm. 

**Exclusion criteria:** Newborns with Birth weight <2.5 kg, septicemia, either ABO or RH incompatibility, direct hyperbilirubinemia >2 mg/dl or >15% of TSB, G6PD deficiency or hypothyroidism (Fig. 1).

These neonates were randomly allocated to the control group (A) and Fenofibrate group (B). Both groups received phototherapy under standard conditions with LED 420-480 nanometer lamps, adjusted to about 30 centimeters above the neonate. Group B received a single oral dose of 100 mg/kg Fenofibrate. Blood samples were drawn from both the groups, after admission and before starting any treatment for laboratory tests such as complete blood count (CBC), total bilirubin (direct and indirect), reticulocyte count, Coomb’s test, G6PD assay and blood groups.

Total serum bilirubin was measured at 0, 24 and 48 hours. S bilirubin was checked by wet biochemistry using modified Jenderassiks and Groff method. Data was analyzed by unpaired and paired t test.
3. RESULTS

Treatment group B receiving Fenofibrate consisting of 20 males and 10 females and Control group A receiving only phototherapy (LED) consisting of 17 males and 13 females. All the 60 newborns enrolled in the present study received phototherapy. There was no statistical overt difference between the two groups regarding sex, age, weight and Total serum bilirubin at the time of admission (Table 1).

The mean values for TSB at 24 and 48 hours after admission in group B were significantly less than group A (Table 2). 27 neonates in group B did not need phototherapy after 48 hours of starting the treatment and 3 after 72 h; whereas in group A it was required for 48 hours for 22, for 72 hours for 6, and for 96 hours for 2 neonates. No neonates required exchange transfusion in either of the groups. During hospitalization, and after discharge till 6 months, none of the neonate demonstrated any side effects related to Fenofibrate.

The average duration of phototherapy in Group B (44.8 hr) was significantly lower than group A (55.2 hr p=0.02).

4. DISCUSSION

In the present study we compared the effect of combination therapy of single oral 100 mg/kg/dose of Fenofibrate and phototherapy (group B) with phototherapy alone (group A) on TSB level of two groups of total 60 neonates with marked hyperbilirubinemia. TSB levels in group B at 24th and 48th hours after starting the treatment were significantly lower than those in group A. Also, the mean time of phototherapy needed in group B was significantly lower than that in group A. However when difference between fall in bilirubin was calculated between 24 to 48 hours, the fall was not significant in study group B compared to control group. Hence it can be considered that the effect of augmentation by Fenofibrate in decreasing bilirubin lasts for first 24 hours after a single dose.

Although unconjugated hyperbilirubinemia is a common neonatal disease, to date there are few drugs introduced to its treatment. Some of these drugs such as Phenobarbital act via similar way as induction of the conjugation of bilirubin, but has complications such as somnolence, stupor and respiratory insufficiency with Phenobarbital and induced neurotoxicity in Chinese remedies such as Artemisia by displacement of bilirubin from albumin [3]. Although Fenofibrate has several side effects in adults after longtime use such as nausea, loose stool, gastrointestinal upset, vomiting, muscle cramp, and pruritus [8]; in the neonatal period with single high dose of Fenofibrate such side effects are unlikely and, so far have not been reported.

In comparison to the study by Mohammadzadeh et al. [9] (100mg/kg), Razieh Fallah et al. [10] (50 mg/kg) and Hamid Badeli et al. [12] (100 mg/kg) on effect of clofibrate and Bijay Kumar [11] et al. on the effect of Fenofibrate (non micronised 10 mg/kg) in neonatal hyperbilirubinemia; we found similar significant decreasing effect of Fenofibrate on TSB levels and shorter duration of phototherapy. Thus there is only one study on the use of Fenofibrate in uncomplicated neonatal hyperbilirubinemia [13].

However in Mohammadzadeh study [9] the mean age of enrolled neonates was 8-9 days (5.04 in their Clofibrate group). This is the time when in most term babies with hyperbilirubinemia the bilirubin level will be on receding trend. In our study neonates were selected near to maximum level of bilirubin elevation found usually ie at 4 days (Table 1). In Razieh Fallah, Bijay Kumar and Hamid study, neonates selected were in first week of life.

In present study, we have studied the development of adverse drug reactions to Fenofibrate in neonates for a period of 6 months, for first time that no other study has reported. We observed no side effects during this follow up.

Table 1. Comparison of age, weight and total serum bilirubin (TSB) in two groups (Gr) of hyperbilirubinemia (mean±sd)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Control Gr A</th>
<th>Fenofibrate Gr B</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (days)</td>
<td>4.37±1.4</td>
<td>4.63±1.58</td>
<td>0.5</td>
</tr>
<tr>
<td>Weight (Kg)</td>
<td>2.81±0.29</td>
<td>2.82±0.4</td>
<td>0.9</td>
</tr>
<tr>
<td>TSB (mg/dl)</td>
<td>21.46±2.46</td>
<td>22.61±3.14</td>
<td>0.12</td>
</tr>
</tbody>
</table>
### Table 2. Total serum bilirubin (mg/dl) and duration of phototherapy (mean ±sd)

<table>
<thead>
<tr>
<th>Time</th>
<th>Control Gr A</th>
<th>Fenofibrate Gr B</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 h</td>
<td>21.46±2.46</td>
<td>22.61±3.14</td>
<td>0.12 NS</td>
</tr>
<tr>
<td>24 h</td>
<td>16.44±1.97</td>
<td>15.42±1.96</td>
<td></td>
</tr>
<tr>
<td>48 h</td>
<td>12.87±2.03</td>
<td>11.82±1.86</td>
<td></td>
</tr>
<tr>
<td>Reduction 0-24 h</td>
<td>5.02</td>
<td>7.19</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Difference 0-48 h</td>
<td>8.59</td>
<td>10.79</td>
<td>0.0001</td>
</tr>
<tr>
<td>Difference 24-48 h</td>
<td>3.6</td>
<td>3.56</td>
<td>0.9 NS</td>
</tr>
<tr>
<td>Phototherapy duration (h)</td>
<td>55.2±15.63</td>
<td>44.8±13.71</td>
<td>0.02</td>
</tr>
</tbody>
</table>

Gr=group, h=hours, NS=not significant

### 5. CONCLUSION

Fenofibrate appears to be an effective and probably safe drug for uncomplicated hyperbilirubinemia in full term neonate. Single oral dose of Fenofibrate (100 mg/kg) with phototherapy decreases the time needed for phototherapy and lessens the duration of hospital stay. No side effect of Fenofibrate was observed after a single dose and during follow up for 6-month. The bilirubin reducing effect of single dose Fenofibrate seems to wane off after 24 hours.

### 6. RECOMMENDATION

A study with a longer follow up period of more than 6 months will reinforce evidence for the safety of drug.

In selected cases a second dose after 24 hours may be considered to further reduce the remaining bilirubin rapidly.

**What is already known on this topic:**

There is evidence on usage of single dose of Fenofibrate (single study) or Clofibrate in neonatal hyper-bilirubinemia in reducing bilirubin significantly when administered in first or second week in healthy term neonates.

**What this study adds:**

Single dose of 100 mg/kg Fenofibrate administered in the first week of life in term neonates to treat hyper-bilirubinemia showed:

- A significant reduction in total serum bilirubin and duration of phototherapy; the effect was seen if the neonate was passing stools daily.
- Effect of single dose seems to wane after 24 hours.
- No adverse effect at 6-month follow up.

### CONSENT

Consent was obtained from parents in local language.

### ETHICAL APPROVAL

Study was approved by Institutional Review Board, Ethics Committee and Scientific Committee and the Trial was registered at www.ctri.nic.in(CTRI/2016/07/007069 [11/Jul/2016]).

### ACKNOWLEDGEMENT

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### COMPETING INTERESTS

Authors have declared that no competing interests exist.

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