Original Article

Effect of Oral Fenofibrate on Serum Bilirubin Level in Term Neonates with Unconjugated Hyperbilirubinaemia: A Randomized Control Trial

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DOI: https://doi.org/10.3329/jafmc.v16i1.53843

Abstract

Introduction: Hyperbilirubinemia is a common problem in the neonatal period. Phototherapy is the most important proposed treatments for hyperbilirubinemia, but several drugs along with phototherapy are used with recent advances.

Aim: To see the effect of oral fenofibrate on serum bilirubin level in term neonates with unconjugated hyperbilirubinaemia.

Methods: This prospective study was carried out in Combined Military Hospital Cumilla from July 2018 to June 2019. Total 60 term and normal birth weight neonates with neonatal jaundice were enrolled in this study. Jaundiced newborns presenting with infection, G6PD deficiency, conjugated bilirubin >2 mg/dl or >15% of total serum bilirubin (TSB) and congenital anomalies were excluded from this study. These neonates were randomly allocated to the Fenofibrate group (30 cases) and Control group (30 cases). Total serum bilirubin was measured every 24 hours till the end of phototherapy and at the time of discharge. Statistical analysis was done using SPSS 22.0 and $p<0.05$ was considered significant.

Results: There were no significant differences in gender, age, weight, gestational age and type of delivery between two groups. Mean duration of hospital stay were 4.0±0.7 and 5.5±1.4 days in Fenofibrate group and Control group respectively ($p<0.001$). In Fenofibrate group, TSB was decreased from 17.2 mg/dl to 15.2 mg/dl after 24 hours, to 13.6 mg/dl after 48 hours, and to 10.1 mg/dl at the time of discharge. In control group, TSB was decreased from 17.0 mg/dl to 16.3 mg/dl after 24 hours, to 15.9 mg/dl after 48 hours, and to 10.3 mg/dl at the time of discharge.

Conclusion: Treatment of neonatal unconjugated hyper-bilirubinemia with fenofibrate reduces neonatal bilirubin levels faster and decreases the need for phototherapy and hospitalization.

Key-words: Bilirubin, Hyperbilirubinemia, Fenofibrate, Jaundice, Neonate, Phototherapy.

Introduction

Hyperbilirubinemia is one of the most prevalent clinical conditions in neonates[1] especially in the first week of life, nearly 5-25% of neonates develop hyperbilirubinemia[2,3]. Jaundice is a yellowish discoloration of the skin and sclera. It is an important symptom of elevated serum bilirubin, which is caused by an abnormality of bilirubin metabolism or excretion. The bilirubin can be either conjugated or unconjugated. Conjugated bilirubin is water-soluble and is excreted into the bile to be cleared from the body. Unconjugated bilirubin is a waste product of hemoglobin breakdown that is taken up by the liver, where it is converted by the enzyme uridine diphosphoglucuronate glucuronosyltransferase (UGT) into conjugated bilirubin[4]. Hyperbilirubinemia in children is usually unconjugated. It is usually caused by problems with red blood cell stability and survival or by defects in the bilirubin conjugating enzyme, UGT. In contrast, disorders that result in conjugated hyperbilirubinemia are usually caused by intrinsic liver dysfunction. However, some diseases cause both unconjugated and conjugated hyperbilirubinemia because they affect several different aspects of hepatocyte function[4].

Severe hyperbilirubinemia (total serum bilirubin [TSB] level of more than 20 mg/dl) occurs in less than 2% in term infants and can lead to kernicterus (i.e., chronic bilirubin encephalopathy) and permanent neurodevelopmental delay[5]. Therefore, it is important to systematically evaluate all infants for hyperbilirubinemia. There are different pharmacological and non-pharmacological modalities for the treatment of hyperbilirubinemia. Phototherapy is the most widely used non-pharmacological therapy, but it has several unexpected complications such as deleterious effect to eyes, high temperature, loose stool and bronze baby syndrome[6]. Phenobarbitone, metalloporphyrins and D-penicillamine are the pharmacological agents used for the treatment of unconjugated neonatal jaundice. But they are not very effective and safe in clinical use[7]. Fibrates, used as a hypolipidemic drug[8] also increase bilirubin conjugation and excretion via induction of glucuronyltransferase activity[9]. Potency to induce bilirubin conjugation is many times more in fibrates than phenobarbitone[10]. The effect of clofibrate on uncomplicated hyperbilirubinemia was proposed in some studies[11] but 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 a comparatively much better safety profile than clofibrate[12]. This study is designed to assess the effect of

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fenofibrate on unconjugated hyperbilirubinemia of neonates during the 1st weeks of life.

Materials and Methods

This prospective study was carried out in Combined Military Hospital (CMH), Cumilla from July 2018 to June 2019 over a period of one year. A total of 60 term and normal birth weight neonates with neonatal jaundice were enrolled in this study. Jaundiced newborns presenting with 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 from this study. These neonates were randomly allocated to the Fenofibrate group (30 cases) and Control group (30 cases) with the permission of their parents and the Ethical Committee of Hospital. Both groups received phototherapy under standard conditions with 4 special white 420-480 nanometer lamps, adjusted to about 30 centimeters above the neonate. Fenofibrate group received a single oral dose of 10 mg/kg of nonmicronized Fenofibrate but Control group received nothing.

Blood samples were taken immediately after admission and before starting any treatment from both of the groups. Complete blood count (CBC), total bilirubin (direct and indirect), reticulocyte count, Coomb's test, G6PD assay and blood grouping (ABO and Rh of neonates and their mothers) were done. Total serum bilirubin and indirect bilirubin were measured every 24 hours till the end of phototherapy and at the time of discharge. Statistical analysis was done using SPSS 22.0. Data were presented as mean ± SD in case of numerical data. On the other hand data were presented as frequency and percentage in case of categorical data. Unpaired t test was done to compare the numerical data between two groups and paired t test was done within groups to see the changes and p value <0.05 was considered statistically significant.

Results

In this study girls were more in number in both Fenofibrate group and Control group. In Fenofibrate group, 10(33.3%) cases were boys and 20(66.7%) cases were girls, in Control group, 13(43.3%) cases were boys and 20(56.7%) cases were girls. Mean age were 4.27±0.7 days and 4.1±0.7 days in Fenofibrate group and Control group respectively. Mean weight were 3.0±0.5 kg and 3.2±0.6 kg in Fenofibrate group and Control group respectively. Mean gestational age were 38.1±1.8 weeks and 37.8±1.1 weeks in Fenofibrate group and Control group respectively. In Fenofibrate group, 20(66.7%) and 10(33.3%) neonates were born by cesarean and vaginally respectively. In the Control group, 16(53.3%) and 14(46.7%) neonates were born by cesarean and vaginally, respectively. There were no significant differences in gender, age, weight, gestational age and type of delivery between two groups. Chi-square test and unpaired t test was done to measure the level of significance. Mean duration of hospital stay were 4.0±0.7 days and 5.5±1.4 days in Fenofibrate group and Control group respectively. Duration of hospital stay was significantly low in Fenofibrate group comparing Control group (Table-I).

In this study, the TSB was decreased from 17.2 mg/dl to 15.2 mg/dl after 24 hours, to 13.6 mg/dl after 48 hours, and to 10.1 mg/dl at the time of discharge in Fenofibrate group. In Control group, the TSB was decreased from 17.0 mg/dl to 16.3 mg/dl after 24 hours, to 15.9 mg/dl after 48 hours, and to 10.3 mg/dl at the time of discharge (Table-II). The level of SGPT was reduced before and after giving Fenofibrate treatment from 29.4±2.3 to 28.0±1.6 respectively (Table-III). Decreased SGPT level was statistically significant among fenofibrate treatment group.

Table-I: Demographic profile and hospital stay time of the study subjects (n=60)

Characteristics		Fenofibrate Group (n=30)	Control Group (n=30)	P value
Gender	Boy	10 (33.3)	13(43.3)	>0.05
	Girl	20 (66.7)	17(56.7)	
Age (days)		4.3±0.69	4.1±0.7	>0.05
Weight (kg)		3.0±0.5	3.2±0.6	>0.05
Gestational age weeks)		38.1±1.8	37.8±1.1	>0.05
Type of delivery	NVD	10(33.3)	14(46.7)	>0.05
	LUCS	20(66.7)	16(53.3)	
Hospital stay (days)		4.0±0.7	5.5±1.4	<0.001

Table-II: Serum total bilirubin level during treatment in study groups (n=60)

Serum total bilirubin (mg/dl)	Fenofibrate Group	Control Group	p-value
At starting	17.19±1.98	17.02±2.26	>0.05
At 24 hours	15.17±2.04	16.34±2.18	>0.05
At 48 hours	13.60±2.34	15.88±3.76	<0.01
At discharge	10.12±1.20	10.27±0.94	>0.05

Note: Unpaired t test was done to measure the level of significance

Table-III: SGPT level before and after giving Fenofibrate treatment (n=30)

Variable	Before Fenofibrate	After Fenofibrate	p value
SGPT (Mean ±SD)	29.6 ± 2.3	28.0 ± 1.6	<0.001

Note: Paired t test was done to measure the level of significance

Discussion

In the present study, the effect of combination therapy of single oral dose of Fenofibrate (10mg/kg) and phototherapy was compared with phototherapy alone on total serum bilirubin level. In this study, there was no significant difference in age, gender, weight, gestational age and type of delivery between

two groups. Jaundice was found more common in females than males in this study. Ahmadpour-kacho et al[13] found similar findings but Kumar B et al[14] and Al-Asy et al[15] found male predominance in their respective study.

There was no significant difference in TSB between fenofibrate group and control group in this study. Total serum bilirubin levels in Fenofibrate group at 48th hour was significantly lower than that of Control group. In this study, mean total serum bilirubin at 48th hour were 13.6±2.3 mg/dl and 15.9±3.8 mg/dl in Fenofibrate group and control group respectively. At the time of discharge it was 10.1±1.2 mg/dl in fenofibrate groupand 10.3±0.9 mg/dl in control group. Kumar et al[14] found mean serum bilirubin level at 48th hour were 14.5±0.2 mg/dl and 16.8±0.2 mg/dl in Fenofibrate group and control group respectively. Mean total serum bilirubin at 48th hour was 12.3 mg/dl and 13.6 mg/dl in Fenofibrate group and Control group respectively in the study of Al-Asyet al[15]. In the study of Chaudhary et al[16] in India, the serum bilirubin level in the Fenofibrate group at 36 and 48 hours after starting the phototherapy and the mean time needed for phototherapy were significantly lower in the Fenofibrate group than in Control group which are consistent with those of the present study.

The mean time of hospital stay in Fenofibrate group was also significantly lower than Control group (4.0±0.7 vs 5.5±1.4 days) in this study, which is similar with the finding of Al-Asy et al[15]. Phenobarbitone, Clofibrates and Fenofibrates drugs are effective in the treatment of unconjugated hyper-bilirubinemia. Phenobarbitone takes little longer period to influence the enzyme and may cause sleepiness, sluggishness, feeding difficulty and also depress the respiratory centre. Compared to Phenobarbitone, Fibrates induce bilirubin conjugation much more effectively. The study of Mohammadzadeh et al[17] showed effectiveness of Clofibrate in treatment and prophylaxis of hyperbilirubinemia of infancy. Mechanism and action of Fenofibrate is similar to clofibrate. It is easily available and much safer to administer in pediatric age group. Prolonged use of Fenofibrate has some side effects like gastrointestinal symptoms and muscle cramp in adults (Bennet & Brown)[8] but in neonatal period with a single dose of Fenofibrate, no side effects were observed in this study.

Conclusion

From this study, we can conclude that, phototherapy is still the corner stone in treatment of neonatal jaundice. The use of a single oral dose of Fenofibrate (10 mg/kg) with phototherapy accelerates bilirubin conjugation and excretion, hence reduces the duration of stay in hospital. Although, no side effects of Fenofibrates were observed after a single dose, 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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