RESEARCH PAPER

Gemfibrozil in Late Preterm and Term Neonates with Moderate Jaundice: *A Randomized Controlled Trial*

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Objective: To determine, if oral Gemfibrozil is effective in decreasing the duration of phototherapy by at least 24 hours in neonates >34 weeks gestation with non-hemolytic jaundice, as compared to placebo.

Design: Double blind placebo controlled randomized controlled trial.

Setting: Tertiary care neonatal unit in north India.

Subjects: Ninety seven neonates >34 weeks gestation with non-hemolytic jaundice within first 7 days of life requiring phototherapy.

Intervention: Two doses of Gemfibrozil (60 mg/kg/dose) or placebo, 12 hours apart. Babies were treated with single surface special blue light phototherapy. Serum total bilirubin (STB) was measured 8 hourly. Phototherapy was stopped if two consecutive STB values were below phototherapy zone.

Primary outcome measure: Duration of phototherapy.

Results: The median (IQR) duration of phototherapy was 40 (30, 60) hours in Gemfibrozil and 36 (19, 55) hours in the placebo group (P=0.13). The peak STB levels were 16.8 ± 2.7 mg/dL and 16.3 ± 2.3 mg/dL in Gemfibrozil and placebo groups, respectively. No side effect of the drug or placebo was noticed.

Conclusion: Two doses of gemfibrozil (60mg/kg/dose) given 12 hours apart were not able to reduce the duration of phototherapy, or peak bilirubin level in babies > 34 weeks gestation with non-hemolytic jaundice in the first week of life. Gemfibrozil was not associated with any side effects.

Key words: Fibric acid, Gemfibrozil, Jaundice, Neonate, Phototherapy.

Phototherapy and exchange transfusion are the standard therapies for neonatal hyperbilirubinemia. However, both have their drawbacks(1,2). The enzymatic pathways of bilirubin production and elimination are well understood and many pharmacological interventions to prevent or treat hyperbilirubinemia have been tried but with limited success. Clofibrate has been shown to be an efficient inducer of bilirubin glucuronyl transferase enzyme and z-transport protein(3,4). This drug is however associated with side effects and there are concerns about its carcinogenic potential(5).

Gemfibrozil, a newer fibric acid derivative, has chemical, pharmacological and clinical similarities with Clofibrate. It acts on peroxisome proliferator activated receptor α (PPAR α). The UDP glucuronyl transferase enzyme 1A1, which leads to glucuronidation of bilirubin is a PPAR α target gene(6-8). Thus gemfibrozil induces glucuronidation of bilirubin. Its safety profile is much better than clofibrate and has been used in children with hyperlipidemia due to persistent nephrotic syndrome and HIV, and no side effects were reported(9,10). The purpose of this clinical trial was to determine, if oral Gemfibrozil would decrease the duration of phototherapy by at least 24 hours in late preterm and term neonates with non-hemolytic jaundice, as compared to placebo.

METHODS

This was a double blind, randomized, placebo

controlled trial (RCT), conducted in the neonatal unit of a tertiary care center in North India, from January 2005 to December 2005. The study was approved by the Institute Ethics Committee and a written informed consent from one of the parents was taken before inclusion into the study.

Subjects

Inborn neonates more than 34 weeks of gestation, with neonatal jaundice requiring phototherapy within first seven days of life, were eligible. Phototherapy was started as per Cockington charts(11). Babies were excluded if they had kernicterus, evidence of hemolysis, serum total bilirubin in exchange zone at enrollment, major congenital malformation, severe birth asphyxia, large internal/external blood collections, necrotizing enterocolitis or dehydration. Those babies who underwent exchange or partial exchange transfusion before enrollment and whose mothers received phenobarbitone in antenatal period were also excluded.

Sample size

In our institution, previous data showed that the mean duration of phototherapy was 75.13±41.4 hours in babies >34 weeks with non-hemolytic jaundice. To detect a difference of 24 hours, with 80% power and 2 tailed α error of 5%, 46 babies were required in each group. It was planned to enroll 5 babies extra, to take care of attrition.

Intervention

Babies were randomized to Gemfibrozil or placebo group using a web based random number generator(12) by a person not involved in the study. Gemfibrozil and placebo were packed in sachets made of aluminum foil and sealed to prevent entry of any moisture. These opaque sealed sachets were numbered serially. Caregivers and those who measured the outcome were blinded to the allocated intervention. The sachets of gemfibrozil were prepared from capsule Lopid, manufactured by Parke Davis (Michigan, USA), which was in the form of white powder. For accurate dose titration, liquid form of the drug was prepared. As Gemfibrozil is insoluble in water or milk, the contents of 2 capsules of Lopid (600 mg) were suspended in 10 mL of a vehicle. The vehicle solution was made 3 monthly with help from National Institute of Pharmaceutical Education and Research (NIPER), Mohali, India. It contained xanthum gum (0.5%w/v), glycerol (5%w/v), sodium methyl paraben (0.2%w/v), sodium propyl paraben (0.2% w/v) and demineralised water q.s. These constituents of vehicle are innocuous and used frequently in eatables and medicines as preservatives. The vehicle solution was stored at 4ºC. Each placebo sachet contained 600 mg of microcrystalline cellulose, which was dispersed in 10 mL of the same vehicle. Whenever babies were enrolled, the sachets were opened serially and the contents suspended in 10 mL vehicle solution and mixed thoroughly by one of the investigators (JK). The solution contained 60 mg/mL of gemfibrozil or placebo and dose was 1 mL/kg. The first dose was given within 60 minutes of enrollment and the second, after 12 hours.

Outcome variables

The duration of phototherapy was the primary outcome parameter. Peak serum total bilirubin (STB), age at peak bilirubin, rate of exchange transfusion and time difference between onset of jaundice and peak STB were secondary outcome measures.

Data collection and monitoring

STB was measured every 8 hourly using a dual wavelength direct spectrophotometer (BIL-100, Cosmo Medical Co. Ltd, Korea). Bilirubinometer was calibrated against bilirubin standards at 3 monthly intervals. Babies were treated with single surface special blue light phototherapy. The irradiance of these phototherapy units was measured daily at the baby's level by Minolta Airshields radiometer. Irradiance was maintained at >12 $\mu W/cm^2/nm$, throughout the study period. Exchange transfusion was done when STB exceeded 20 mg/dL or threshold limit as per Cockington charts. Every baby underwent blood grouping, direct Coombs test, reticulocyte count and peripheral blood film examination and glucose 6 phosphate dehydrogenase (G6PD) estimation. All babies were breast fed and formula milk was added wherever

there was inadequate breast milk output. Conjugated fraction of bilirubin was checked once after enrolling. SGOT and SGPT levels were measured 24 hours after administration of first dose. Babies under phototherapy were examined daily for any rash.

Statistical analysis

Intention to treat analysis was done in a blinded manner, using the statistical software package SPSS version 10.0. The code was broken only after complete analysis. Comparison between control and treatment groups for duration of phototherapy and peak STB was performed with Student's *t* test for equality of means while the rate for exchange transfusions was compared by Chi square test. It was decided *a priori* that oral gemfibrozil will be considered an efficient treatment modality if there is at least 24 hours reduction in duration of phototherapy, without any serious adverse effects.

RESULTS

A total of 178 inborn babies >34 weeks gestation and <7 days of age developed neonatal jaundice requiring phototherapy during the study period. Of these, 97 were enrolled into the study. Forty nine babies were allocated to Gemfibrozil group and forty eight to placebo; 48 babies in Gemfibrozil group and 45 in placebo group completed the study (***Fig.* 1**). The mean gestation, weight and age at enrollment of the study population were 36.9±1.6 weeks, 2461± 658 grams and 78±29 hours, respectively. The gestation, birth weight, sex distribution and G6PD deficiency status of those not randomized was similar to that of randomized infants. The basic demographic profile of the studied babies was similar in Gemfibrozil and placebo groups (***Table* I**). The factors at enrollment which could affect subsequent serum bilirubin levels were not different between Gemfibrozil and placebo groups, except G6PD deficiency, which was more prevalent in gemfibrozil group (***Table* II**). ***Table* III** shows the primary and secondary outcomes of the study. The duration of phototherapy (***Fig.* 2**), number of babies undergoing exchange transfusion, peak STB and age at peak STB were not different between the treatment and control groups. A Kaplan Meier survival curve did not demonstrate any difference in the probability of babies remaining under phototherapy at different ages between the two groups (log rank test: $P = 0.48$) (***Fig.* 3**). The results

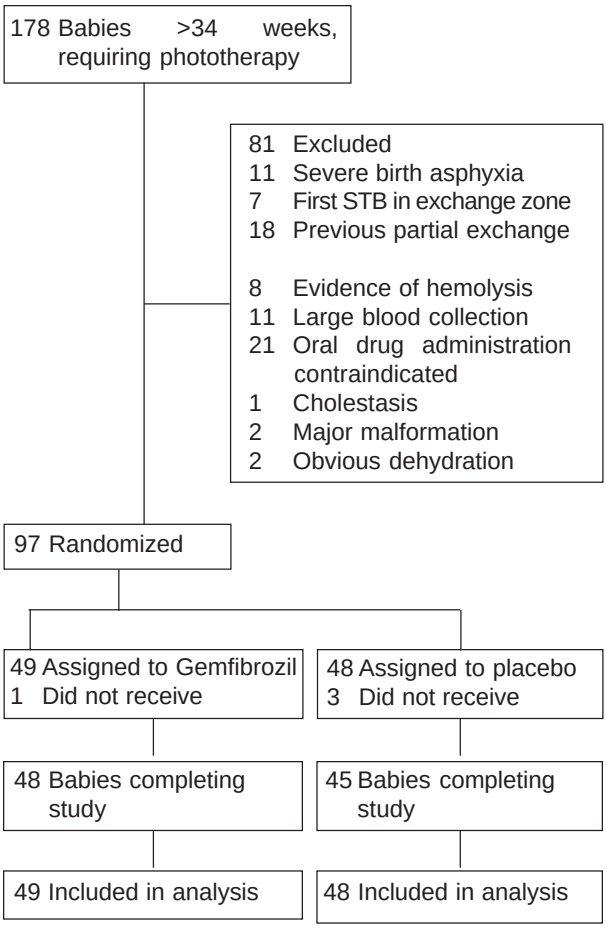

FIG.1 *Flow of study patients.*

TABLE I DESCRIPTION OF STUDY POPULATION

Characteristic	Gemfibrozil (*n*= 49)	Placebo (*n*= 48)
Males (%)	27 (55)	28 (58)
SGA < 2SD (%)	4 (8)	5 (10)
LGA (%)	0 (0)	4 (8)
Mode of delivery (%)		
Normal vaginal delivery	25 (51)	34 (71)
Cesarean section	18 (37)	11 (23)
Outlet forceps delivery	6 (12)	3 (6)
Gestation (weeks) (mean ± SD)	36.9 ± 1.7	36.8± 1.6
Birth weight (g) (mean ± SD)	2431 ± 592	2494 ± 727

Difference between the two groups was not significant (P>0.05).

TABLE II BASELINE VARIABLES AFFECTING SERUM TOTAL BILIRUBIN

Characteristic	Gemfibrozil (*n*= 49)	Placebo (*n*= 48)
Weight loss (% of birth weight) (mean ±SD)	5.55 ± 2.9	5.57 ± 3.7
Oxytocin use in mother (%)	25 (51)	18 (37)
Age at enrollment (h) (mean ± SD)	80 ± 28	77 ± 31
STB at enrollment (mg/dL) (mean ± SD)	15.7 ± 2.7	15.6 ± 3.1
Irradiance (μwatt/cm^2/nm) (mean ± SD)	13.0 ± 3.3	12.8 ± 3.1
G6PD deficiency* (%)	26 (53)	12 (25)
ABO setting (%)	9 (18)	8 (17)

* *P*= 0.01, All other *P* values >0.05.

were not different when late preterm and term infants were analyzed separately (data not shown).

Interaction of G6PD deficiency and Gemfibrozil: A total of 38 babies were G6PD deficient, 12 in placebo and 26 in Gemfibrozil group. The duration of phototherapy was 50.7±46.3 hours in Gemfibrozil G6PD deficient subgroup in comparison with 53.4± 35.9 hours in placebo G6PD deficient subgroup (*P* >0.05). The peak bilirubin level and rate of exchange transfusion were also not different between the two groups. A logistic regression analysis was done with Gemfibrozil/placebo, G6PD deficiency and gestation as independent variables and phototherapy duration as dependent variable. After adjusting for G6PD deficiency, there was no significant difference in phototherapy duration between Gemfibrozil and Placebo group.

Side effects: No rash was noted in either Gemfibrozil or Placebo groups. The mean SGOT and SGPT levels were similar in both groups. Three babies in Gemfibrozil and one in Placebo group had SGOT levels >30 units/L, while 3 babies in each group had SGPT level >30 units/L (***Table* III**). None of the babies developed cholestasis in either group. No other untoward side effects were noted.

DISCUSSION

Oral drug treatment of neonatal jaundice, if effective and safe, is a more attractive option as compared to phototherapy and exchange transfusion. Clofibrate, a fibric acid derivative increases the hepatic clearance of bilirubin by 100% within 6 hours in rats(13). Studies from France and Iran have shown that it decreases the intensity and duration of neonatal jaundice (3,4,14). Gemfibrozil, is a newer drug of the same class with similar effect on PPARα but an improved safety profile.

We were able to ensure effective blinding of the investigators, caregivers, laboratory and the statistician. The duration of phototherapy was chosen as primary outcome and a difference of 24 hours as clinically relevant because that would

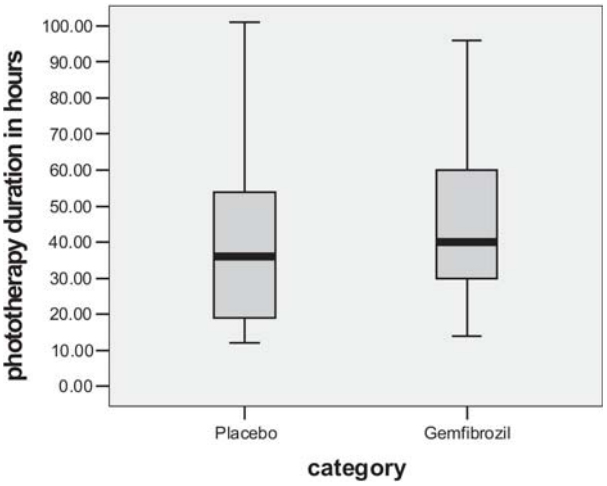

FIG.2 *Box and whisker plot of duration of phototherapy.*

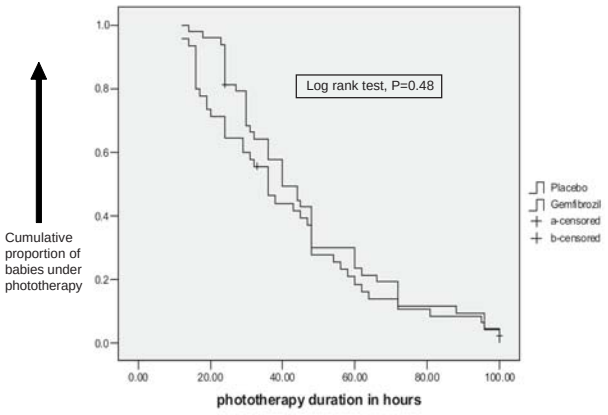

FIG.3 *Kaplan-Meier survival plot showing the probability of babies remaining under phototherapy at different ages.*

TABLE III PRIMARY AND SECONDARY OUTCOMES

Outcome	Gemfibrozil (*n*= 49)	Placebo (*n*= 48)
Duration of phototherapy (h)*		
Mean ± SD	50.4 ± 38.8	41.6 ± 26.6
Median (IQR)	40 (30, 60)	36 (19, 55)
Exchange transfusion (%)	1 (2)	2 (4)
Peak STB (mg/dL) (mean ± SD)	16.8 ± 2.7	16.3 ± 2.3
Time between onset of jaundice and peak STB (h)		
Mean ± SD	8.9 ± 12.2	7.3 ± 10.7
Median (IQR)	3.5 (0, 15)	0 (0, 12)
Age at peak STB (h) (mean ± SD)	88.5 ± 27.7	85.0 ± 30.7
SGOT >30 IU/L (%)	3(6)	1(2)
SGPT >30 IU/L (%)	3(6)	3 (6)

**The data of babies who underwent exchange transfusion were excluded from the analysis of duration of phototherapy. All P values >0.05.*

translate into lesser duration of hospital stay and cost of treatment. However there was no significant difference in the duration of phototherapy between Gemfibrozil and placebo groups. There were more number of babies with G6PD deficiency in the Gemfibrozil group which may have potentially masked the benefits of Gemfibrozil. It has been documented that phototherapy is less effective in G6PD deficient babies(15,16). The duration of phototherapy in our study was however not different between Gemfibrozil and placebo groups even when analyzed for the sub-group of G6PD deficient babies. This was also corroborated by a regression analysis. The initial two randomized controlled trials of clofibrate from France were reported in 1981 and 1985(3,4). In the initial study in term babies, from the 16th hour after clofibrate administration, the treated group had a significantly lower bilirubin level compared with placebo. The intensity and duration of the jaundice was lower and less intensive phototherapy was needed. In the second study by the same authors(4), clofibrate given to preterm neonates (31-36 weeks gestation) at 24 and 48 hours reduced the bilirubin levels, number of bilirubin estimations and phototherapy duration. The one recently published controlled trial of clofibrate by Mohammadzadeh, *et al.*(14) was not blinded and no placebo was used. Most of the babies were enrolled beyond one week of life, which doesn't represent the normal pattern of neonatal jaundice.

Induction of bilirubin-conjugating UGT1A1 enzyme by fibric acid derivatives in microsomes from liver has been shown in rats(17). However finofibrates do not increase bilirubin glucuronidation in mice, underscoring the species specificity(18,19). There is a possibility of racial variations in the UGT1A1 gene in humans which may make certain populations more responsive to fibrates. There is no pharmacokinetic data available on Gemfibrozil in infants. We chose the dose and schedule by extrapolating adult data and did not measure serum Gemfibrozil levels. Food may also affect the rate and extent of Gemfibrozil absorption. In neonates, who are fed very frequently, drug absorption might be erratic and not reach the therapeutic concentrations. We enrolled the babies when the STB levels reached phototherapy zone at a mean age of 80 hours. Induction of UGT1A1 genes by Gemfibrozil in humans may take more time than shown in animals. Hence, starting the drug earlier may be more effective. Lindenbaum, *et al.*(4), in 1985, studied the prophylactic role of clofibrate in newborns of 31-36 weeks of gestation by giving the drug at 24 and 48 hours. Those babies who received prophylactic clofibrate had lesser bilirubin level, lesser need for bilirubin determination and less duration of phototherapy. However this approach would imply unnecessary administration of the drug to many babies. The sample size calculation was based on mean phototherapy duration (75.13 ± 41.43 hours) among the same kind of babies in last year in our unit. However, the average duration of phototherapy during the study period (46.1±33.6 hours) was much lesser, probably due to better phototherapy lights and closer monitoring of irradiance. As a result, the study was underpowered to detect a 24 hours difference; to detect that, one would need to enroll 71 babies in each group.

To conclude, two doses of gemfibrozil (60mg/kg/dose) given 12 hours apart were not able to reduce the duration of phototherapy in late preterm and term babies presenting with moderate non-hemolytic jaundice in the first week of life. Gemfibrozil was however well tolerated and was not associated with

WHAT IS ALREADY KNOWN?

- Gemfibrozil, a newer fibric acid derivative induces glucuronidation of bilirubin.

WHAT THIS STUDY ADDS?

- Two doses of Gemfibrozil (60mg/kg/dose) given 12 hours apart were not able to reduce the duration of phototherapy in late preterm and term babies presenting with moderate non-hemolytic jaundice in the first week of life.

any side effects. Whether Gemfibrozil given earlier, from first day of life, or in different therapeutic doses will be effective is an area for further investigation.

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Contributors: JK recruited subjects, collected and analyzed data and wrote the manuscript, PK designed the study, checked the data and edited the manuscript, AN helped in planning the study and edited the manuscript.

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Competing interests: None stated.

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