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STUDY TO COMPARE THE EFFECT OF ORAL FENOFIBRATE AS AN ADJUNCT OF PHOTOTHERAPY AND PHOTOTHERAPY ALONE ON UNCONJUGATED NEONATAL HYPERBILIRUBINEMIA

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ABSTRACT

Background: Neonatal hyperbilirubinemia is one of the most observed clinical conditions found during the first week of life. In neonates, bilirubin tends to be deposited in body tissues, especially the skin and mucous membranes. **Objective:** The aim of this study was to determine the efficacy of fenofibrate with phototherapy in hyperbilirubinemia in term infants and to assess the effect of fenofibrate adjunct to phototherapy on duration of phototherapy and hospital stay. **Methodology:** The study was performed in two groups of healthy and term neonates. 75 neonates were treated with a single oral dose of fenofibrate plus phototherapy while other 75 were given only phototherapy. Serum bilirubin levels were monitored at admission, 12, 24, 48 and 72 hours of admission. **Result:** The mean bilirubin levels of 12th, 24th, 48th hours were significantly decreased in the fenofibrate treated group A as compared to the controlled group B. Fenofibrate administration decreased total serum bilirubin, especially from the second day onwards, and also reduced hospitalization time, hospital costs and side effects from hospitalization. **Conclusion:** Although standard therapy for unconjugated hyperbilirubinemia includes phototherapy and exchange transfusion but pharmacological interventions are into current use. Fenofibrate can be used as a primary treatment along with phototherapy with no side effects and reduced hospital duration.

KEYWORDS : neonatal hyperbilirubinemia, serum bilirubin, phototherapy, fenofibrate

INTRODUCTION

Neonatal jaundice also known as hyperbilirubinemia is one of the most observed clinical conditions found during the first week of life that is affecting 60% of term neonates and 80% of the preterm infants.[1] It is due to the result of an imbalance between bilirubin production and elimination. It manifests as yellowish discoloration of the skin, sclera, body fluids and mucous membrane.

Bilirubin is an end product of heme catabolism which results from a series of enzymatic reactions by heme-oxygenase and biliverdin reductase enzymes. For hyperbilirubinemia increased heme catabolism is an important mechanism. Physiological jaundice results in first week of life. The major cause of it is deficient uridine glucuronyl transferase (UDPGT) activity that results in bilirubin conjugation impairment. During the first few days of life, the activity of UDPGT in all the neonates are usually less than 1% of adult.[2] Causes of elevated unconjugated hyperbilirubinemia may be due to either increased bilirubin production by liver cells or reduced transferase enzymes activity. Also due to reduction of bilirubin uptake by the liver cells.

This free bilirubin gets deposited in sclera, skin and mucous membrane thus producing jaundice. If it gets into brain it may cause transient dysfunction and neurological consequences referred as 'Kernicterus' damaging the basal ganglia and causing scarring of brain stem nuclei.

Phototherapy has emerged as the most commonly non-pharmacological therapy for the treatment of hyperbilirubinemia but it has few complications of prolonged use like loose stools, retinal damages, hyperthermia, and bronze baby syndrome.[3]

Exchange transfusion is recommended when phototherapy fails to reduce unconjugated hyperbilirubinemia but it has certain early and late complications. Few pharmacological agents like Phenobarbital, D-penicillamine, immunoglobulins and Metalloporphyrins have been proved very less effective in routine practices.[4]

Fibrates group of drugs like fenofibrate has been used for several years as a hypolipidemic drug. The mechanism is that it increases bilirubin conjugation and excretion by affecting glucuronyl transferase activity. Its potency is three times more than phenobarbital in the induction of bilirubin conjugation.[5] Fenofibrate does not cause any side effect in neonatal period. This study was basically done to establish the efficacy of the fenofibrate in hyperbilirubinemia when given with phototherapy.

MATERIAL AND METHODS

This study was conducted in term neonates admitted with hyperbilirubinemia in the Neonatal Intensive Care Unit (NICU) tertiary care centre. A total of 150 term neonates with birth weight >= 2.5 kg with total serum bilirubin value meeting the threshold for phototherapy according to Age Specific nomogram by Bhutani chart for phototherapy[6] were included in this comparative study.

Exclusion criteria consisted of (a) Preterm babies (b)Newborn with sepsis, asphyxia, shock (c)Congenital anomalies or inborn error of metabolism (d)Small for Gestational age/intra uterine growth retardation (e)Neonate already started on phototherapy before referral (f) Neonate with leave against medical advice/ expired.

Sample Collection was done in following ways: Routinely in our NICU one unit gives fenofibrate with Phototherapy in hyperbilirubinemia and other unit gives phototherapy only. So those patients who were given phototherapy with fenofibrate were kept in GROUP A and those who were given phototherapy alone were in GROUP B. Fenofibrate single oral dose of 10 mg/kg dissolved in expressed breast milk, through paladai was given before the start of phototherapy. Babies of both the groups were given phototherapy continuously at the distance of 20 cm under phototherapy unit with 6 fluorescent lamps of blue light spectrum. Interruption of phototherapy was only during breast feeding.

Babies were continuously monitored clinically and evaluated for development of side effect of either therapy in both the

groups. Blood sample were collected for total and indirect bilirubin of at admission, 12th, 24th, 48th, 72th hours of admission in both groups. Routinely in our set up Serum glutamic pyruvic transaminase (SGPT) is done before and after 24 hours of giving fenofibrate to see any effect of Fenofibrate on liver.

Statistical Analysis:

Data obtained were analyzed for statistical significance. Slovenes' formula was applied that is $n=N/(1+Ne^2)$ where e = margin of error at 95% Confidence Interval (0.05), n = sample size, N= population size. For comparing categorical data of both groups, Chi square (2) test was performed. P value of <0.05 was considered statistically significant. The present study was ethically approved by the Institutional Human Ethics Committee.

RESULTS

Total 150 term neonates were enrolled in the study. 40In group A (Fenofibrate group) 40 male (53.3%) and 35 female (46.6%) babies whereas in group B 38 male (50.6%) and 37 female (49.3%) babies were there. Though there were more number of male babies in either group but the sex distribution was statistically insignificant with p value> 0.05.

The mean hours of life at start of fenofibrate with phototherapy (GROUP A) was 80 hours and 78 hours in phototherapy (GROUP B) respectively which was statistically insignificant in either group with p value>0.05.

Babies were predominantly presenting in the age group of 24-72 hours. Age in hours at the start of phototherapy is depicted in table below for babies of either group.

Table 1: Age Distribution Ranges In Either Groups At Start Of Phototherapy

Hours of life	GROUP A	GROUP B	TOTAL
<24 hours	00	00	00
24-72 hours	44(58.6%)	47(62.7%)	91(60.7%)
72-120 hours	30(40%)	25(33.3%)	55(36.7%)
>120 hours	01(1.3%)	03(4%)	04(2.6%)

There were more of O +ve (44% in group A and 33.3% in group B) blood group babies affected in both the groups. That was statistically insignificant with p value> 0.05.

The study showed that the lower socio-economical (58.7 % in group A and 74.7% in group B) class was affected more that was statistically insignificant with p value> 0.05.

Though there were more number (93.3%in group A and 78.7 % in group B) of babies of 2.5 to 3.0 kg in either group but the weight distribution was statistically insignificant with p value>0.05.

The increase in number of babies presenting jaundice substantiates the fact that 2.5 to3.0 kgs babies are at increased risk of jaundice. Though babies were not evaluated for minor group incompatibility, ABO incompatibility was the most common form of incompatibility. There were same number of babies with ABO incompatibility in either groups. That was statistically insignificant with p value>0.05. There was one baby with Rh incompatibility (1.3%) in Group B (phototherapy group). That was statistically insignificant with p value> 0.05.

Table 2: Comparison Of Serum Bilirubin Levels In Both The Groups.

Time (hours)	Group A Serum bilirubin (mg/dl)	Group B Serum bilirubin (mg/dl)	P value
0	19.2±2.86	19.18±1.95	0.9602
12th	14.15±2.57	16.29±2.44	<0.0001
24th	10.08±1.98	12.72±2.72	<0.0001
48th	8.22±1.63	8.9±1.95	0.0219
72th	5.4±1.24	6.05±1.84	0.0122

The study showed that maximum neonates (69.3%) of group A presented with serum bilirubin 16-20 mg/dl at the time of admission. At 12th hour of admission, 73.3% of neonates had fall in bilirubin within 10-15mg/dl range. At 48th hour of admission, 78.8% of neonates had fall in bilirubin within normal limits. And by 72nd hour all neonate's serum bilirubin levels had fallen within normal limits. The study showed that maximum neonates (76%) of group B presented with serum bilirubin 16-20 mg/dl at the time of admission. At 12th hour of admission, 52% of neonates had fall in bilirubin within 10-15mg/dl range. At 48thhour of admission, 50% of neonates had fall in bilirubin <10mg/dl. And by 72nd hour 94.7% neonate's serum bilirubin levels had fallen within normal limits.

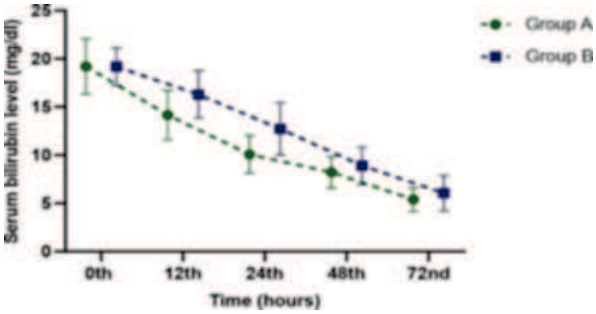

Figure 1: Serum Bilirubin Value During Treatment In Group A And Group B.

The mean values for total serum bilirubin at 12th, 24th, 48th, 72 hours after admission in group A were significantly less than group B. The rate of decline in serum bilirubin levels at 12th hour of admission in group A with fenofibrate with phototherapy was 4.7 mg/dl in 12 hours. Whereas in group B with only phototherapy the rate of decline was 2.8 mg/dl in 12 hours.

The rate of decline in serum bilirubin levels at 24th hour of admission in group A with fenofibrate with phototherapy was 9 mg/dl/day. Where as in group B with only phototherapy the rate of decline was 6.2 mg/dl/day.

This study showed that mean duration of Phototherapy was given for 46 hours in GROUP A and 58 hours in GROUP B. Hence we can do the early discharge of babies in group A as compare to group B and duration of hospital stay can be decreased in group A.

Table 3: Distribution Of Duration Of Phototherapy In Either Groups

Duration Of Phototherapy (HOURS)	GROUP A	GROUP B	P value
12 HOURS	02(2.6%)	00	0.0005
24 HOURS	22(56%)	06(8%)	0.0005
48 HOURS	59(78.7%)	38(50%)	0.0005
72 HOURS	75(100%)	71(94.7%)	0.0005

There were 56 % of babies in Group A and 8% of babies in GROUP B in whom serum bilirubin had fall below 10 mg/dl within 24 hours of treatment.

There were 78.7% of babies in A and 50% of babies in GROUP B in whom serum bilirubin had fall below 10 mg/dl within 48 hours of treatment. There were 100% of babies in Group A and 94.7% of babies in GROUP B in whom serum bilirubin had fall below 10 mg/dl within 72 hours of treatment. Hence our study showed that we can do early discharge of the babies in GROUP A as compared to GROUP B.

Peak bilirubin value of both the group were analyzed. This peak bilirubin corresponded to the bilirubin at the start of phototherapy. Data of peak bilirubin is given in the following table.

This result analyzed by chi square test was found to be statistically insignificant (p value>0.05).

Group A	19.2 mg/dl±2.86
Group B	19.18mg/dl±1.95

Table 4: Peak Bilirubin Range At The Time Of Admission

Bilirubin range(mg/dl)	GROUP A	GROUP B
<10	00	00
10.0-15	07(9.3%)	01(1.3%)
15.1-20	52(69.3%)	57(76%)
20.1-25	16(21.3%)	17(22.7%)

There was statistically insignificant difference in number patient presenting their peak bilirubin between the two groups (P value >0.05) There was no difference in the SGPT levels of neonates receiving fenofibrate. There was statistical insignificance in either groups. Babies were followed up during hospital stay, at discharge and at 1 week following discharge and they had no complication in either group. Babies were gaining weight adequately.

DISCUSSION

Neonatal jaundice is mostly occurred between 25 hours and 144 hours of life in most of the neonates (approx. 70-80%). About 20-30 % of neonates require phototherapy. Management with phototherapy reduces brain damage and need for exchange transfusion, still the duration of hospital stay and need for exchange transfusion is required in case of hemolytic jaundice. Thus adjunctive therapy is needed along with phototherapy.

In the present study, the effect of combination therapy of single oral dose of Fenofibrate (10mg/kg) and phototherapy (Group A) was compared with phototherapy alone (Group B) on total serum bilirubin level.

In this study hours of life, the bilirubin level on admission was statistically insignificant and mean of serum bilirubin is similar in both groups. Peak value in this study is also statistically insignificant in both the groups. There were no rise in serum bilirubin after starting of therapy hence phototherapy is effective modality of treatment jaundice. No failure of phototherapy was seen in any patient in this study.

In this study 75 number of neonates enrolled in either GROUP A or GROUP B. Male predominance was observed in both groups. Hence male babies has increased risk of jaundice in this study. Similar male preponderance has been reported from studies conducted by Kumar B etal.(2011). [7]

In this study more number of babies having weight 2.5 to 3 kgs present as compare to >3 kgs. Similar results of maximum number of jaundice cases in 2.5 to 3 kgs have been reported in studies by Chaudhary G. Chaudhary V. et al (2016)[8].

In blood group distribution O+ve blood group babies more affected in either groups with O +ve mother blood groups babies were affected more in either groups.

Total serum bilirubin levels in group A at 12th,24th, 48th and 72th hours after starting the treatment were significantly lower than those in group B. Similar results of Chaudhary G. And Chaudhary V. et al. (2016)[8] Kumar B et al. (2011)[7].

In our study mean age at admission was 80 hours and 78 hours in group A and group B respectively. Similar mean was presented in Al Asy HM et al. (2015)[9] TSB in fenofibrate groups was 15.8 mg/dl and TSB of control group was 16.59 with statistical insignificance in both groups at start of phototherapy. In extramural babies early age of presentation was seen because of early referral Peak bilirubin levels were 19.2 & 19.1 mg/dl in GROUP A and GROUP B consecutively. In this study both groups are statistically insignificant. Similar results of age, gestational age, birth weight and baseline total serum bilirubin , mean have been reported in studies by Chaudhary G. And Chaudhary V. et al. (2016).[8]

A study by Bijay K et al.[7] showed comparison of therapy with single dose of Fenofibrate (10mg/kg) & phototherapy (Group B) with phototherapy alone (Group A) on serum bilirubin levels. Level of serum bilirubin in group B at 24th hours, 36th hours & 48th hours after giving the treatment were markly lower than those in group A. Mean time was also reduced in group B than group A. In a study of Mohammad zadeh et al. (2010)[10] results Single oral dose of clofibrate(100mg/kg) in newborns with hyperbilirubinemia has a drop in bilirubin within 12 hours as compared to control group in that no decrease in 24 & 48 hours. In the study 78.8% of patients has decrease in bilirubin to normal limit in GROUP A as compare to GROUP B (50 %) 48 hours of life and all patients had fall in bilirubin upto normal limit in GROUP A at 72 hours of treatment as compared to GROUP B (71 %). Similar result has been found in.

Al Asy HM (2015)[9].

Our study showed mean duration of phototherapy in Group A (46±17 hours) and in Group B (58±15.3 hours). Similar result found in Shahien A Dabour et al. (2010)[11] as mean of 5.3 in fenofibrate groups and 5.8 in phototherapy alone group. Hence in phototherapy along with fenofibrate, we can do early discharge and shorten the duration of hospital stay. This study showed statistically significant decline in duration of phototherapy and duration of hospital stay with peak bilirubin level between in 15 -20 mg/dl in Group A as compare to Group B.

CONCLUSION

The study was done to see the effect of Fenofibrate with Phototherapy and Phototherapy alone on unconjugated hyperbilirubinemia in neonatal jaundice. Result shows that Fenofibrate lessens the duration of hospital stay and decreases the time needed for phototherapy. Hence, Fenofibrate is effective and safe for neonatal hyperbilirubinemia with no side effects observed. By this study we can recommend FENOFIBRATE use as a primary treatment along with phototherapy in neonatal hyperbilirubinemia.

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