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Effect of Single Dose Fenofibrate as an Adjunct to Phototherapy on Unconjugated Neonatal Hyperbilirubinemia: A RCT

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Abstract

Background: *Fenofibrate is used as an adjunct therapy to reduce bilirubin level and duration of phototherapy. This study was done to determine the efficacy of fenofibrate in the treatment of unconjugated neonatal hyperbilirubinemia.*

Materials & Method: *Total 60 neonates were enrolled and devided into two groups. In group A, a single dose of oral fenofibrate (10mg/kg) was given along with phototherapy, and Group B only phototherapy. Blood samples were collected every 24 hours for total and indirect bilirubin. SGPT was done before and after 24 hours of giving fenofibrate.*

Result: *Baseline serum bilirubin was 16.86± 0.89 in group A and 17.31± 1.19 in group B. After 24 hours of starting phototherapy, the bilirubin level came down to a lower value of 14.83 ± 0.95 mg/dl in group A and 15.73 ± 1.32 mg/dl in group B. After 48 hours it was 12.85 ± 1.06 mg/dl and 14.20 ± 1.24 mg/dl in group A and group B respectively. (P-value 0.004 and 0.001). The mean time needed for phototherapy was 51.20 ± 8.29 hours in group A and 70.40± 6.08 hours in group B (P-value 0.001). The duration was shorter in the fenofibrate group in comparison to the control group. No side effects of fenofibrate were observed after a single dose administration.*

Conclusion: *Administration of a single dose of fenofibrate as an adjunct along with phototherapy to neonates showed a significant reduction of serum bilirubin and duration of phototherapy.*

Keywords: *Fenofibrate, Phototherapy, Uncomplicated Neonatal Hyperbilirubinemia*

Introduction:

Neonatal jaundice is one of the most prevalent clinical conditions observed during the first week of life affecting 60% of term and 80% of preterm infants.[1] It is the result of an imbalance between bilirubin production and elimination. Bilirubin is one of the end products of heme catabolism from a series of enzymatic reactions by heme-oxygenase and biliverdin reductase. Increased heme catabolism is an important mechanism for hyperbilirubinemia. In neonates, this is more significant because of high red cell mass and relative immaturity for bilirubin conjugation. Deficient uridine glucuronyl transferase (UDPGT) activity that results in bilirubin conjugation impairment has been considered a major cause of physiologic jaundice. In the first 10 days of life, the UDPGT activity in full-term and premature neonates are usually less than 1% of adult.[2,3]

This free bilirubin deposits in the skin and mucous membrane and produces jaundice. It may also deposit in the brain where it causes transient dysfunction and occasionally permanent neuronal damage. ''Kernicterus'' refers to neurological consequences of the deposition of unconjugated bilirubin in brain tissue by damaging and scarring of the basal ganglia and brain stem nuclei.[4]

Unconjugated hyperbilirubinemia may be increased by any factor that: (a) increases bilirubin production

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by liver cells (hemolytic anemias, polycythemia, bruising or internal hemorrhage, shortened red blood cell life, increased enterohepatic circulation, infection); (b) reduces the activity of the transferase enzymes (c) blocks the transferase enzymes; (d) reduction of bilirubin uptake by liver cells.[5]

Phototherapy has emerged as the most widely used non-pharmacological therapy for the treatment of neonatal unconjugated hyperbilirubinemia but it has several untoward complications such as retinal damages, hyperthermia, loose stool, and bronze baby syndrome, etc.[6] Pharmacological agents introduced for the treatment of unconjugated neonatal jaundice include Phenobarbital, Metalloporphyrins, and D-penicillamine. They have not been proved very effective and safe in clinical use.[7]

Fenofibrate has been used for several years as a hypolipidemic drug.[8] It also increases bilirubin conjugation and excretion via induction of glucuronyl transferase activity.[9] Its potency is three times more than Phenobarbital in the induction of bilirubin conjugation.[10] Fenofibrate acts on peroxisome proliferative activated receptor á (PPAR á). The UDP glucuronyl transferase enzyme 1A1, which leads to glucuronidation of bilirubin is a PPAR á target gene.[11]

Thus fenofibrate induces glucuronidation of bilirubin. The effect of fenofibrate on uncomplicated hyperbilirubinemia was also proposed in some studies conducted in India, Egypt, and Iran.[12-14] Fenofibrate doesnot cause any side effect in neonatal period. Study by Badely et al. & Mahammad zadeh et al. in Iran shows that a single dose of clofibrate which has similar M/A like fenofibrate didn't produce any side effect.[13-14] Mild, transient serum aminotransferase elevations develop in up to 20% of adult patients receiving fenofibrate for long time.[15]

The purpose of this study was to determine, if oral fenofibrate would decrease the duration of phototherapy in neonates with hyperbilirubinemia as an adjunct with phototherapy. Thereby it may reduce the burden of phototherapy units in hospitals. As there is scarcity of clinical trial in Bangladesh this study will help to evaluate the effectiveness of fenofibrate in neonatal hyperbilirubinmia.

Materials & Method:

This Randomized controlled clinical trial was done at Neonatal ward, Dhaka Shishu (Children) Hospital, from April 2016 to March 2017 after taking ethical permission from local assigned authority. Sixty neonates enrolled in this study after fulfilling the inclusion criteria like unconjugated hyperbilirubinemia needed phototherapy according to American Academy of Paediatric (AAP) criteria (phototherapy graph), term baby, age 0-14 days, body weight 2500 to 3999 gm. Neonate with conjugated hyperbilirubinemia, Rh incompatibility, congenital anomalies, and very sick neonates with jaundice were excluded. Total study subject was randomized in 2 groups- 30 in each group (group A and group B). This division was done by lottery. Group A or interventional group (n=30) received a single dose of oral tablet fenofibrate (10mg/kg) with phototherapy and Group B or control group (n=30) received only phototherapy. Fenofibrate tablet (160mg) was dissolve in 10 ml of distilled water to get 16mg fenofibrate in 1 ml. Another dose was repeated after 10 minute in case of vomiting or spillage. Informed written consent from the parents or caregiver was taken. Double source (panel) of 10 fluorescent (5+5) tubes lights of 40 watts (Philips Co of Germany) was used for phototherapy. Immediately after admission and before starting any modalities, blood samples were drawn from both groups for complete blood count (CBC), total bilirubin (direct and indirect), reticulocyte, CRP, Coombs test, blood group and Rh typing of neonates. The blood sample was collected every 24 hours for total and indirect bilirubin until the bilirubin level falls below the phototherapy range. Skin rash, loose stool, dehydration were monitored by assigned medical personel. SGPT was done before and after 24 hours of giving fenofibrate.

Data was collected (level of serum bilirubin, rate of fall of serum bilirubin, duration of phototherapy) in a preset questioner and statistical analysis was performed by using Statistical Package for Social Sciences version 23.0 for Windows (SPSS, Chicago, IL). Results of the findings were verified by standard test for significance like chi-square test and Student 't' test. Statistical significance was defined as $p<0$ .05.

Results:

During the study period total of 398 neonates were assessed for eligibility. Out of them 338 were excluded according to exclusion criteria and 60 eligible neonates were assessed and randomized in two groups, 30 in Group A (intervention group) and 30 in Group B (Control group). Baseline demographic (age, sex, gestational age, birth weight) and hematological values (blood group, Hb%, reticulocyte, serum SGPT)

were compared and no significant differences were found between two groups. There was a slight female preponderance in both groups.

Mean birth weight was found at 2880.00±304.44 gm in group A and 2906.66±323.69 gm in group B. The mean gestational age was found 39.00± 1.4 weeks in group A and 39.00 ± 1.6 weeks in group B. Those difference was not statistically significant (P-value >0.05). Comparing Hb level, absolute reticulocyte count & SGPT between two groups no significant difference was found (Table-I).

The mean difference of serum bilirubin between two groups on admission was not significant, but at 24 hours and 48 hours was statistically significantly low in groups who got fenofibrate along with phototherapy (Table II).

Rate of fall of serum bilirubin after 24 and 48 hours; the changes of serum bilirubin level between groups after 24 hours and 48 hours were statistically significant (Table III).

Distribution of the study population by the duration of phototherapy. Mean duration of phototherapy was found statistically significant ($p<0.05$) between the groups (Table IV).

Distribution of the intervention group (group A) by SGPT before and after giving fenofibrate to see the side effect of fenofibrate; here mean serum SGPT was found normal before and after giving fenofibrate (Table V).

Side effects of fenofibrate were looked for but there was no single case with any effect.

Table-I

Baseline characteristics of the study subjects (N=60)

Variables	Group A Mean ±SD	GroupB Mean ±SD	P-Value
Birth weight(gm)	2880.00±304.44	2906.66±323.69	0.744
Gestational age(weeks)	39.00± 1.4	39.00 ± 1.6	1.00
Hb level (gm/dl)	13.6± 0.89	13.70 ± 0.99	0.731
Absolute Reticulocyte (thous/µL)	57.2 ± 0.48	59.7 ± 0.72	0.530
SGPT(Ur/L)	29.83± 5.55	27.98± 4.43	0.250

Table II

Comparison of plasma bilirubin values during treatment between fenofibrate group (group A) and control (group B) (N=60)

Serum bilirubin level(mg/dl)	Group A (n_1=30) Mean± SD	Group B (n_2=30) Mean ± SD	P-value
On admission	16.86 ± 0.89	17.31± 1.19	0.107
At 24 hours	14.83 ± 0.95	15.73 ±1.32	0.004
At 48 hours	12.85 ± 1.06	14.20 ± 1.24	0.001

Table III

Rate of fall of serum bilirubin after 24 and 48 hours (N=60)

Change of serum bilirubin level	Group A (n_1=30) Mean± SD	Group B (n_2=30) Mean± SD	P-value
24 hours	11.89 ± 5.55	9.07 ± 5.11	0.045
48 hours	23.75 ± 5.47	17.87± 5.46	0.001

Table IV

Distribution of the study subject by the duration of phototherapy (N=60)

Duration of phototherapy (hrs)	Group A (n_1=30) Mean± SD	Group B (n_2=30) Mean± SD	P value
	51.20 ± 8.29	70.40 ± 6.08	0.001

Table V

SGPT level before and after giving fenofibrate

SGPT(U/L)	Before fenofibrate Mean ±SD	After fenofibrate Mean ± SD	P-value
	29.83 ± 5.55	28.20± 5.33	0.163

Discussion:

After 24 hours and 48 hours of starting phototherapy, the bilirubin level came down to a lower value. This difference was statistically significant (P-value 0.004 and 0.001). This result was similar to another study in Egypt and India in 2010 & 2016.[16-18] A study showed the difference in serum bilirubin levels between both the groups after 24 h was statistically nonsignificant (p=0.269); however, it became significant after 36 and 48 hours of phototherapy (p<0.0001).[19] But the result of the present study was contrary to the study done by another author where there was no significant difference in bilirubin levels at 12, 24, and 48 hours respectively among the fenofibrate exposed and unexposed group.

In this study, the rate of fall of serum bilirubin was significantly higher in the fenofibrate treated group than phototherapy alone. A study conducted by Mohammadzadeh et al.(2005) showed a reduction of TSB in 72 hours of treatment was near to significant (P-value 0.061). Clofibrate is another hypolipidemic drug which has a similar mechanism of action like fenofibrate.[20]

This study showed there was a significant difference in the duration of phototherapy between two groups. The mean duration of phototherapy in the fenofibrate group (51.20± 8.29 hours) was lower (70.40± 6.08 hour) than that of the control group and the result was statistically significant (P-value 0.001). A study conducted by Chaudhary et al in India in 2008 showed the infants in the fenofibrate group needed an average of 38.40 ± 11.20 hours of phototherapy while the control group required 46.67 ± 4 hours which was a significant difference (p<0.0001).[14] In 2016 a study conducted by El-Frargy et al. in Egypt also had a significant difference in phototherapy duration (p<0.03); the fenofibrate group requiring a mean of 4 ± 1.8 days and the control group 5 ± 1.8days.[21] Another study by Al-Asy et al. showed that the fenofibrate group received an average of 5.366 days phototherapy while the control group received 5.633 days and this finding was significant (P-value 0.0058).[15] The short duration of phototherapy is an important goal in the treatment of jaundiced neonates because it leads to more bonding between mother-infant, less hospitalization, and decrease money expense and side effects of phototherapy.

In the present study administration of a single dose of fenofibrate was well tolerated and no side effects were observed. There was no significant difference in pre and post-treatment serum SGPT (p>0.05). Several medications were tried as adjuvant therapy in neonatal jaundice during the last two decades. Among these phenobarbitone has shown a significant role in the treatment of neonatal hyperbilirubinemia. Compared to phenobarbitone, fibrates induce bilirubin conjugation much more effectively and readily converts unconjugated bilirubin to conjugated bilirubin, thus, hasten its clearance.[22] Moreover phenobarbitone takes days to influence the enzyme and may produce sleepiness, sluggishness, and feeding difficulty. This study showed fenofibrate has some role in the improvement of neonatal jaundice as adjuvant therapy. The study findings could have important implications on a child survival program in developing countries like Bangladesh. Hopefully, fenofibrate would act as an adjuvant in neonatal jaundice.

It is not a double-blinded, no placebo control single-center study and the study did not provide long term follow up of all possible side effects of fenofibrate. Longer follow-up, long-term effects of fenofibrate, and large multicenter study is recommended.

Conclusion:

Oral fenofibrate is an effective adjunctive therapy when combined along with phototherapy for the treatment of neonatal jaundice. The use of a single dose of fenofibrate with phototherapy decreases the level of serum bilirubin more rapidly and shortened the time needed for phototherapy. Fenofibrate is well tolerated and is not associated with any side effects.

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