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Fenofibrate As an Adjuvant to Phototherapy in Term Neonates with Hyperbilirubinemia; A Randomized Controlled Clinical Trial

Khaled Abouelenin Khafaga*, Lofty Mohamed Alsaid, Raafat Hassan Salama, Maged Taher Abougabal
Department of Paediatrics, Faculty of Medicine, Zagazig University, Zagazig, Egypt
***Corresponding author:** Khaled Abouelenin Khafaga, **Mobile:** (+20) 01061788891, **E-Mail:** drkhaledkhafaga@gmail.com

ABSTRACT
Background: Neonatal jaundice results from accumulation of bilirubin as fetal hemoglobin is metabolized by the immature liver. It may be physiological or pathological. Although most infants recover without major morbidity, yet some might develop sever hyperbilirubinemia and acute bilirubin encephalopathy as result of high levels of serum bilirubin**.** Fenofibrate is a member of the fibrates group. It is a safe and inexpensive orally administered fibric acid derivative conventionally used to treat dyslipidemia. In contrast to clofibrate, studies investigating value of fenofibrate in treatment of the conditions are scarce. The aim was to assess Fenofibrate as an adjuvant to phototherapy in Term Neonates with Hyperbilirubinemia; a prospective randomized controlled trial.
Patients and Methods: The study recruited 74 patients randomly divided into 2 equal groups. Patients were assigned to receive either phototherapy with single oral dose of fenofibrate suspension (10 mg/kg) on day 1 of phototherapy (Group 1), or phototherapy alone (Group 2).
Results: The 2 studied groups were comparable regarding the basic clinical and laboratory data. The whole series comprised 45 (60.8%) males and 29 (39.2%) females. Comparison between total serum bilirubin levels during treatment and on discharge levels showed significant improvement of bilirubin levels in the two studied groups (P-value 0.0001). Comparison between bilirubin levels in the 2 studied groups revealed significantly lower bilirubin levels in fenofibrate treated group when compared with the control group starting at 36 hours after admission till discharge. **Conclusion:** Fenofibrate as an adjuvant to phototherapy in neonates with hyperbilirubinemia is associated with significant reduction of serum bilirubin levels.
Keywords: Oral Fenofibrate, Serum Bilirubin, Term Neonates, Hyperbilirubinemia.

INTRODUCTION
Neonatal jaundice is a common disease in neonates. Based on current statistics, 60% of term neonates and 80% of preterm neonates suffer from jaundice during the first week of birth [(1)]. Although the disease usually has a good prognosis; but in cases where its intensity increases it can cause irreversible lesions of the central nervous system (Kernicterus) [(2)].

There are several non-pharmacological and pharmacological modalities for treating hyperbilirubinemia. Phototherapy has emerged as the most widely used non-pharmacological therapy for the treatment and prophylaxis of neonatal unconjugated hyperbilirubinemia, but it has several untoward complications such as deleterious effect to eyes, high temperature, loose stool and bronze baby syndrome [(3)].

There are little pharmacological agents for the treatment of hyperbilirubinemia, including intravenous immunoglobulin (IVIG), D-penicillamine, metalloporphyrin, phenobarbital, zinc sulfate and colofibrate [(4)].

Fibrates have been used as a hypolipidemic drug for several years; it also enhances the bilirubin conjugation and excretion through induction of glucuronyl transferase activity. Most studies focused on the effect of fibrates on hyperbilirubinemia have been done with clofibrate [(5)]. Clofibrate has been used for prophylaxis and treatment of hyperbilirubinemia in neonates at a dose of 100 mg/kg [(6)].

Mohammadzadeh *et al.* [(7)] studied Clofibrate effect on reducing serum bilirubin level of neonates beyond the first week of life. Clofibrate, however, is 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 [(8)].

Although fenofibrate is as the same as clofibrate in terms of the mechanism of action, it has fewer side effects than clofibrate so it is much safer than clofibrate in the pediatric group. However, no side effects of fenofibrate have been observed by a single dose administration in the neonatal period[(6)].

The aim of the present study was to assess Fenofibrate as an adjuvant to phototherapy in term neonates with hyperbilirubinemia.

PATIENTS AND METHODS
Study design and period: Randomized controlled clinical trial. The study was carried out from June 2020 to May 2021.

Setting: Neonatal intensive care unit (NICU) of Zagazig University Children Hospital.
Patients: 74 newborns were selected to participate in this study, on the basis of the following criteria;

Inclusion criteria: Appropriate for gestational age full-term (37 to 41 weeks), TSB levels between 15 to 21mg/kg and weight between 2500 to 3500 gm infants with uncomplicated neonatal hyperbilirubinaemia who are candidate for phototherapy according to American academy guidelines [(9)] were included in the study.

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Exclusion criteria: Preterm infants, small for gestational age, newborns with congenital malformations, conjugated hyperbilirubinemia, newborns who need exchange transfusion, newborns presenting with ABO or Rh incompatibility, G6PD deficiency and newborns with skin abrasions or infections were excluded from our study.

The current research involved only term babies, as the guidelines for premature ones are dissimilar and the preterm infants are more vulnerable to neurotoxicity from hyperbilirubinemia owing to the immature blood brain barrier and other associated-morbidity [(9)].

Randomization: After informed consent obtained, the enrolled infants were randomly assigned to treatment groups (1:1) using computer-generated random table technique with cards in opaque sealed envelopes. Only the nurse assigned to our study opened the envelope to see the key for the group assignment.

Study intervention: Phototherapy alone or with oral fenofibrate on a serum bilirubin level in term newborns hospitalized due to the neonatal hyperbilirubinemia.

The participants in our study were divided in two groups:

Group A (Fenofibrate Group): included 37 full term neonates with neonatal hyperbilirubinemia 22 males and 15 females. All the neonates in this group received phototherapy plus a single oral dose of 10 mg/kg of non-micronized fenofibrate.

Group B (Control Group): included 37 full term neonates with neonatal hyperbilirubinemia, they were 23 males and 14 females. All the neonates in this group received phototherapy only.

Phototherapy:

The decision to start phototherapy was based on American Academy of Pediatrics (AAP) guidelines for term and near-term infants [(9)]**.** The phototherapy system composed of six fluorescent specialized blue light lamps with intensity (=10 4W/cm2 /nm) and spectrum were around 450- 560 nm. Lamps were replaced before the recommended replacement usage time of 1000 hours. The distance between the infant and the phototherapy lamps was approximately 30 cm.

Babies were placed naked under phototherapy except for eye pads and diapers. Rooming-in and breast feeding were encouraged. Mother was permitted to turn-off the lights throughout nursing and diaper change. Neonate's temperature was observed every six hours. Adverse effects like diarrhea, feeding intolerance, and dermal allergy were reported. Phototherapy was stopped when total serum bilirubin levels were below 2 mg/dL from the lowest limit for phototherapy. Conventional phototherapy was supposed to be failed if at any time throughout phototherapy a TSB of more than 20 mg/dL was reported. This baby was treated with intensive phototherapy with a LED [(9)]**.**

All patients underwent:

1) **Detailed history taking.**
2) **Clinical Examination:** A thorough clinical examination was done at the beginning and end of the study. General condition, presence of pallor, ecchymosis, cephalohematoma, plethora, hepatosplenomegaly and evidence of dehydration if present. The infant's vital signs were assessed, anthropometric measures were taken.
3) **Laboratory investigation:**
   Serum total and conjugated bilirubin.
   Serum bilirubin was taken at 12th, 24th, 36th, 48th, 60th hours from start of phototherapy, and then every 12 hours if needed until phototherapy can be stopped according to AAP guidelines.

Outcome: (1) Decline in total serum bilirubin values per unit of time after 12, 24, 36, 48 hours from intervention. (2) Total duration of treatment with phototherapy (hours).

Ethical consent:

An approval of the study was obtained from Zagazig University Academic and Ethical Committee. The guardians signed an informed written consent for acceptance of participation in the study. This work has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for studies involving humans.

Statistical analysis:

The collected data were encoded, processed and analyzed using the SPSS (Statistical Package for Social Sciences) version 23 for Windows® (IBM SPSS Inc, Chicago, IL, USA). Data were tested for normal distribution using the Shapiro Walk test. Qualitative data were represented as frequencies and relative percentages. Chi square test ($\chi 2$) to calculate difference between two or more groups of qualitative variables. Quantitative data were expressed as mean ± SD (Standard deviation). Independent samples t-test was used to compare between two independent groups of normally distributed variables (parametric data). P value ≤ 0.05 was considered significant.

RESULTS

Table 1 shows that the 74 neonates (37 each in fenofibrate and control group) received phototherapy. The fenofibrate (A) group included 22 males (59.46%) and 15 females (40.54%), 23 (62.16%) delivered by cesarean section and 14 (37.84%) by normal vaginal delivery. While, control (B) group comprised 23 males (62.16%) and 14 females (37.84%), 27 (67.57%) delivered by cesarean section and 12 (32.43%) by normal vaginal delivery. There were no statistical differences between the two studied groups regarding age, gender, and mode of delivery, ($p>0.05$) **(Table 1)**.

Table (1): Comparison between Fenofibrate and control groups regarding demographic data.

Items	Fenofibrate Group (n=37)	Control Group (n=37)	t-test	P-value	95% CI	
					Lower	Upper
Age/day						
Mean ± SD	3.64 ± 1.03	3.48 ± 1.19	0.625	0.534	-0.35	0.67
Median (Range)	4 (2-6)	3 (2-6)				
Gender						
Males	22 (59.46%)	23 (62.16%)	X^2= 0.057	0.812	---	----
Females	15 (40.54%)	14 (37.84%)				
Mode of delivery						
NVD	14 (37.84%)	12 (32.43%)	X^2= 0.000	1.00	----	----
CS	23 (62.16%)	27 (67.57%)				

NVD: normal vaginal delivery, CS: caesarean section, t: independent t-test, X^2: Chi-square test, CI: confidence intervals

There was a statistically significant difference between the studied groups regarding duration of phototherapy (p=0.015). Mean duration of phototherapy was significantly shorter among Fenofibrate group (39.56 ± 4.12 hours), than control group (47.67 ± 11.80 hours) **(Table 2)**.

Table (2): Duration of phototherapy among fenofibrate and control groups.

Time in hours	Fenofibrate Group (n=37)		Control Group (n=37)		X^2	P-value
	No.	Hours No.	No.	Hours No.		
12 hours	0 (0.0%)	0	0 (0.0%)	0	NA	----
24 hours	8 (21.62%)	192	5 (13.51%)	120	1.37	0.085
36 hours	12 (32.43%)	432	6 (16.21%)	216	5.11	0.012*
48 hours	15 (40.54%)	720	16 (43.24%)	768	0.67	0.420
60 hours	2 (5.4%)	120	5 (13.51%)	300	7.15	0.002*
72 hours	0 (0.0%)	0	5 (13.51%)	360	20.88	0.001*
Total	**37 (100%)**	**1464**	**37 (100%)**	**1764**	4.09	0.031*
Mean ± SD **	**39.56 ± 4.12**		**47.67 ± 11.80**		3.71	**0.015***

X^2: Chi-square test. *Significant. **Student's t-test.

The difference in mean total serum bilirubin levels in neonates between fenofibrate and control groups at the time of admission was statistically non-significant (P-value 0.259). However, the fenofibrate group had significantly lower mean total bilirubin values after 12, 24, 36, and 48 hours of phototherapy as compared to control group **(Table 3)**.

Table (3): Mean total bilirubin level during treatment among fenofibrate and control groups.

Bilirubin level (mg/dl)	Fenofibrate Group (n=37)	Control Group (n=37)	t-test	P-value	95%CI	
					Lower	Upper
At admission Mean ± SD	19.07 ± 0.87	19.07 ± 0.96	1.13	0.259	-13.27	4.02
At 12 hours Mean ± SD	17.70 ± 0.88	18.01 ± 0.77	2.67	0.009*	2.01	29.17
At 24 hours Mean ± SD	15.79 ± 1.44	16.42 ± 1.14	2.954	0.004*	-2.84	0.55
At 36 hours Mean ± SD	13.39 ± 0.88	14.5 ± 1.45	3.463	0.001*	-3.01	0.80
At 48 hours Mean ± SD	10.05 ± 1.58	12.08 ± 2.44	3.310	0.002*	-3.38	0.681

GA: gestational age, t: independent t test , CI: confidence intervals

Mean differences (%) of bilirubin level at 12, 24, 36, and 48 hours of phototherapy was high significantly different compared at admission among fenofibrate group (P-value <0.001) **(Table 4)**.

Table (4): Mean differences (%) of bilirubin level at 12, 24, 36, and 48 hours compared at admission among fenofibrate group.

Variable	Fenofibrate group				
Time in hours	Mean ± SD	t-test	*P-value*	95%CI	
				Lower	Upper
At admission					
At 12 hours	2.17 ± 0. 41	12.119	<0.001*	1.81159	2.53976
At 24 hours	4.71 ± 0.66	17.264	<0.001*	4.16216	5.27027
At 36 hours	6.88 ± 1.64	22.503	<0.001*	6.25624	7.50928
At 48 hours	9.02 ± 1.31	28.301	<0.001*	8.34763	9.69943

Mean differences (%) of bilirubin level at 12, 24, 36, and 48 hours of phototherapy was high significantly different compared at admission among control group (P<0.001) **(Table 5)**.

Table (5): Mean differences (%) of bilirubin level at 12, 24, 36, and 48 hours compared at admission among control group.

Variable	Control group				
Time in hours	Mean ± SD	t-test	*P-value*	95%CI	
				Lower	Upper
At admission					
At 12 hours	1.38 ± 0.31	10.47	<0.001*	1.11435	1.64881
At 24 hours	3.35 ± 0.34	15.40	<0.001*	2.90930	3.79070
At 36 hours	5.12 ± 1.52	19.36	<0.001*	4.58782	5.66672
At 48 hours	6.98 ± 1.87	19.30	<0.001*	6.23791	7.72505

DISCUSSION

In our study, the studied groups were comparable regarding the basic clinical and laboratory data. Of note, there were no significant statistical difference between the studied groups regarding the clinical data as age, sex, weight, gestational age and other risk factors. This is similar to that reported by the study of **Chaudhary *et al.*** [10].

Comparison between total serum bilirubin levels during treatment and on discharge showed significant improvement of bilirubin levels in the two studied groups (P=0.0001). In addition, comparison between bilirubin levels in the studied groups revealed significantly lower bilirubin levels in fenofibrate treated group when compared with the control group at 36 and 48 hours after admission and on discharge

Our results are in accordance with the study of **Kumar *et al.*** [11] which was conducted on 40 normal term newborns with uncomplicated jaundice. Patients were divided into two groups: one group received only phototherapy and the other group received phototherapy plus fenofibrate. Average levels for total bilirubin in fenofibrate plus phototherapy group at 12, 24, 36, and 48 hours following beginning of therapy were markedly reduced than those treated with phototherapy alone.

The results of our study confirms the findings of study of **Awad *et al.*** [12] who evaluate the efficacy of fenofibrate in treatment of pathological unconjugated neonatal hyperbilirubinemia. The study recruited 90 patients randomly divided into 3 equal groups. Patients were assigned to receive either phototherapy with single oral dose of fenofibrate suspension (10 mg/kg) on day 1 of phototherapy (group 1), phototherapy and two doses of oral fenofibrate suspension 10 mg/kg in the 1st and 2nd days of phototherapy (group 2), or phototherapy alone (group 3). They reported a statistically significant reduction of bilirubin levels at 36, 48, and 72 h from the start of intervention in comparison to phototherapy alone. They also added that, there is no statistically significant difference between the group who received single dose of fenofibrate and those who received double dose as regards the decline of total serum bilirubin on 12, 24, 36, 48, or 72 h from the start of intervention.

Our results are also in agreement with the study of **Chaudhary *et al.*** [10] who evaluated the role of oral fenofibrate for lowering neonatal hyperbilirubinemia as compared to placebo. In their double-blind, randomized, placebo-controlled trial, 50 neonates were assigned randomly to receive either single dose of oral fenofibrate at 10 mg/kg/dose on day 1 of admission and distilled water on the following next day or a single dose of oral glucose solution on day 1 and distilled water on the following next day. Results showed that average levels for total bilirubin in fenofibrate group at 36 and 48.h following

beginning of therapy were markedly reduced in the study group than those in the control group ($p<0.00001$).

In conclusion, Fenofibrate as an adjuvant to phototherapy in neonates with hyperbilirubinemia is associated with significant reduction of serum bilirubin levels.

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