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Evaluation of the Effect of Oral Clofibrate Intake on Neonatal Total Serum Bilirubin: a Randomized Clinical Trial

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ABSTRACT

***Background*:** Clofibrate is a pharmacological agent, which affects the lipid metabolism. This compound could be involved in bilirubin accumulation and excretion process. Therefore, this study aimed to evaluate the effect of oral clofibrate intake on total serum bilirubin (TSB) of neonates hospitalized at Khatam Hospital.

***Methods*:** This clinical trial was conducted on 73 neonates with hyperbilirubinemia. Samples were divided into clofibrate (n=41) and control (n=32) groups. In the Clofibrate group, samples were given a single oral dose of 100 mg/kg clofibrate, whereas the control group received distilled water in an equal amount and color as placebo. Birth weight, type of delivery, gender, age and primary TSB level were recorded prior to the intervention and TSB was measured 24, 48 and 72 hours after the intervention.

***Results*:** In this study, no significant difference was observed between the groups on the first and third day of intervention in terms of mean TSB in neonates. However, a significant reduction was found on the second day in mean TSB of neonates, who received clofibrate (P=0.04).

Conclusion: According to the results of this study, application of clofibrate was associated with faster alleviation of mean TSB and shorter duration of hospital stay without major side effects. Therefore, it is recommended that clofibrate be only used for clinical management of neonatal hyperbilirubinemia.

Keywords: Bilirubin, Clofibrate, Hyperbilirubinemia, Neonate

Introduction

Hyperbilirubinemia is one of the most common problems during the neonatal period (1). This disease leads to transitional morbidity in newborns and is a leading cause of hospitalization in the first week of life worldwide (2). Management of neonatal hyperbilirubinemia is one of the most challenging topics among pediatricians due to probable neurological complications associated with bilirubin toxicity (3, 4). Incidence of severe neonatal hyperbilirubinemia is more frequent among Asian newborns, compared to white infants (5). In total, 5–10% of all newborns require intervention to manage hyperbilirubinemia (6). Causative factors for this disease are overproduction of bilirubin, decrease in liver absorption and increase in bilirubin enterohepatic cycle or a combination of all of them, as well as some procedures, including phototherapy, exchange transfusion and drug administration (2, 6, 7).

Prevention of encephalopathy in newborns with hyperbilirubinemia can be achieved through early management of the affected neonates (8). One of the previous studies have reported wide variation in neonatal hyperbilirubinemia management (9). Recognition of enzymatic pathway leads to production or elimination of bilirubin through using medications, such as D-penicillamine, phenobarbital and clofibrate. These pharmacologic agents are associated with numerous/certain beneficial effects (10, 11).

Clofibrate is known as a peroxisome proliferator-activated receptor (PPAR), affecting the lipid metabolism (12, 13). This compound could be involved in bilirubin accumulation and excretion process (14, 15). In a double-blind controlled trial, a significant reduction was observed in neonatal TSB in the intervention group 16 hours after using clofibrate, compared to the newborns in the control group (16). Moreover, treatment with clofibrate reduced the duration of phototherapy and jaundice (16, 17). With this background in mind, this study aimed to evaluate the therapeutic effect of oral

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clofibrate intake on neonatal TSB.

Methods

This double-blind randomized clinical trial was conducted on 73 neonates with hyperbilirubinemia, referred to Ayatoalah Khatami Hospital affiliated to Shahid Sadoughi University of medical sciences, Yazd, Iran during March 2009-March 2011. Randomization was performed by assigning random numbers from a random number table. Inclusion criteria were health of infants regardless of their jaundice, breastfeeding, delivery at 38th and 41th gestational week after an uncomplicated pregnancy, use of a single balance to weigh all of the samples (ABE-M10811, Germany), TSB level between 15 and 25 mg/dl, body weight between 2500gr-4000gr and age between 72 h-264 h. Exclusion criteria were existence of hemolytic anemia (reticulocyte count >5%), Rh or ABO incompatibility, positive glucose-6-phosphate dehydrogenase (G6PD) test, positive direct Coombs test, conjugated serum bilirubin >1.5 mg/dl or 15% of TSB, venous hematocrit (HCT) >65%, dehydration (>7% or need for IV fluid administration), infection (congenital or acqui-red), sepsis suspicion (general health deter-ioration and need for blood transfusion), suspicion of porphyria, preterm and postterm neonates (gestational age: 38-42 weeks) and a history of phenobarbital intake either by mother or infant.

Samples were randomly divided into two groups of clofibrate (n=41) and control (n=32) using the random allocation software. Both groups received phototherapy and each phototherapy unit used four special blue light (Philips Co., Germany), adjusted at a height to 25cm above the cots. Samples in the clofibrate group received a single dose of 100 mg/kg (normal saline dissolved) clofibrate orally just before the initiation of phototherapy, whereas the control group received distilled water (same color and volume) as placebo.

In this study, laboratory tests (e.g., reticulocyte count and TSB level) were performed and TSB was measured by the colorimetric method. In addition, birth weight, type of delivery (i.e., vaginal and cesarean section), gender, age and primary TSB level were recorded prior to the intervention and TSB was measured 24,48 ,and 72 hours after the intervention. Exchange blood transfusion was used for neonates with TBS>25 mg/dl, for which phototherapy management was failed. Infants were examined during the study period at their outpatient visits for evaluation of their jaundice and any side effects of medication.

This research project was approved by the ethics committee of Shahid Sadoughi University of Medical Sciences, Yazd, Iran and written informed consents were obtained from all the parents prior to the study. Data analysis was performed in SPSS version 16 using independent-samples t-test (to evaluate quantitative variables of the study groups), as well as Chi-square and Fisher's exact test (to assess the categorical variables of study groups). Moreover, P-value less than 0.05 were considered statistically significant.

Results

This study was performed on 41 (20 male [48.78%] and 21 female [51.22%]) samples, who received clofibrate and 32 (16 boys [50%] and 16 girls [50%]) cases, receiving distilled water. Both groups were homogenous regarding mean age, birth weight, reticulocyte count and primary bilirubin (Table 1). In addition, no significant difference was observed between the clofibrate and control groups in terms of mean TSB one day after the intervention. However, mean TSB was significantly decreased in the clofibrate group on the second day, compared to the control group (P=0.04). On the third day of intervention, no significant difference was found in mean TSB between the study groups (P>0.05). In addition, no significant difference was portrayed in the mean TSB between the samples with different types of delivery (normal vaginal delivery and cesarean section) at different times (24, 48 and 72 hours) after the intervention (P>0.05) (Table 2).

Table 1. Demographics of the participants

	Clofibrate group	Control group	P-value
Age (h)	153.95±67.88	140.25±51.41	0.34
Weight (gr)	3490±420	2990±340	0.35
Primary bilirubin	17.38±2.46	15.61±2.83	0.06
Reticulocyte count	133±63	115±78	0.20

Table 2. Total serum bilirubin level of the clofibrate and control groups during the intervention

	Clofibrate group	Control group	P-value
First day	13.19±2.34	12.92±1.84	0.39
Second day	10.98±1.70	11.80±1.33	0.04
Third day	10.44±1.68	11.26±2.09	0.38

Discussion

According to the results of the current research, no significant difference was observed between the samples of study groups on the first day of management with clofibrate in terms of mean TSB level in neonates. Nevertheless, a significant reduction was observed in mean TSB of the samples of the clofibrate group on the second day of management, compared to the control group. On the third day, no significant difference was observed between the groups in this regard. Therefore, application of clofibrate led to a significant reduction in mean TSB in neonates only on the second day of intervention. Consistent with our results, Zahedpasha et al. reported that a single dose of clofibrate (100 mg/kg) in premature infants with considerable jaundice (TSB >15 mg/dl) significantly decreased the indirect level of bilirubin on the second day of therapy and immediately after discharge from hospital (18).

Caballero-Noguez et al. conducted a study to compare therapeutic effect of treatment with phenobarbital and clofibrate, along with the use of placebo, on the management of neonatal hyperbilirubinemia. According to the results of the aforementioned study, both of these medications significantly reduced mean TSB level on the second day after the initiation of management (17). Mohammadzadeh et al. reported that a single dose of clofibrate with phototherapy led to a significant reduction in mean TSB at 12, 24 and 48 hours after the initiation of management, compared to only phototherapy (19). Moreover, Lindenbaum demonstrated that a single dose of oral clofibrate was associated with a significant decrease in the intensity of hyperbilirubinemia after 48 hours (16).

In one controlled trial, clofibrate was used as glucuronosyltransferase, causing a significant reduction in mean TSB of neonates of the clofibrate group, compared to the placebo group. In the present study, mean TSB was significantly reduced in neonates, who received a single oral dose of clofibrate after 16 hours of therapy, compared to the bilirubin level in 46 infants of the control group, who were just given corn oil (16) . All of the results of the mentioned studies are in congruence with our findings, which is indicative of the significant impact of clofibrate on decreased mean TSB in neonates.

No complications caused by clofibrate was observed in the studied samples after follow-ups. Consistent with our findings, several previous studies have revealed that consumption of 50-100 mg/kg of clofibrate is associated with no side effects (19, 20). However, some complications (e.g., nausea, gastrointestinal problems and loose stool) were reported in a study, which might be due to antilipidemic activities of clofibrate (21). In another study, muscle cramping, fatigue, pruritus and alopecia were pointed out as rare side effects of this compound (22). Clofibrate-induced conjugation and excretion of bilirubin lead to an increase of hepatic bilirubin clearance within six hours of administration (23).

In conclusion, clofibrate can significantly decrease mean TSB in neonates, especially on the second day. Therefore, it is recommended that clofibrate be used only for clinical management of neonatal hyperbilirubinemia due to faster reduction of mean TSB and shorter hospital stay without any major side effects.

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Conflicts of interests

The authors declare no conflicts of interest.

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