

Comparison of the efficacy of Clofibrate with Phenobarbital in decreasing neonatal hyperbilirubinemia

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ABSTRACT

Background:

Hyperbilirubinemia is a common problem in newborn infants. It can progress to kernicterus in severe forms, unless an intervention is initiated. The objective of this study was to compare the efficacy of Clofibrate with Phenobarbital in full-term neonates with nonhemolytic jaundice.

Methods:

this double blind clinical trial study was performed on 60 neonate who were divided randomly in two groups of full-term jaundiced neonates: the clofibrate-treated group (n = 30) and the Phenobarbital group (n = 30). Infants in the clofibrate group received a single oral dose of 100 mg.kg clofibrate while the neonates in the Phenobarbital group received a single oral dose of 5 mg.kg Phenobarbital; both groups received phototherapy. Total serum and direct bilirubin levels were measured at the beginning, 12 and 24 hours after the initiation of treatment.

Results:

The mean \pm SD total serum bilirubin level of the Phenobarbital group and clofibrate groups at enrollment was 17.84 ± 1.017 and 18.04 ± 0.852 mg.dL, respectively. The mean \pm SD total serum bilirubin in Phenobarbital group and clofibrate groups after 24 hours was 11.11 ± 1.273 and 12.55 ± 1.008 mg.dL, respectively ($P = 0.000$). After 72 hours of intervention, 25 (83%) neonates of the Phenobarbital group and 23 (76%) of the clofibrate group were discharged with a total serum bilirubin of <10 mg.dL ($P = 0.000$). No side-effect was observed on serial examination during hospitalization, and on the first and seventh day after discharge.

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Conclusion:

Phenobarbital in the compared with clofibrate results in a faster decline in total serum bilirubin, shorter duration of hospitalization and had no side effects in jaundiced full-term neonates.

Keywords:

clofibrate, Phenobarbital, hyperbillirubinemia, neonatal jaundice

Introduction

Hyperbilirubinemia is the most common medical problem during neonatal period; about sixty percent of full term neonates develop non-hemolytic hyperbilirubinemia. About six to ten percent of newborn infants suffer from severe hyperbilirubinemia, which must be treated (amount of serum bilirubin is above the 90% percentile for age) (2, 3). Moreover, hyperbilirubinemia is the most common cause of re-hospitalization during the neonatal period (4, 5). On the other hand, one of the serious complications of severe indirect hyperbilirubinemia is its toxic effect on central nervous system (CNS), which causes mental retardation and physical disability (6-8). The therapeutic goal of neonatal hyperbilirubinemia is prevention of CNS toxicity of indirect bilirubin (6, 9). Phototherapy and exchange transfusion are used as common methods for treatment of indirect hyperbilirubinemia. However exchange transfusion and phototherapy are costly for families. In addition in these methods, the infant is limited into the incubator, so the relationship between the mother and infant is interrupted. Infection, dehydration and neonatal death are some of disadvantages of exchange transfusion (10, 11). Moreover, several studies have shown that when total serum bilirubin level passes more than 20 mg.dl; the efficacy of phototherapy will be reduced about 10-17%

(12). Pharmaceutical agents that have been suggested for this purpose are Metalopurphyrins, intravenous immunoglobulin and Phenobarbital (13-16). Clofibrate is a proxisome proliferator-activated receptors (PPAR) agent, so it influences on lipid metabolism and reduces the serum level of cholesterol and triglycerides. This medication has been used for reducing of serum lipids in adults for years (17, 18). It can also increase the amount of conjugation and excretion of bilirubin in the liver (19) and therefore has been suggested for treatment of hyperbilirubinemia (20). Side effects such as nausea, vomiting, gastrointestinal disturbances and watery stool have been reported duo to consumption of this drug. The use of a single dose of 100 mg per kg of body weight of Clofibrate for infants that suffering hyperbilirubinemia has no side effect. Phenobarbital is known as an anticonvulsant drug but it has some another applications. It is the drug of choice for treatment of autosomal dominant Crigler–Najjar syndrome (type II). It functions as an enzyme-inducer for glucuronosyl transferase and therefore increases its efficacy. In addition, Phenobarbital reduces the level of serum indirect bilirubin by increasing of its excretion from the liver (21). Common side effects of this drug are nausea, vomiting, skin eruptions and drowsiness. Clofibrate and Phenobarbital both can be used with some safety in

neonates. On the other hand, there is confusion about an effective drug for treatment of neonatal hyperbilirubinemia. In this study, we have compared the efficacy of Phenobarbital with Clofibrate in treatment of neonatal hyperbilirubinemia.

Materials and Methods

This study is a double blind randomized clinical trial that was carried out in neonatal ward of Sabalan hospital in Ardabil in 1388. Full term neonates (gestational age between 38-42 weeks) with non-hemolytic hyperbilirubinemia (a total serum bilirubin of 16-25 mg.dl) without any infection or other abnormalities were included in this study. Exclusion criteria were neonates with sepsis, body weight more than 4 or less than 2 kg, cardiopulmonary problems, extensive scalp hematoma, G6PD deficiency, hemolytic hyperbilirubinemia, direct bilirubin more than 2 mg.dl (or more than 20% of total serum bilirubin), total serum bilirubin less than 16 or more than 25 mg.dl. Neonates that fulfilled inclusion criteria were divided into two groups. Both groups were inclusive of 30 neonates: the first group were treated with Clofibrate plus phototherapy and the second group with Phenobarbital plus phototherapy. Division of samples in these two groups was accidental. In the first group, Clofibrate was prescribed as pearl tablet with a dose of 100 mg per kilogram of body weight. In the second group, Phenobarbital was prescribed as tablet with a dose of 5 mg per kilogram of body weight. Blood group and Rh of both mother and neonate, direct coombs test, peripheral blood smear and G6PD were studied in both groups. The amount of total serum bilirubin and hematocrit of patients were documented on

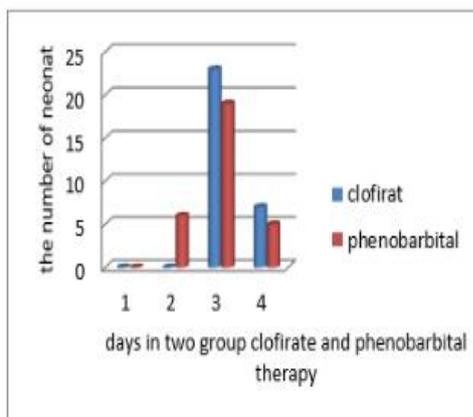
admission and again 12 and 24 hours thereafter. Measuring of serum bilirubin had been continued till the bilirubin level dropped back to 10 mg.dl. The laboratory personnel's had been blinded regarding the samples. The patients were monitored for side effects of the drugs including diarrhea, skin rashes and dehydration during hospitalization and for 72 hours after that. Collected data were analyzed by SPSS software. In both groups, changes in total serum bilirubin level were evaluated on admission and 12 and 24 hours after that, separately. The differences were considered significant if the P-value was less than 0.05.

Results

Sixty neonates were included in this study that females comprised a slightly higher percentage (56.6% versus 43.3 %). Sex distribution in Clofibrate group was 16 females and 14 males and in Phenobarbital group were 18 females and 12 males. The age ranges of neonates in the Phenobarbital group were 3 days and 19 days, respectively with the mean of age of 6.03 ± 2.08 days. The age range of infants in Clofibrate group was 3 days and 18 days, respectively. The mean of age of patients in this group was 2.09 ± 6.01 . Statistically, the mean age of two groups had no significant difference. In both groups, 29 patients were RH+ and one patient was RH- which showed no significant statistical differences between two groups. The range of body weight of patients in both groups was between 2500 and 4000 grams. Therefore there was no significant difference between the mean body weights of two groups.

The level of total serum bilirubin during the first hour of hospitalization was

18.04±0.852 mg.dl in Clofibrate group and 17.84±1.17mg.dl in Phenobarbital. The total serum bilirubin level 12 hours after onset of treatment in Clofibrate group was 14.51±1.015 mg.dl and 13.44±1.037mg.dl (P-value<0.05) in Phenobarbital group. The decreasing rate of bilirubin in the first 24 hours of admission was 0.28 mg.dl.h in Clofibrate group and 0.22 mg.dl.h in Phenobarbital group. It reveals that bilirubin decreases with a greater slope in first 24 hour of admission in Clofibrate group compared to Phenobarbital group. In regard to hospitalization days, 20% of infants in the phenobarbital group were hospitalized for two days under phototherapy while no infant in the Clofibrate group was hospitalized less than 72 hours. In the phenobarbital group, 63.3% of infants confined to bed for 72 hours and less under phototherapy; 16.7% confined to bed for 94 hours and less under phototherapy. Meanwhile, in the Clofibrate group 76.7 % of infants were confined for 72 hours and 23.3% of them confined for 96 hours as well as under phototherapy. In average, the hospitalization time in the phenobarbital group was 2.9 days and 3.2 days in the Clofibrate group (graph 1).



Discussion and conclusion

This study investigated the effect of two different remedies for the non-hemolytic hyperbilirubemia in full-term infants. Bilirubin was examined in the routine hours of zero, 12 and 24 of phototherapy. The addition of Phenobarbital to the remedy in hours 12 and 24 led to a significant difference (P= 0.001) in decreasing bilirubin for the Phenobarbital group (13.44±1.037) compared to the Clofibrate group (18.04±0.852). It seemed that addition of Phenobarbital to phototherapy had a better effect on treatment of hyperbilirubemia. This result is consistent with Kumar. *Et al* on preventing effect of phenobarbital on infants under 1500 grams (22). In another study, 80 infants with non-hemolytic hyperbilirubinemia were divided to two groups of 40 in which the Phenobarbital group received 3 milligrams per body weight and the other group received only phototherapy. On the third day, significant changes were observed in the Phenobarbital group compared to the phototherapy group while duration of hospitalization was the same (23). In consistence to our study, the length of hospitalization in the phenobarbital recipients compared to the Clofibrate group was significantly reduced. Caballero-Noguez *et al* studied 30 infants affected with indirect hemolytic hyperbilirubemia in a randomized clinical trial at their first week of life. These infants were randomly divided into three groups. The first group received phenobarbital, the second group received Clofibrate and the third group received placebo. All the groups also received phototherapy. Their total and indirect bilirubin was measured at the start of the trial, 24 and 72 hours later. The amount of bilirubin in the Phenobarbital

and the Clofibrate was significantly reduced at 48 and 72 hours compared to the placebo group (24). In a study by Zahedpasha et al done on two groups of thirty full-term infants affected with jaundice, the infants who received 100 milligrams per body weight of single dose of Clofibrate had their bilirubin serum level reduced after 48 hours. Seventy-two hours later, 83% of Clofibrate group and 53% of the control group were released with bilirubin level of less than 10 mg.dl (1). In a cohort study done by Miloni and his colleagues on 66 infants with the G6PD deficiency showed that 7 milligrams per infant body weight of phenobarbital reduces the need for blood transfusion from 33% down to 6% (25). Our study differs from other studies mentioned for number of reasons. First, a lower dose of Phenobarbital was prescribed to avoid some side effects such as drowsiness and mother-child communication interruption (26). Secondly, in our study the effect of two regimens in reducing the serum level of hyperbilirubemia of non-hemolytic full-term infants was compared. In contrast, most previous studies compared the effectiveness of these medications and phototherapy or placebo (1, 22, 24). In the study of Moslehi *et al*, they compared the effects of different small doses of Clofibrate (25 milligrams per kilogram body weight). They resulted that Clofibrate is better in increasing production of glucuronosyl transferase and causes the 100% increase of bilirubin clearance in the liver over 6 hours (27). This study is in discrepancy with our study regarding the time for onset of bilirubin reduction. In another study, Zahedpasha *et al* presented that Clofibrate like the previous studies caused the reduction of bilirubin in infants. The only difference of their study was the

starting time of the administration to the effect. One of the possible reasons could be the different rate of the medication metabolism in human body as well as different background ethnicities (1). In accordance to the previous studies, we documented the reducing effects of Clofibrate and Phenobarbital in the blood bilirubin of infants with hyperbilirubemia. In conclusion, phenobarbital with phototherapy causes higher and faster reduction of bilirubin in 24 hours that continues up to 48 hours compared to Clofibrate with phototherapy. It also causes lesser hospital stay.

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