The Effect of Clofibrate on Hyperbilirubinemia of Term Neonates

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Abstract- Clofibrate is a glucuronosyl transferase inducer that has been proposed to increase the elimination of bilirubin in neonates with hyperbilirubinemia. This study was conducted to determine the therapeutic effect of clofibrate in term neonates with non-hemolytic jaundice. This study was conducted on 52 newborns with pathologic unconjugated jaundice in Qazvin children hospital. Newborns divided randomly in two groups. Case group treated with clofibrate and intensive phototherapy, while control group treated only with intensive phototherapy. Serum bilirubin level was measured before and 6, 12, 24 and 48 hours after treatment. Results were compared and analyzed. The mean serum level of bilirubin before treatment in the case and control groups were 20.78±2.38 and 20.52±2.44 mg/dl, respectively (*P*=0.69). The mean serum level of bilirubin in 6, 12, 24 and 48 hours after treatment in the case group were 18.20±2.20, 14.70±2.06, 10.72±2.40 and 8.90±0.83 mg/dl , respectively. These values in control group were 18.26±2.42, 15.36±2.59, 12.29±2.28 and 10.23±1.50 mg/dl, respectively. There was significant difference between two groups regarding mean serum level of bilirubin 24 hours (*P*=0.019) and 48 hours after treatment (*P*=0.005). In conclusion, clofibrate was effective in reducing neonatal jaundice and its effect appeared 24 hours after treatment.

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Keywords: Clofibrate; Hyperbilirubinemia; Neonate

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 (12,15,22). Although the disease usually has a good prognosis, but in cases where its intensity increases, can cause irreversible lesions of the central nervous system (Kernicterus) (2,13,19). Different method of therapy such as phototherapy and blood exchange are used to treat jaundice and prevent kernicterus (12,15,22). Phototherapy is the most common therapeutic method. Although today the use of photo blanket at home have made outpatient treatment of neonates possible, still many neonates have to be hospitalized receiving phototherapy. This method of treatment is followed by hospitalization cost, risk of nosocomial infections and losing social activity of parents (12,22). Exchange transfusion is recommended when phototherapy fail to reduce unconjugated bilirubin (12,15,22). Mortality of exchange transfusion, even If done by experts physician is about 0.3 per thousand. In addition this procedure may results in many early and late complications (15). Many drugs such as Phenobarbital, intravenous immunoglobulin (IVIG), D-penicillamine, metalloporphyrins and Sn-mesoporphyrin have been used in treatment of pathologic unconjugated hyperbilirubinemia (1,5,16). The study of Mohammad Zadeh and colleagues showed that clofibrate is effective in the treatment of unconjugated hyperbilirubinemia (14). The present study was conducted to determine the efficacy of clofibrate in the treatment of pathologic unconjugated hyperbilirubinemia of neonates in Qazvin children hospital (Qazvin province, Iran).

Materials and Methods

This single blind clinical trial study was performed on 52 neonates with pathologic unconjugated hyperbilirubinemia in Qazvin children's hospital, in 2007. This hospital is affiliated to Qazvin University of Medical Sciences. Qazvin is a historical city 140 kilometers away from Tehran (Iran). Inclusion criteria in case and control groups included: 1) Term neonate (gestational age between 38-41 weeks). 2) Weight between 2500-4000 g. 3) Age between 2-7 days. 4)

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Serum total bilirubin level between 17-26 mg/dl with priority of unconjugated bilirubin. 5) Level of direct bilirubin less than 2 mg/dl or less than 15% of total serum bilirubin. 6) Exclusive breast feeding.

Premature neonates and neonates with diseases such as sepsis, meningitis, congenital anomalies, dehydration, hemolytic diseases and conjugated hyperbilirubinemia were excluded. Hemolytic diseases included RH and blood incompatibility and G6PD deficiency. Neonates were randomly divided in case and control groups. Samples were selected in sequence. Placing in case or control groups was based on randomly numbers table. Case group were treated by clofibrate and intense phototherapy, while control group treated only by intense phototherapy. Clofibrate was administered as a single dose of 100 mg/kg as pearl. Neonates who vomited after taking the drug were excluded. Clofibrate was made by Zahravi Company (Tehran, Iran) with batch number: 196 and registered number: 1228098598. Intense phototherapy was done by blue light with 8 lamped set Tusan model (made in Iran). The lamps were with brand name of Philips (20 watt lamp and 2500 hours lifetime). The distance of lamps from patients was 25cm approximately. Phototherapy was carried out in compliance with all standard conditions. Both groups were matched in terms of gender, age, weight and initial bilirubin (on admission). Bilirubin levels in both groups were measured before and after treatment. In addition it was also measured 6, 12, 24 and 48 hours after starting phototherapy. Bilirubin was measured by spectrometry method with autoanalyser, Technicon RA 1000 model (Technicon Instrument Corporation, Tarry town, New York, USA). Phototherapy was stopped when serum bilirubin level met lower than 10mg/dl. Besides serum bilirubin level, hemoglobin, hematocrit, reticulocyte, G6PD, direct coombs test and peripheral blood smear were tested. In addition, mother and neonate blood groups were checked .The results of two groups were compared and analyzed by Chi-square and students t test using SPSS software. *P*-value less than 0.05 was considered significant.

Ethics

All parents were given clear explanations regarding the methodology of the research and also lack of any harmful effect due to the dose of clofibrate administered. The present study was ethically confirmed by ethical committee of Qazvin University of Medical Sciences with code: 154. The neonates were included in the study only if their parents were satisfied and signed the consent form.

Results

Of 52 neonates, 26 (11 girls and 15 boys) treated with clofibrate and intense phototherapy (case group) and 26 (11 girls and 15 boys) treated with only intense phototherapy (control group). There was no significant difference between two groups regarding gender, age and weight. In addition, serum level of conjugated and total bilirubin (on admission) also showed no significant difference (Table 1) ($P>0.05$).

The mean serum level of bilirubin 6, 12, 24 and 48 hours after treatment in case group were 18.20±2.20, 14.70±2.06, 10.72±2.40 and 8.90±0.83 mg/dl, respectively. These values in control group were 18.26±2.42, 15.36±2.59, 12.29±2.28 and 10.23 1.50 mg/dl, respectively. There was significant difference between two groups regarding mean serum level of bilirubin 24 hours ($P=0.019$) and 48 hours after treatment ($P=0.005$) (Table 2, Figure 1).

The rates of bilirubin decline in case and control groups were 0.247 and 0.215 mg/dl per hour, respectively. Serum bilirubin decline rate was higher in case group than the control group (12 to 48 hours after starting treatment) (Figure 1). None of neonates in case group required phototherapy more than 48 hours. On the other hand, phototherapy continued for more than 48 hours in eight neonates of the control group.

Table 1. Comparison of variables in case and control groups.

Variables	Case Group (Mean ± SD)	Control Group (Mean ± SD)	*P*
Sex	11female, 15 male	11female, 15 male	1
Age (day)	3.31±1.1	3.19±0.98	0.56
Weight (g)	3057±301	3105±337	0.57
TSB (on admission) mg/dl	20.78±2.38	20.52±2.44	0.69
SCB (on admission) mg/dl	0.19±0.769	0.723±0.21	0.411

TBS= Total serum bilirubin

SBC= Serum conjugated bilirubin

Table 2. Comparison of serum bilirubin level in case and control groups.

Hour	Group	N	Serum bilirubin level (Mean± SD)	*P*	95% confidence interval	
					Lower	Upper
0	Case	26	20.788±2.3852	0.69	-1.0803	1.6111
	Control	26	20.523±2.4458		-1.0803	1.6111
6	Case	26	18.200±2.2062	0.91	-1.3578	1.2271
	Control	26	18.265±20.4287		-1.3581	1.2274
12	Case	26	14.700±2.0684	0.31	-1.9675	0.6444
	Control	26	15.362±2.5909		-1.9691	0.6460
24	Case	26	10.723±2.4052	0.019	-2.8805	-0.2657
	Control	26	12.296±2.2871		-2.8806	-0.2656
48	Case	14	8.907±0.8334	0.005	-2.2258	-0.4266
	Control	21	10.233±1.5028		-2.1335	-0.5189

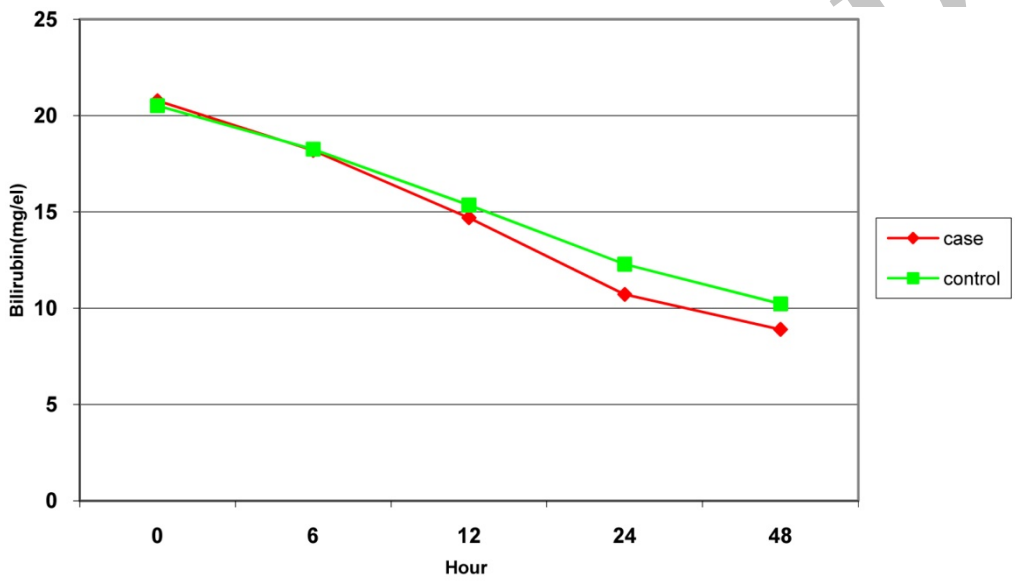

Figure 1. Comparison of bilirubin levels in case and control groups.

Discussion

Hyperbilirubinemia is a common disease of neonates. The disease is divided into two types, unconjugated and conjugated. Unconjugated type is more common and the excessive increase may lead to irreversible brain damage (kernicterus) (12,15,22).

Phototherapy and blood exchange have been used for many years for treatment and prevention of complications. Although these two methods are very effective, each has different complications (12,15,22). In recent years several studies have been carried out to evaluate the effectiveness of pharmacologic agents such as clofibrate in the treatment of neonatal hyperbilirobinemia (1,4,5,14,16). The purpose of these studies is to decrease exchange transfusion, hospital stay and health care costs. Studies have shown that a dose of 100 mg clofibrate per kg of body weight as single dose combined with phototherapy decreases serum bilirubin faster than phototherapy alone (1,14,16). In another study, clofibrate at a single dose of 50 mg per kg of body weight showed the same effect (18). In present study, clofibrate showed effect 24 hours after treatment. While in other studies effectiveness has been reported 12 and 16 hours after administration of clofibrate (8,14). This difference can depend on factors such as age of the newborns and fullness of stomach. Clofibrate activates peroxisome proliferator-activated receptors (PPARs) and regulates plasma lipid by lowering very-low density lipoproteins. The drug is absorbed from the

gastrointestinal tract and rapidly hydrolyzed to active metabolite (clofibric acid). This active metabolite ultimately excreted through urine as conjugated glucuronide (3,20). Clofibrate, like sodium phenobarbital and Chinese herbal remedies is a strong stimulator of glucuronyltransferase. This process results in increased conjugation of bilirubin and ultimately excretion of bilirubin. The drug increases liver bilirubin clearance rate to 100% within 6 hours. Clofibrate does not cause drowsiness and respiratory depression in comparison with sodium phenobarbital. In addition, it results liver bilirubin clearance (3,5,10-12,20). Clofibrate does not increase the chance of neurotoxicity comparing Chinese herbal remedies (5). Although clofibrate intake in adults may cause complications such as nausea, vomiting, diarrhea, alopecia and itching, no complications have been reported following a single dose of the drug consumed in neonates (4,14). In the present study, no symptoms were observed in our patients during treatment and follow up. Lack of an appropriate placebo for control group was limitation of this study. So it is possible to use clofibrate in mild jaundice along with phototherapy according to results of this study. But we have to pay attention that administration of clofibrate dos not let us to postpone exchange transfusion in severe hyperbilirubinemia. More studies are required to evaluate probable long term complications of clofibrate. This drug can be used routinely in neonates if it is proved to be harmless. In conclusion, clofibrate was effective in reducing neonatal jaundice and its effect will appear 24 hours after treatment. More research in this regard is recommended.

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