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The effect of clofibrate in near term newborns with non hemolytic jaundice

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The aim of this study was to evaluate the efficacy of clofibrate in reducing total serum bilirubin levels in near term neonates with non hemolytic jaundice. A randomized controlled study was carried out in the neonatal ward of Children's Hospital, Tabriz, Iran, over one year period. Sixty eight healthy near term infants with non hemolytic hyperbilirubinemia were randomized to receive phototherapy plus clofibrate (n=35) or phototherapy and placebo (n=33). There were no significant differences in the weight, gender, modes of delivery and age of neonates between two groups. Similarly, the mean total serum bilirubin (TSB) level at the time of admission was not significantly different between the two groups (19.72±1.79 versus 20.05±2.82 mg/dl, P=0.57). The mean TSB 48 h after phototherapy (8.06±1.34 versus 10.94±2.87 mg/dl P=0.02) and the mean duration of phototherapy (64.32±12.48 versus 87.84±29.76 h P<0.0001) was significantly lower in clofibrate treated group. Clofibrate is an effective adjunctive drug in neonatal hyperbilirubinemia and results to lower TSB level and reduced duration of phototherapy in near term newborns.

Key words: Clofibrate, near term neonate, non hemolytic jaundice, phototherapy.

INTRODUCTION

Most newborns experience benign hyperbilirubinemia. Severe elevation of serum bilirubin levels can result in brain damage known as kernicterus (American Academy of Pediatrics, 2004; Maisels, 2005; Halamek and Stevenson, 2006; Shortland et al., 2008; Alkalay and Simmons, 2005). It is important to promptly initiate appropriate therapy. The intensity and invasiveness of therapy is determined by the many factors such as gestational age, relative health of the neonate, the current level of total bilirubin and the etiology of jaundice. In the neonates, hyperbilirubinemia is usually due to a combination of an increased bilirubin load and decreased bilirubin elimination (American Academy of Pediatrics, 2004; Maisels, 2005; Halamek and Stevenson, 2006; Shortland et al., 2005; Alkalay and Simmons, 2005). Phototherapy and exchange transfusion are two main interventions used to decrease total serum bilirubin (TSB) (Maisels, 2005; Halamek and Stevenson, 2006). Despite an understanding of the enzymatic pathways leading to bilirubin production and degradation, very few pharmacologic interventions are utilized and the mainstay of treatment remains phototherapy.

Pharmacologic agents used in the management of hyperbilirubinemia can accelerate the normal metabolic pathways for bilirubin clearance, inhibit the enterohepatic circulation of bilirubin or interfere with bilirubin formation by either blocking the degradation of heme or inhibiting hemolysis (Avery et al., 2005; Martin et al., 2006; Dennery, 2002).

Clofibrate as a hypolipidemic drug is a glucuronyl transferase inducer which accelerates bilirubin elimination (Bruns et al., 1999; Wang et al., 2007).

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Table 1. Baseline characteristics of the infants in two groups.

Characteristic	Study group	Control group	P-value
Male [n (%)]	20 (57.1)	18 (54.5)	0.82
Weight (kg)	2.33±0.61*	2.39±0.45*	0.92
Cesarean section [n (%)]	16 (45.7)	18 (54.5)	0.47
Age at admission (days)	6.20±2.62*	6.03±3.14*	0.44
Gestational age (week)	35.04±1.56*	35.16±1.44*	0.72
Hemoglobin (g/dl)	16.90±2.16*	16.23±1.94*	0.18
Direct bilirubin (mg/dl)	0.86 ±0.39*	0.79 ±0.43*	0.61
Reticulocyte count	1.22±1.46*	2.00 ±0.21*	0.07

*Mean±SD.

Hyperbilirubinemia is a common problem in Iranian newborns and consists of approximately 1/3 of admissions in our neonatal ward. The efficacy of clofibrate has been shown in term neonates in several studies (Lindenbaum et al., 1981; Mohammadzadeh et al., 2005; Badeli et al., 2008; Zahed et al., 2007). A little is known about the usefulness of this drug in preterm infants. We hypothesized that near term infants are not very different from preterm neonates. So, this study was conducted to assess the efficacy and safety of clofibrate in the treatment of non hemolytic jaundice in near term infants.

MATERIALS AND METHODS

This study was a prospective randomized clinical trial conducted between January and December, 2008 in the neonatal ward of Tabriz Children Hospital, which is the major teaching and referral center in Northwest of Iran. Ethical committee of the institute approved the study protocol. Criteria for enrollment in this study included healthy newborns with non hemolytic jaundice, gestational age 34 to 37 weeks, jaundiced neonates who did not need urgent exchange transfusion. It is routine to use 2004 American Academy of Pediatrics (AAP) hyperbilirubinemia guidelines for management of admitted newborn infants in our neonatology department (AAP, 2004).

Neonates with major congenital anomalies, hemolytic disorders, glucose-6-phosphate dehydrogenase (G6PD) deficiency, urinary tract infection, sepsis or significant illness requiring NICU admission, dehydration and hypothyroidism were excluded. Healthy near term infants admitted for non hemolytic jaundice were eligible for the trial. Sixty eight neonates were enrolled in this study. They were randomized into the study or control groups by a random-number table sequence after informed parental consent were obtained. The allocations were contained in opaque sequentially numbered sealed envelops. Study group received phototherapy plus clofibrate (n=35) and control group was treated with phototherapy plus placebo (n=33). Corn oil was used as placebo clofibrate or placebo was administered to patients by a nurse who was not involved in the care of the infants according to orders from sealed envelope.

A single dose of clofibrate 100 mg/kg was administered orally to infants in the study group within 12 h of admission. All patients received phototherapy until discharge. Each phototherapy unit contained 8 special blue fluorescent tubes labeled TL 52/20 W (Philips, Eindhoven, Netherlands) adjusted at a 20 cm distance above infant.

Lamps of phototherapy units were changed regularly after 1500 h of usage. Total and direct serum bilirubin levels were measured 12, 24, and 48 h after admission and then daily until phototherapy became discontinued. TSB measurement was performed by spectrophotometric method using Bilimeter 3 (Germany) and direct serum bilirubin was measured by autoanalyser system (Selectra E, Netherland) and Pars Azmoon kit, Iran. Laboratory workers measuring them were blind about the type of intervention. The equipments were standardized periodically.

Routine laboratory tests such as complete blood count, total and direct serum bilirubin, reticulocyte count, direct Coombs agglutination test, maternal and neonatal blood group, G6PD level and peripheral blood smear were performed for all jaundiced infants in both groups. Our plan for discharge was TSB less than 50% of exchange level which was ordered by a physician who did not know the infants group assignment and duration of phototherapy was recorded by a nurse who was not involved in drug administration.

All infants were examined 48 h and 1 week after discharge with a careful physical examination for any probable side effects of therapy and laboratory tests for detection of rebound hyperbilirubinemia, leucopenia, and renal failure.

All data were analyzed by using Statistical Package for Social Sciences (SPSS) 14. Statistical analysis of the data was performed by Chi square and independent t-test. P values less than 0.05 were considered significant.

RESULTS

The main cause of admissions in 144 cases of 446 admitted neonates was hyperbilirubinemia (32%) during the study period. Seventy neonates had inclusion criteria. Two patients were excluded from the study, because of subsequent positive blood culture and refusal of parents for blood sampling. Remaining 68 newborn infants were assigned randomly into two groups. Of 68 neonates enrolled in this study, 33 patients in control group received phototherapy plus placebo and 35 neonates in study group treated with phototherapy plus clofibrate. There was no significant difference in gender, weight, age at admission and cesarean section rate between the two groups (Table 1). Sixty five percent of neonates were first offspring. Ninety seven percent of the studied newborns (66 cases) were exclusively breastfed.

Mean total serum bilirubin levels at the time of admission were 20.05±2.82 mg/dl (range: 15.8 to 23.6

Table 2. Laboratory tests results in patients of both groups.

Laboratory test	Study group (Mean±SD)	Control group (Mean±SD)	P-value
TSB 1	20.05±2.82	19.72±1.79	0.57
TSB 2	14.77±2.73	14.23±3.09	0.44
TSB 3	9.60±2.99	10.21±3.65	0.46
TSB 4	8.06±1.34	10.94±2.87	0.02*
Duration of phototherapy	64.32±12.48	87.84±29.76	<0.0001*

TSB 1: At the time of admission; TSB 2: 12 h after initiation of treatment; TSB 3: 24 h after initiation of treatment; TBS 4: 48 h after initiation of treatment.

mg/dl) in the study group and 19.72±1.79 mg/dl (range: 16.5 to 23.9 mg/dl) in the control group (P=0.57). Mean duration of phototherapy was significantly shorter in the study group in comparison with the control group [64.32±12.48 h (range: 45 to 90 h) versus 87.84±29.76 h (range: 70 to 210 h) P<0.0001]. The results of the laboratory tests of patients in the two groups are shown in Table 2. None of the cases in the present study required exchange transfusion.

None of the babies receiving clofibrate developed vomiting, diarrhea or had other side effects of drug. Only one case of rebound hyperbilirubinemia was noted from the control group in the follow up of neonates. White blood cell count, blood urea nitrogen (BUN), and creatinine levels were normal one week after discharge.

DISCUSSION

Clofibrate has been used for many years in adults. It is an activator of peroxisome proliferator-activated receptors (PPARS) which decreases serum cholesterol and triglyceride levels (Bruns et al., 1999). Liver fatty acid binding protein expression is known to be regulated by PRAR agonists such as clofibrate. In the study of Wang (2007), the up regulation of liver fatty acid binding protein was associated with a significant decrease in serum bilirubin and alanine aminotransferase by reduction of hepatic oxidative stress and improvement of hepatic function in bile duct ligated rats (Wang et al., 2007).

There are reports (Lindenbaum et al., 1981; Mohammadzadeh et al., 2005; Badeli et al., 2008; Zahed et al., 2007) that clofibrate treatment resulted in the decrease of the duration of jaundice and a lowered use of phototherapy in term infants, but there are few studies in preterm infants (Mohammadzadeh et al., 2008; Lindenbaum et al., 1985). A few studies showed the usefulness of clofibrate in neonates with G6PD deficiency (Zahedpasha et al., 2008), but were excluded from the study.

In a double blind controlled study of infants without ABO incompatibility, 47 infants treated with a single dose of clofibrate demonstrated significantly lower bilirubin levels after 16 h of treatment as compared to 46 controls given corn oil alone (Lindenbaum et al., 1981). Many studies showed significant decrease of total serum bilirubin 12 h after clofibrate administration for full term infants (Mohammadzadeh et al., 2005; Badeli et al., 2008). In our study, serum bilirubin was significantly decreased only after 48 h in clofibrate group. One possibility for the cause of difference in time needed for bilirubin reduction is lower gestational age of our patients that may affect the time needed for clinical response to drug. There was a 24 (Mohammadzadeh et al., 2008) and 48 h (Lindenbaum et al., 1985) interval for bilirubin reduction in other studies of clofibrate efficacy in premature neonates.

This study shows the usefulness of this drug in near term infants' jaundice. Occurrence of hyperbilirubinemia results in the prolonged hospital stay with increased cost. In developing countries, this intervention would reduce costs of treatment and hospitalization.

A common side effect of clofibrate is nausea. Other gastrointestinal (GI) disturbances including vomiting and loose stools have been reported. Although, complications such as muscle cramping, fatigue, pruritus, alopecia, leukopenia, renal failure and peripheral neuropathy have been described (Wazir et al., 2006), but they are very rare with single dose of this drug (Bruns et al., 1999). Side effects were not found in the studied neonates during hospitalization and until one week after discharge, but the long term safety of clofibrate is debatable and need more studies for longer period follow up and with lower doses and lower doses before recommending wide spread use of this drug as adjunctive therapy for neonatal hyperbilirubinemia.

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