Treatment Effect of Clofibrate in Jaundiced Low Birth Weight Neonates

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ABSTRACT

In this study we determined the treatment effect of clofibrate in low birth weight neonate with hyperbilirubinemia.
In a randomized double blind placebo - controlled study, 60 low birth weight neonates who were jaundiced and had hyperbilirubinemia were selected. The treatment group received a single oral dose of clofibrate (100 mg/kg) and the control group received sterile water as placebo. Also both group received Phototherapy in addition of the treatment. Serum bilirubin level was measured at entrance to study and 12, 24, 48 and 72 hours of study. Serum bilirubin decreased in 72 hours in clofibrate group that it was nearly significant (p= 0.061), but there were no significant difference between two groups in 12, 24, 48 hours of study (p= 0.7, p= 0.22, p= 0.19 respectively). Duration of phototherapy in clofibrate group was significantly shorter than control group (p= 0.023). Based on physical exam and liver function tests no side effects were seen.
Our result showed that there wasn't significant difference between two groups after administration of single dose of clofibrate (100 mg/ kg) in 12, 24, 48 and 72 hour. Although effect of clofibrate on treatment of jaundice wasn't significant between two groups, duration of phototherapy has been decreased significantly in clofibrate groups.

Key Words: Clofibrate, Hyperbilirubinemia, Low birth weight neonates, Treatment

ÖZET

Sarılığı Olan Düşük Doğum Ağırlıklı Yenidoğanlarda Klofibratın Tedavi Etkisi

Bu araştırmada hiperbilirubinekili düşük doğum ağırlıklı yenidoğanlarda klofibratın tedavi etkis incelendi. Randomize çift kör plasebo-kontrol çalışmada, 60 düşük doğum ağırlıklı sarılığı ve hiperbilirubinemisi olan olgu seçildi. Tedavi grubuna tek doz klofibrat (100 mg/kg) uygulanırken kontrol grubuna plasebo olarak steril su verildi. Her iki gruba ilave olarak fototerapi uygulandı. Serum bilirubin seviyeleri çalışma başlangıcında, 12, 24, 48 ve 72. saatte ölçüldü. Serum bilirubin seviyesi klofibrat grubunda 72. saatte azaldı (p= 0.061), ancak 12, 24 ve 48. satte her iki grup arasında anlamlı fark gözlenmedi Fototerapi süresi klofibrat grubunda kontrol grubuna kıyasla daha kısaydı (p= 0.023). Fiziksel muayene bulguları ve karaciğer fonksiyon testi sonuçlarına göre yan etki gözlenmedi.
Bu çalışma sonucunda, 12, 24, 48 ve 72. saatte tek doz klofibrat (100 mg/ kg) uygulamasının sarılık tedavisindeher iki grup arasında fark oluşturmadığı saptandı. Bununla beraber, fototerapi süresinin anlamlı olarak azaldığı saptandı.

Anahtar Kelimeler: Klofibrat, Hiperbilirubinemi, Düşük doğum ağırlıklı yenidoğanlar, Tedavi

INTRODUCTION

Approximately 60% of full term and 80% of premature infants have jaundice during the first week of life. The increased intensity and duration of hyperbilirubinemia in preterm infants as well as immaturity of the blood brain barrier have led to concern about greater risk of bilirubin encephalopathy in preterm infants.[1-3] The incidence of severe neonatal hyperbilirubinemia is highest in Asians. Five to ten percent of all newborns require intervention for pathologic jaundice.[4]

Phototherapy is used worldwide for treatment of hyperbilirubinemia in newborn infants.[5] Some pharmacological agents such as D-penicillamine, phenobarbital, agar, oral charcoal, metalloporphyrins and clofibrate have been suggested to treat neonatal jaundice.[6] Clofibrate is an activator of peroxisomeproliferated activated receptors (PPARs), and thus it affects lipid metabolism. This drug can also increase bilirubin conjugation and excretion (Elimination of bilirubin).[7,8] Clofibrate has some side effects such as nausea, gastrointestinal disturbances, vomiting and loose stools in adults when used as an antilipidaemic agent.[9] but in the neonatal study with a single high dose of clofibrate, none of these side effects were reported.[10] Hyper bilirubenemia is a common problem in Iranian newborns and consist approximately 1/3 of admission. The efficacy of clofibrate has been shown in neonates in different studies and they report that clofibrate treatment resulted decreased the duration of jaundice and a lowered use of phototherapy in term infants.[11-13]

In his study we determined the effectiveness of oral clofibrate in the treatment of nonhemolytic jaundice in low birth weight neonates.

PATIENTS AND METHODS

In a randomized double blind controlled-placebo trial From March 2007 to July 2008, 60 low birth weight neonates with jaundice who were admitted to the Neonatal Ward of Emamreza Hospital, affiliated to Mashhad University of Medical Sciences in north eastern Iran, entered to study. Written consent was provided from each patient's parents and the study was approved by the University Ethical Committee. The inclusion criteria were healthy, breastfed and birth weight less than 2500 gr, the exclusion criteria were the presence of any Congenital anomaly, hemolytic disease (Rh or ABO incompatibility and a positive Coombs' test), Infection (congenital or acquired), dehydration, G6PDdeficiency, and a history of Phenobarbital intake either by Mother or infant. After consent of parents, babies randomly were divided in two groups. Each participant received either clofibrate 100mg/kg (clofibrate group n=30) or sterile water as volume as clofibrate (control group n=30). Sample size determined by mean and standard deviation of our previous study.

The clofibrate and placebo were coded, nor physician neither laboratories known about type of treatment and selection of case and control group was randomly. In the end of study codes were opened and data were analyzed. They received clofibrat or placebo as a single dose by orogastric tube.

The clinical examination birth weight, gender, age, and weight at enrollment, serial Total Serum Billirubin (TSB), direct bilirubin, and duration of phototherapy were recorded. Laboratory tests included complete blood count, reticulocyte count, serum bilirubin level (total and direct), erythrocyte glucose-6-phosphate dehydrogenase (G6PD) level, T4, and TSH. TSB levels were determined using a Unistat® Bilirubinometer (a stat photometric analyzer for determining total bilirubin concentration in newborn infants, Reichert-Jung, Germany). The determination of direct bilirubin was made by the colorimetric method of Lathe and Ruthven. All infants in this study were examined by a neonatologist during hospitalization and two days after discharge in the outpatient clinic for evaluation of their jaundice and any side effects of the drug. All neonates in both groups received phototherapy. Each phototherapy unit had four special blue lamps (Philips Co, Germany) and adjusted to 25 cm above the infants' cots.

Total and direct serum bilirubin levels were measured at the beginning, 12, 24, 48, and 72 hours after the start of phototherapy. Duration of phototherapy was checked in two groups. Liver function tests (SGOT, SGPT) were checked finally.

Data were analyzed with SPSS. The anthropometric data are presented as means ± SD. For quantitative variables, differences between groups were tested by using independent t test and in nonparametric distribution Mann Whitney test were used. Ca-

Table 1. Characteristic of newborn and laboratories in clofibrate and control groups

Item	Control n= 30	Clofibrate n= 30	p value
Birth weight (gram)	2042 ± 386.5	2186 ± 243.3	0.051
male n (%)	20 (66.6%)	12 (40%)	0.71
Gestational age (week)	31.5 ± 1.6	31.46 ± 1.44	0.704
Age at enrollment (day)	9.6 ± 5.08	8.7± 5.75	0.228
Hematocrit (%)	48.4 ± 6.77	45.5 ± 7.46	0.272
Reticulocyte count (RBC %)	1.8 ± 3.37	0.67± 0.48	0.556
TSB on admission	19.5 ± 4.7	22.7 ± 5.28	0.099
Direct Bilirubin on admission	0.458 ± 0.26	0.566 ± 0.26	0.272

* Data shown as mean ± SD.

tegorical variables were analyzed using the chi squared test and fisher's exact test when indicated. For control of confront variables, general linear model regression were used. The cut- off level for significance was chosen at $p \leq 0.05$.

RESULTS

Sixty jaundiced low birth weight (LBW) neonates (30 case, 30 control group) were enrolled in this study. There were no significant difference between two groups in birth weight, gestational age and age enrolment (Table 1). Also total and direct serum bilirubin, Hemoglobin, Hemotocrit and Retic count in admission were insignificant between two groups (Table 1).

Result show that there was no significant difference in mean total serum bilirubin (TSB) and mean direct serum bilirubin in 12, 24, 48 and 72 hours of study between two groups (Table 2).

Changes of TSB in 12, 24, 48 and 72 hours from baseline in two groups were calculated. reduction in 12, 24 and 48 hours from baseline was more in clofibrate group than control group but it was not significantly (p= 0.7, p= 0.22, p=0.19 respectively). Only reduction of TSB in 72 hours of treatment was near to significant (p= 0.061) (Table 3). Mean duration of phototherapy in clofibrate group was 3.47 days and in control group was 4.47 days. So duration of phototherapy in clofibrate group were significantly shorter than control group (p= 0.023). On serial examinations during hospitalization, on discharge and seventh days after discharge in the outpatient clinic no drug side-effects were observed. There was no significant difference between two groups in SGOT and SGPT on discharge (p= 0.9, p= 0.74 respectively) and they were in normal range. Two neonates in our population needed to exchange transfusion during treatment, one in clofibrate group and other in placebo group.

DISCUSSION

This study showed that after administration of single dose of clofibrate (100 mg/kg), there was no significant difference between mean TSB and direct serum bilirubin and change of TSB from base line between two groups.

Studies stated that clofibrate is an inducer of glucuronosyl transferase and causes 100% increase of hepatic bilirubin clearance within 6 hours.[9,10,14,15] Previous studies with 50 and 100 mg/kg of clofibrate on TSB levels demonstrated efficacy in reducing bilirubin levels in term neonates.[4,10,14-16]

Lindenbaum studied the preventive effect of clofibrate in 47 premature neonates in case group and 46 neonates in control groups with gestational ages ranging between 31-36 weeks. He showed a less in-

Table 2. Plasma bilirubin level during treatment in the control and clofibrate-treated groups

	Plasma bilirubin level (mg/dl)		
	Clofibrate group (n= 30) Mean ± SD	**Control group (n= 30) Mean ± SD**	**p values**
12th hours			
Total	16.2± 4.74	18.7± 3.47	0.105
Direct	0.583± 0.23	0.497± 0.21	0.31
24th hours			
Total	13.09± 1.67	11.7± 3.4	0.189
Direct	0.587± 0.40	0.656± 0.32	0.616
48th hours			
Total	10.6± 2.17	9.89± 2.78	0.396
Direct	0.591± 0.37	0.582± 0.43	0.95
72th hours			
Total	8.4± 2.12	8.7± 2.28	0.467
Direct	0.529±0.19	0.655± 0.38	0.269

tensity of jaundice after 48 hours of treatment.[9] We recently studied the prophylactive effect of clofibrate in low birth weight neonate's hyperbilirubinemia. Result showed that clofibrate had prophylactic effect on total serum bilirubin in first 24 hours after drug administration and caused shorter duration of phototherapy.[17] In Lindenbaum and our recent study prophylactic effect of clofibrate on premature infants was investigated but in this study we focused on treatment effect of clofibrate on LBW infants. Studies have demonstrated significant effect of clofibrate on treatment of jaundice in term infants or significant prophylactic effect on low birth weight infants. But our study determined treatment effect of clofibrate and demonstrating that clofibrate can not significantly reduce serum bilirubin level for treatment of low birth weight neonates. In this study duration of phototherapy in clofibrate group such as was significantly shorter than control group. This finding supported by our previous research that had investigated effect of clofibrate in term and low birth weight neonates that it is vulnerable finding.[16,17] Birth Weight of our neonates according to their gestational age was in percentile 90 and they had appropriate weight. Maybe the reason is that our hospital located in high place of city and they had good economic status and education. Finally although there wasn't significant difference between TSB levels in two groups but duration of phototherapy significantly has been decreased in clofibrate group. Short duration of phototherapy is an important goal in the treatment of jaundiced neonates because it led to more bonding between mother-infant, low hospitalization and decrease money expense and side effect of phototherapy. Kangaroo mother care is useful way for physical and mental growing of neonates and decrease anxiety and stress in mother. With short duration of phototherapy we can more use from this technique (KMC) for neonate and mother.

In the present study such as other studies, administration of a single dose of clofibrate was well tolerated and no side effects were observed. These data are also in agreement with previous studies which demonstrated that a single dose of 50-100 mg/kg of clofibrate was well tolerated with no side effects.[16-18]

CONCLUSION

This is the first study that investigated treatment effect of clofibrate on low birth weight neonates. Although our results showed that there wasn't significant difference in TSB between two groups after administration of single dose of clofibrate (100 mg/kg) in 12, 24, 48 and 72 hour but duration of pho-

Table 3. Change of TSB from baseline in clofibrate and control group

	Plasma bilirubin level (mg/dl)		
	Clofibrate group (n =30) Mean ± SD	**Control group (n = 30) Mean ± SD**	**p values**
12th hours	3.92±5.58	3.34±1.44	0.7
24th hours	9.6±4.7	7.8±3.11	0.227
48th hours	12.02	9.6±3.77	0.189
72th hours	14.28±5.6	10.7±3.98	0.061

totherapy has been decreased significantly in clofibrate groups. We suggest that more investigation on treatment effect of clofibrate in low birth weight neonates is needed.

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