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Prophylactic Effect of Clofibrate on Hyperbilirubinemia in Very Low Birth Weight Twins

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Authors' contributions

This work was carried out in collaboration between all authors. Author MA designed the study, wrote the protocol, and wrote the first draft of the manuscript. Author FA managed the literature searches. Authors EH and JN performed the statistical analysis. All authors read and approved the final manuscript.

Original Research Article

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ABSTRACT

Aims: To determine the prophylactic effects of clofibrate on hyperbilirubinemia in very low birth weight twins.

Study Design: A randomized double blind clinical trial

Place and Duration of Study: Department of Neonatal Research Center, Imam Reza Hospital, Faculty of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran, between Oct 2010- Sep 2011.

Methodology: Forty neonates with very low birth weight (20 pairs of twins) having same blood group and sex were elected. Infants with congenital anomalies, metabolic diseases, hemolytic disease, and infections were excluded. Case group received a single dose of clofibrate 100 mg/kg and control group received sterile water. Both clofibrate and sterile water were administrated through orogastric tube and were the same volume. Serum

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bilirubin levels were measured before administration, 24, 48, 72 and 96 hours after the administration. Data was analyzed using repeated measure ANOVA.

Results: Total serum bilirubin after clofibrate administration was lower than control group ($F= 6.48$, $P=0.02$); however, the duration of phototherapy and hospitalization were not significantly different between the two groups ($P=0.39$ and 0.91 respectively). No side effects of drug were observed based on the physical exam and liver function tests.

Conclusion: These findings suggest that clofibrate maintained total serum bilirubin lower in very low birth weight neonates but without effect on duration of phototherapy and hospitalization.

Keywords: Clofibrate; hyperbilirubinemia; very low birth weight twins; Newborn.

1. INTRODUCTION

Hyperbilirubinemia occurs in 80% of preterm infants. In these babies bilirubin levels are higher, more persistent of longer duration and more likely to be associated with neurological injury than term neonates. The increased intensity and duration of hyperbilirubinemia in preterm infants as well as the immaturity of the blood – brain barrier may pose a greater risk of bilirubin encephalopathy in preterm infants [1,2,3]. Deficient uridin glucuronyl transferase (UDPG-T) activity that results in bilirubin conjugation impairment has long been considered a major cause of physiologic jaundice. In the first 10 days of life the UDPG-T activity in full term and premature neonates is usually less than 1% of adult values [3,4].

There are three methods for the treatment of hyperbilirubinemia such as: Exchange transfusion for mechanical removal of bilirubin, phototherapy for photoisomerization and bilirubin excretion in stool or urine and accelerating normal metabolic pathway for bilirubin excretion pharmacologically. Exchange transfusion is an invasive procedure with many complications and one percent mortality. The most common approach for treatment and prevention of neonatal hyperbilirubinemia is phototherapy, which reduces the incidence of exchange transfusion. This method has some disadvantages including parental anxiety due to increased hospitalization of the infant, disrupted mother- infant bonding and high cost of care.

Infant UDPG-T activity is very low in neonates and especially very low birth weight; therefore any inducer of UDPG-T activity will prevent hyperbilirubinemia. Several pharmacologic agents are capable of stimulating the hepatic glucuronyl conjugating system and some have even been used to reduce the concentration of serum bilirubin in newborn infants.

Phenobarbital is the most widely used drug in human studies. It is a potent inducer of microsomal enzymes that increase bilirubin conjugation. Clofibrate is also a glucuronyl transferase inducer and can increase bilirubin conjugation and excretion [5-6]. We found previously that clofibrate is effective in treatment of jaundice in term and preterm newborn [7,8]. Our studies showed that clofibrate has significant therapeutic effect on term newborns but it does not show a full therapeutic effect on preterm infants. We also studied the prophylactic effect of clofibrate on very low birth weight neonates. In this study administration a clofibrate reduced the levels of bilirubin significantly 24 hours after administration and the duration of phototherapy was also shortened [9]. In the present study, our aim was to assess prophylactic effect of clofibrate on hyperbilirubinemia in very low birth weight twins with the same blood group and sex.

Medical treatment is practical, economical and acceptable to parents and therefore such a study would have advantageous.

2. MATERIAL AND METHODS

Forty very low birth weight neonates who admitted in the NICU at our hospital were selected for this study. Babies with congenital anomalies, metabolic diseases, hemolytic disease and infections and twins with different sexes were excluded. These neonates were healthy, breastfed twins with birth weights equal to or less than 1500 grams with the same blood group and sex. Each pair of twins was boys or girls with same blood types. Laboratory investigations included complete blood count, red blood cell morphology, blood groups of the newborn and their mothers, direct and indirect coomb's tests, reticulocyte count and erythrocyte G6PD level. The clinical examination, gestational age, birth weight, sex, serial total serum bilirubin (TSB), direct bilirubin, duration of phototherapy and hospitalization were recorded. TSB was measured by using a Unistat bilirubineometer (Reichert – Jung, Germany).

The colorimetric method of Lathe and Ruthven were used for measurement of direct bilirubin [10]. As all neonates were healthy preterm babies, phototherapy was started when total serum bilirubin concentration reached a threshold level based on AAP recommendation (TSB 5 grams/dl in babies with less than 750 grams birth weight, TSB 6 grams/dl in 751-1000, TSB 7 grams/dl in 1001-1250 and TSB 8 grams/dl in more than 1250 grams birth weight) [3].

Phototherapy was discontinued when bilirubin decreased to 50% of starting level. Each phototherapy unit contained six blue lamps. Energy output or irradiance of the phototherapy light was being maintained at 8-12 $\mu\text{w}/\text{Cm}^2/\text{nm}$. Level irradiance of phototherapy was checked routinely by fluoro-LITE meter 451, Minolta camera co. LTD, and maintained at 8 - 12 $\mu\text{W}/\text{Cm}^2/\text{nm}$.

The protocol of study was approved by the local ethical committee of Mashhad University of medical science. The study was described to the parents of neonates, and written informed consents were obtained. Babies were randomly divided in two groups. One group received clofibrate 100mg/kg (clofibrate group n=20) and the other group received sterile water (control group n=20). Both clofibrate and sterile water were with same volume. The clofibrate and placebo were coded, using an even number for clofibrate and an odd number for placebo, one of each pair of twins received the medication or the placebo on day one. Both physicians and laboratory staff did not know about type of administration for each neonate. Each twin pair received clofibrate or placebo as a single dose by orogastric tube in the first 24 hours of age. Total serum bilirubin level was checked before, 24, 48, 72 and 96 hours after administration of the drug. Liver function tests (SGOT, SGPT) were also performed in order to check the side effects of drugs. Codes were opened at the end of study. Data were analyzed with Statistical Package for Social Science (SPSS version 11.5). The used test was repeated measure ANOVA. P- Value less than 0.05 was considered statistically significant.

3. RESULTS

As two groups were the same blood group and same sex twins therefore, gestational age and demographic factors of mothers and newborns were the same in both. Mean gestational

age was 31.95±1.60 weeks. Mean birth weight of the study group was 1396±154 grams and that of the control group was 1408±106 grams. Some of the twin pairs were boys and some girls. All types of blood groups were found in participants but each pair of twins had the same blood group. Table 1 shows laboratory results obtained from the two groups were nearly the same.

Table 1. Laboratories workup of newborns

Lab Tests	Clofibrate (No=20) (Mean±SD)	Control (No=20) (Mean±SD)	P value
Hemoglobin g/dl	16.70 (5.30)	17.80 (4.55)	1.00
Hematocrit (%)	49.40(14.68)	52.20(13.60)	0.78
Reticulocyte (%)	5.34±2.36	6.78±2.45	0.19

Table 2 and Fig. 1 show that the total serum bilirubin levels of clofibrate group were lower than the control group on all days of the study and the difference was significant by using repeated measure analysis. (F= 6.48, P= 0.02). Changes of bilirubin based on the time also were significantly different (F= 20.8, P<0.001).

Table 2. Total serum bilirubin level in the two groups

Test Mean±SD	Clofibrate Mean±SD	Control group Mean±SD	Difference
bilirubin before clofibrate mg/dl	4.79±2.10	4.8±1.62	0.01±1.7
Bilirubin 1 day after intervention mg/dl	6.42±2.41	7.56±2.00	1.14±2.3
Bilirubin 2 days after intervention mg/dl	7.67±1.80	8.62± 2.07	0.95±2.26
Bilirubin 3 days after intervention mg/dl	7.64±2.31	8.15±2.25	0.5±3.05
Bilirubin 4 days after intervention mg/dl	5.10±2.32	6.72±3.11	1.62±3.6

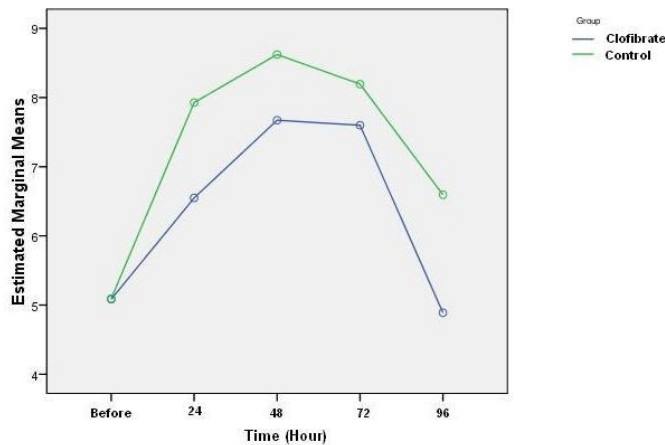


Fig. 1. Estimated Marginal Means of Two Groups

Differences in duration of phototherapy and hospitalization between the two groups were not significantly different Table 3.

Table 3. Phototherapy and hospitalization duration in two groups

	Clofibrate Mean±SD	Control group Mean±SD	P Value
Duration of Phototherapy (days)	5.89±5.03	6.35±6.01	0.39
Duration of hospitalization (days)	15.05±14.28	16.86±20.34	0.91

Liver function tests (SGPT, SGOT) were normal in both the groups at the end of study.

4. DISCUSSION

Various reagents affect the metabolism of bilirubin. Metalloporphyrins inhibit heme oxygenase, depenicilamin, phenobarbital and clofibrate are potent inducers of microsomal enzymes that increase bilirubin conjugation and excretion. Agar and charcoal decrease enterohepatic circulation. The effect of phenobarbital on TSB levels begins within a few days of administration; in addition phenobarbital causes respiratory failure, drowsiness and also worsens bilirubin toxicity by alteration of bilirubin oxidation in the brain. Clofibrate like phenobarbital is also microsomal enzymes inducer; in addition it can cause 100% increase in hepatic bilirubin clearance within six hours, with no drowsiness [6]. Our study showed that total serum bilirubin remained lower in clofibrate group after intervention compared to the control group.

Gabilan found that clofibrate is a better glucuronyl transferase inducer than other drugs [11]. They recommended that clofibrate is probably the best pharmacological treatment of neonatal jaundice.

Bourget et al [6] suggested that a single oral dose of 50 mg/kg clofibrate may be a better treatment for jaundice compared to a single oral dose of 100 mg/kg.

Lindenbaum et al. [12] showed that after 16 hours of treatment mean plasma bilirubin levels are significantly lower in treated group compared to control group. Clofibrate also resulted in a shorter duration of jaundice and a restricted use of phototherapy.

In previous study, we also found that the mean plasma total bilirubin levels at 12, 24 and 48 hours after clofibrate administration were significantly lower in term jaundiced neonates compared to the control group ($P < 0.0001$, $P < 0.0001$ and $P = 0.004$, respectively). And also, treatment with clofibrate resulted in a shorter duration of phototherapy ($P < 0.0001$) [7].

Zahedpasha et al. [13] assessed the efficacy of clofibrate in full term G6PD deficient neonates with jaundice. They also showed that clofibrate induces a faster decline in total serum bilirubin level, decreases duration of phototherapy, and lowers the duration of hospitalization. No side effects were observed in these full-term G6PD deficient neonates.

Eghbalian et al. [14] performed a study to assess the therapeutic effect of clofibrate in full term neonates who presented with nonhemolytic jaundice. Based on this study, a single dose of clofibrate (100 mg/Kg) accompanied with phototherapy is more effective than phototherapy alone for the treatment of non-hemolytic hyperbilirubinemia in term healthy newborn infants.

There is a little information available about effects of clofibrate on preterm infant. Preterm infants are susceptible to bilirubin encephalopathy even at physiologic levels. Lindenbaum et al studied the preventive effect of clofibrate in 46 premature neonates with gestational ages ranging between 31-36 weeks [15]. According to their study, the serum concentration of clofibrate equal to or above 140 micrograms per deciliter which is the therapeutic level during the first 24 hours of treatment leads to lesser intensity of jaundice 48 hours after treatment, lesser need for repeated bilirubin assay and lesser use of phototherapy.

In a previous study we showed that clofibrate was not affect in reducing bilirubin levels in low birth weight infants with hyperbilirubinemia, however the duration of phototherapy was significantly less in the treated group [8]. We have also previously shown that clofibrate used prophylactically in very low birth weight neonates decreased serum bilirubin level in the first 24 hours after drug administration and shortened the duration of phototherapy [9].

In the present study, prophylactic effect of clofibrate was assessed in very low birth weight twin infants who had the same blood group, and sex. Although patients of the two groups had similar characteristics, we observed a decrease in TSB after clofibrate administration. Duration of phototherapy and hospitalization were nearly the same in the two groups.

Results of our studies show that although clofibrate lowers bilirubin in term neonates affected with jaundice, the therapeutic effect is not significant on jaundiced preterm neonates. Immaturity of liver cells might be the reason for lack of effectiveness of clofibrate in preterm neonates, perhaps glucuronyl transferase activity could not be induced by clofibrate in immature liver cells. Another reason for the lack of effectiveness of clofibrate in preterm neonates could be the immaturity of the gastrointestinal system which may not absorb the drug properly.

Clofibrate has some side effects such as nausea, gastrointestinal disturbances, vomiting and loose stool in adults. Other possible side effects are muscle cramping, fatigue, pruritus, and alopecia. Chronic use of clofibrate has been reported as a hepatic carcinogen [16,17,18,19]. In neonatal studies with a single dose of clofibrate no side effects have been reported. We also did not find any side effects. As long-term follow up studies have not been conducted, safety of clofibrate cannot be concluded [6,16].

5. CONCLUSION

In conclusion clofibrate in very low birth weight twins with same sex and blood group maintains lower serum bilirubin levels but does not decrease the duration of phototherapy or hospitalization. Further investigation should be conducted to assess the effect of multiple doses and drug metabolism in preterm neonates in order to discover all its therapeutic and prophylactic properties and side effects.

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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