Preventive Effect of Clofibrate on Neonatal Hyperbilirubinemia

Original Article

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Abstract

Background: Neonatal jaundice is a common problem that can result in serious neurological side effect such as Kern icterus. Several drugs are used to prevent neonatal jaundice. The effect of clofibrate in the prevention of hyperbilirubinemia in healthy term neonates has not been paid attention to. This study aimed to evaluate the preventive effect of clofibrate on neonatal jaundice in term neonates.

Methods: This clinical trial was conducted on 80 healthy newborns randomly divided in to cases and control groups. The case group received clofibrate (50 mg/kg of body weight) orally in the first hour after birth and after the first period of breastfeeding. Serum bilirubin levels were measured in cord blood and again at 24, 48 and 72 hours after birth in both groups and were compared. Babies with clear jaundice on the first day, direct neonatal jaundice>1 mg/dl, sick infants, and infants of mothers treated with phenobarbital and preterm infants weighing less than 2500 gr were excluded.

Results: The mean bilirubin level in cord blood and its level at 24, 48 and 72 hours after birth in control groups were 1.99±0.46, 2.88±0.88, 5.94±1.15, 7.65±1.69, respectively and in the case group were 2.12±0.75, 2.89±0.95, 5.8±1.16, 7.18±1.57, respectively. Thus, the mean bilirubin in the case group is lower, but it was not statistically significant. Also, sex distribution, Rh-blood group incompatibility and G6PD deficiency in both groups showed no significant difference.

Conclusions: Our results showed that prophylactic clofibrate application reduced neonatal hyperbilirubinemia, but wasn't statistically significant.

Keywords: Clofibrate, Neonatal, Jaundice, Prevention

Introduction

Jaundice is a common problem in neonatal period that its severe type can lead to serious neurological problems like Kernicterus [1]. Every year, a huge hospital cost is imposed on parents for the treatment of neonatal jaundice. Moreover, it leads to the mother-child separation and subsequent mental health problems. Proven treatments for jaundice include phototherapy and blood exchange transfusion in which each one has its own complications [2]. In recent years, medication has also been used to prevent and treat neonatal jaundice Including IVIG, protoporphyrin, phenobarbital and clofibrate. Clofibrate is an activating factor (Peroxisome Proliferators Activated Receptors, PPARS) that increases conjugation and excretion of bilirubin [3]. This medicine has been used to treat it has been to jaundice combined with phototherapy in hospitalized infants [2, 4]. Also, used treat phototherapy at home [5] and for prolonged jaundice [6]. Clofibrate has not been used as prophylaxis of hyperbilirubinemia in newborns with or without risk factors including: ABO and Rh incompatibilities and G6PD deficiency.

Protoporphyrin is used as medication to prevent jaundice but unlike clofibrate, this is not easily available and abundant [7]. This study was conducted to evaluate the effect of clofibrate on the prevention of jaundice in neonate, with or without the mentioned risk factors.

Methods

This clinical trial was done in term neonates delivered in Ayatollah Rouhani Hospital affiliated to Babol University of Medical Sciences (BUMS). Umbilical cord blood samples were collected from all newborns that have the inclusion criteria in the study and bilirubin level, blood group, Rh and G6PD were checked. The infants were randomly divided into cases and control groups and clofibrate was (50 mg/kg) administered orally in the case group in the first hour after birth and after the first period of breastfeeding.

The total bilirubin levels were checked with Bilirubinometer (Transcutaneous jaundice detector, kJ-80000, China) at 24, 48 and 72 hours in both groups. If the level of bilirubin in the baby's skin was more than 8 mg/dl on the first day and more than 11 mg/dl on the third day, the plasma level of bilirubin was rechecked with other Bilicheck device made in Iran (Measuring equipment Company, Isfahan, Iran). If it was necessary and in accordance with Amirkola Children's Hospital's medical protocol, the eligible infants were hospitalized. According to this protocol, the neonate must be admitted and undergo phototherapy if their bilirubin is more than 5 mg/dl on the first day, more than 10 mg/dl second day and more than 15 mg/dl the third day. All healthy term neonates (with gestational age 37-41 weeks) were enrolled in the study.

The exclusion criteria included infants with overt jaundice on the first day, umbilical cord bilirubin level ≥ 5 mg/dl, newborns with direct bilirubinemia more than 1 mg/dl, sick newborns, infants of mothers treated with phenobarbital, infants weighing less than 2500 gr, infants under 37 weeks of gestational age (GA) and older than 42 weeks GA and infants with Rh incompatibility. Demographic data included gender; gestational age and birth weight were collected using patient's medical document review. The data were analyzed using SPSS software, version 18, chi-square and Anova and T-test. A p-value of 0.05 or less was considered significant.

This study was approved by Ethic Committee of Babol University of Medical Sciences. The informed parental consents were obtained for the administration of clofibrate.

Results

The control groups comprised of 40 patients, 23 cases (57.5%) were males while the case group compared of 40 patients as well, 24 cases (60%) were female.

There was no significant difference (p-value=0.18) in the two groups in terms of sex distribution. As show in table 1, there was no significant difference between the frequency distribution of the maternal and neonatal blood groups in the case and the control groups. Also, there was no significant difference between the frequencies of ABO incompatibility; Rh groups and G6PD deficiency in both groups (tables 2, 3).

The mean umbilical cord bilirubin level was 2.12±0.75 and 1.99±0.46, respectively with no significant difference in both groups. As with bilirubin, changes in the case group compared with the control group had further downward slope, although, initially it started with higher bilirubin levels (figure 1).This decrease in trend of bilirubin change and was not statistically significant. Bilirubin changes in terms of time in both groups are shown in table 3.

Table 1: The frequency of maternal and neonate blood group in Case and Control groups

BG& Rh	Mother		Neonate	
	Controls* N (%)	Cases* N (%)	Controls* N (%)	Cases* N (%)
A	6 (15)	11 (27.5)	9 (22.5)	10 (25)
B	12 (30)	10 (25)	13 (32.5)	6 (15)
AB	10 (25)	3 (75)	1 (2.5)	0 (0)
O	12 (30)	16 (40)	17 (42.5)	24 (60)
Rh⁻	4 (10)	4 (4)	4 (10)	2 (5)
Rh⁺	36 (90)	36 (90)	36 (90)	38 (95)

* P. Value>0.05

Table 2: Frequency of blood group and Rh incompatibility and G6PD deficiency in Case and Control groups

Risk Factors	Positive/Negative	Case*	Control*
Rh incompatibility	Positive	2	4
	Negative	28	36
ABO incompatibility	Positive	3	3
	Negative	27	27
G6PD deficiency	Positive	1	1
	Negative	29	29

*P. Value>0.05

Table 3: Mean bilirubin level in Case and Control groups

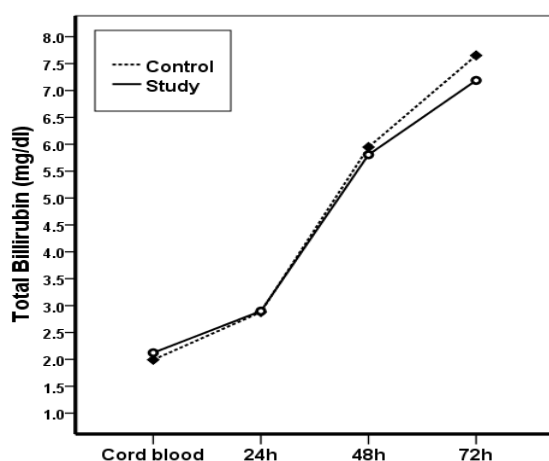| Bilirubin level	Case* Mean±SD	Control* Mean±SD
Umbilical cord	2.12±0.75	1.99±0.46
First day	2.89±0.95	2.88±0.88
Second day	5.8±1.16	5.94±1.15
Third day	7.18±1.57	7.65±1.69

*P. Value>0.05

Figure 1: Bilirubin changes in the case group compared with the control group in hours

Discussion

The results of our study showed that prophylactic clofibrate application reduced neonatal hyperbilirubine-mia, but it was not statistically significant. Literature review revealed that all studies about clofibrate and jaundice, has been combined with phototherapy and studies of its use as a preventative is limited to two studies. Clofibrate was given to 46 preterm infants between 31 to 36 weeks GA (Gestational Age), bet-ween 24 and 48 hours at birth.

Their study showed that clofibrate -treated group has lesser need to recheck for developing jaundice than control group with a significant decrease in photo-therapy and jaundice severity [8]. In another study conducted in 2008 by Mohammadzadeh et al.'s prophylactic clofibrate was given to LBW (Low Birth Weight) infants (weighing less than 2500 gr) who were admitted to the NICU (Neonatal Intensive Care Unit). Twenty-six infants were in the case group and the 26 others in the control group and all of them had no other risk factors for developing jaundice. Case group was prescribed 100 mg/kg clofibrate in the first 24 hours of

birth and bilirubin was checked at 24, 48, 72 and 96 hours later. This restricted study indicated the preventive effect of clofibrate on jaundice in the first 24 hours of birth and the length of hospital stay was also reduced for those receiving clofibrate [1]. Zahed Pasha Y et al.'s in their study on 30 term infants (in the first 72 hours of life) with jaundice who were treated with phototherapy and clofibrate showed clofibrate led to the rapid decrease in serum bilirubin concentration and earlier discharge from the hospital [9].

The effect of clofibrate in reducing bilirubin levels in infants receiving phototherapy at home were studied by Sharafi et al.'s In this study, 60 infants were treated with a single dose of 50 mg/kg clofibrate. The bilirubin level at 48 and 24 hours after treatment showed significant decrease and they have a significant reduction in the duration of phototherapy at home [5]. Habibi et al.'s studied on 52 neonates with pathologic indirect hyperbilirubinemia in 2012. The case group was treated with both intensive phototherapy and clofibrate and the control group only received intensive phototherapy. Their data analysis revealed a significant reduction in bilirubin level in case group [10]. Our study showed that clofibrate does not have a preventive effect on the incidence of neonatal jaundice. One of the limitations of this project can be early cessation of follow-up (up to 72 hours). We think that if the infants were followed-up until the end of 7 days after birth, we would be able to see more preventive effects of clofibrate on neonate jaundice.

Acknowledgment

Ethical approval: This study obtained ethics committee approval.
Conflict of interest: There was no conflict of interest.

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