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Original Article

Clofibrate in the Treatment of the Non-hemolytic Hyperbilirubinemia in Preterm Neonates in Western Iran

Fatemeh Eghbalian[1], Ensiyeh Jenabi[2*], Elham Hatami[1], Behnaz Basiri[1], Katayoun Derakhshandeh[3], Nasrollah Pezeshki[1], Elham Khanlarzadeh[3]

1. Hamadan University of Medical Sciences, Hamadan, Iran
2. Autism Spectrum Disorders Research Center, Hamadan University of Medical Sciences, Hamadan, Iran
3. Department of Pharmaceutics, School of Pharmacy, Hamadan University of Medical Sciences, Hamadan, Iran

ABSTRACT

Background: No studies, to the best of our knowledge, have been conducted on the effect of Clofibrate in reducing hyperbilirubinemia in preterm infants. Therefore, this study aimed at investigating the therapeutic effect of Clofibrate in treating hyperbilirubinemia of preterm neonates.

Methods: This clinical trial was performed from April 4 to December 20, 2019, on neonates in Hamadan in western Iran. The allocation remained concealed to the researcher, neonates' parents, and analyzer during the study. A dose of Clofibrate of 25 kg/mg was given on the first day of hospitalization. The neonates in the placebo group received the oral placebo 25 kg/mg in the same way as the oral Clofibrate. The data were analyzed using SPSS 16 with P-value < 0.05.

Results: No statistically significant difference was observed in the baseline characteristics of the two groups based on the neonate's age and gender, delivery method, and gestational age. The prescription of Clofibrate significantly reduced the duration of hospitalization (p= 0.002) and phototherapy (p= 0.001). Prescribing a single oral dose of Clofibrate (25 mg/Kg) along with phototherapy in preterm neonates significantly reduced total serum bilirubin levels at 24 and 48 hours after treatment compared with phototherapy alone (p= 0.001). However, this association was not significant in admission (p= 0.095).

Conclusion: The findings of this study showed the effect of Clofibrate in treating hyperbilirubinemia of preterm neonates. In addition, prescribing Clofibrate significantly reduced the duration of hospitalization and phototherapy.

Keywords: Clofibrate, Hyperbilirubinemia, Iran, Preterm neonate

Introduction

One of the common problems in Iranian newborns is hyperbilirubinemia and approximately one-third of admissions are related to icterus (1). The prevalence of neonatal hyperbilirubinemia in term and preterm neonates is 50% and 80%, respectively (2). Overproducing bilirubin, decreasing liver absorption, impairing conjugation, and increasing bilirubin enterohepatic cycle can lead to hyperbilirubinemia (3).

Bilirubin may accumulate in the gray matter of the central nervous system and potentially causing irreversible neurological damage in neonates. This condition is called acute bilirubin encephalopathy and the permanence of this injury may lead to kernicterus (4).

Phototherapy is the most widely used treatment for neonatal hyperbilirubinemia. There are several treatments for neonatal jaundice including Phenobarbital, Metalloporphyrins, Agar, Bile salts, and D–penicillamine. However, further research is needed to prove the efficacy and safety of these drugs before their usual clinical use (1).

Clofibrate has pleiotropic effects including activating the peroxisome proliferator-activated

* *Corresponding author*: Ensiyeh Jenabi, Autism Spectrum Disorders Research Center, Hamadan University of Medical Sciences, Hamadan, Iran. Email: En.jenabi@yahoo.com

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receptors and decreasing serum cholesterol and triglyceride levels. It also stimulates glucuronosyltransferase, which may increase the composition and excretion of bilirubin (5). Some studies were conducted on the usefulness of Clofibrate in treating hyperbilirubinemia in newborns (5).

Hamidi et al. in Iran reported that using Clofibrate and phenobarbital in icteric neonates reduced the serum bilirubin level and the duration of hospitalization and phototherapy (6). Another study reported that a single dose of Clofibrate (100 mg/Kg) with phototherapy was more effective than phototherapy alone in treating non-hemolytic hyperbilirubinemia in the newborn (7). However, no study has been conducted in Iran on the effect of low-dose Clofibrate and phototherapy in treating non-hemolytic hyperbilirubinemia in preterm neonates. Therefore, we performed the effect of low-dose Clofibrate and phototherapy for treating hyperbilirubinemia in preterm neonates.

No study has been conducted, to the best of our knowledge, on the effect of Clofibrate on the reduction of hyperbilirubinemia in preterm infants. Therefore, this study aimed to investigate the therapeutic effect of Clofibrate in treating hyperbilirubinemia of preterm neonates.

Methods

This clinical trial was conducted from April 4 to December 20, 2019, on neonates in Hamadan in western Iran. The study protocol was approved by the Research Ethics Committee of Hamadan University of Medical Sciences and was registered in the Iranian Registry of Clinical Trials with the code IRCT20120215009014N343. Written consent was obtained from the parents.

Inclusion criteria were (a) preterm neonates with a gestational age of 35-37 weeks, (b) healthy and suckling neonates with birth weight ≥2500g, and (c) total serum bilirubin level between 15-25 mg/dl. The exclusion criteria were (a) congenital anomalies, (b) hemolytic diseases, (c) sepsis symptoms or dehydration, and (d) need for exchange transfusion.

Eghbalian et al. reported in a clinical trial that the difference of mean ± standard deviation (SD) of total bilirubinemia was 1.1 ± 0.5 in the intervention and control groups (7). Therefore, we reached a sample size of 54 for each group with an error of 5% and 90% statistical power. Of the 108 initial samples, 8 failed to meet the inclusion criteria (6 neonates with hemolytic hyperbilirubinemia and 2 others had other causes of hyperbilirubinemia). Finally, a total of 100 neonates were randomly assigned to the Clofibtate or placebo group by block randomization method.

Therefore, we prepared four sheets of paper, two with 'C' showed for the Clofibrate and two with 'P' showed for the placebo. These sheets were placed in a container and then randomly drawn once for each neonate without any replacement to finish four sheets. The four sheets were then placed back in the container and repeated until all 97 infants were randomized. The allocation was concealed for the researcher, neonates' parents, and analyzer during the study. Therefore, the clinical trial had a triple-blind design. A dose of oral Clofibrate of 25 kg/mg was prescribed on the first day of hospitalization. The placebo group received 25 mg of oral starch in the same way as the Clofibrate. The Clofibrate and placebo were packed in similar packages.

All neonates in both groups received phototherapy. Each phototherapy unit which was made by Parsa Company included eight blue lamps and was placed at 25 cm above the infants. Total and indirect serum bilirubin levels were measured by Techinca R A1000 device. We continued phototherapy and bilirubin measurements until the total serum bilirubin concentration decreased to less than 12 mg/dl.

The data were collected using a checklist which included the neonate's age and gender, delivery method, and gestational age, duration of hospitalization, phototherapy, and laboratory tests such as total serum bilirubin on admission, 24, 48, and 72 hours after treatment. The validity of the questionnaire was confirmed using the viewpoints of 10 neonatologists. The reliability of the questionnaire was investigated by calculating internal consistency.

The data were analyzed using SPSS 16. Chi-square was used to compare the neonate's gender and delivery method. Also, the T-test was utilized for changes in total bilirubin level with P-value < 0.05.

Results

Of the 100 identified neonates, 3 in the Clofibrate group were transferred to other hospitals by their parents after taking drugs and did not return for the follow-up visits. Therefore, they were excluded and the analysis was performed on the remaining 97 neonates (47 in the Clofibrate group and 50 in the placebo group) (Figure 1).

No statistically significant difference was observed in the baseline characteristics of the two

groups based on the neonates' age and gender, delivery method, and gestational age (Table 1)

Table 2 reports that the prescription of Clofibrate significantly reduced the duration of hospitalization (p= 0.002) and phototherapy (p= 0.001).

Table 3 presents that prescription of an oral dose of Clofibrate (25 mg/Kg) with phototherapy in preterm neonates suffering from non-hemolytic hyperbilirubinemia significantly reduces total serum bilirubin levels at 24 and 48 hours after treatment compared with phototherapy alone (p= 0.001). However, this association was not significant in admission (p= 0.095).

Table 4 shows that neonates were 47 (100%) and 50 (100%) on admission and 24 hours after treatment, respectively. Neonates were 32 (68%) in the Clofibrate group and 45 (90%) in the placebo group 48 hours after treatment. At 72 hours after treatment, 16 (32%) were being treated with phototherapy in the placebo group. All neonates in the Clofibrate group except one were discharged 72 hours after treatment. Then, they were examined two days after discharge. No side effects were reported during hospitalization and two days after discharge.

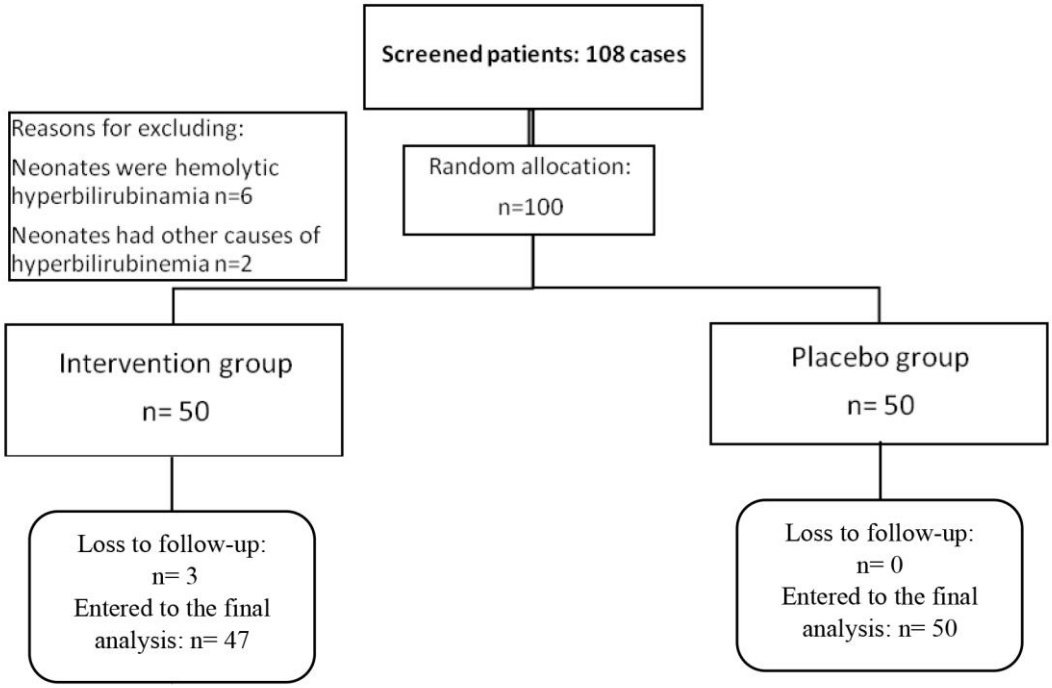

Figure 1. Flowchart of allocation of neonates to the studied groups

Table1. Baseline characteristics in Clofibrate and placebo groups

Variables	Clofibrate N=47	Placebo N=50	P-value
Neonate's gender N (%)			
Girl	26 (55.3)	28 (56.0)	0.946
Boy	21 (44.7)	22 (44.0)	
Delivery method N (%)			
Vaginal	23 (48.6)	28 (56.0)	0.545
Cesarean	24 (51.1)	22 (44.0)	
Neonate's age (hours) (M±SD)	70.40±26.54	69.18±27.75	0.506
Gestational age (Wk) (M±SD)	36.02±0.76	36.00±0.81	0.895

Table 2. Duration of hospitalization and phototherapy in Clofibrate and placebo groups

Variables	Clofibrate N=47	Placebo N=50	P-value
	Mean±SD	Mean±SD	
Duration of hospitalization (day)	1.93±0.91	2.41±0.88	0.002
Duration of phototherapy (hours)	43.09±16.03	56.76±19.73	0.001

Table 3. Changes in Total bilirubinemia in Clofibrate and placebo groups

Treatment groups	Total bilirubinemia on admission Mean ±SD	Change in total bilirubinemia in 24 hours Mean ±SD	Change in total bilirubinemia in 48 hours Mean ±SD	Change in total bilirubinemia in 72 hours Mean ±SD
Clofibrate	17.97±2.90	3.45±2.81	3.41±0.96	2±0
Placebo	18.14±1.39	2.33±0.75	2.40±0.94	2.63±0.59
P-value	0.095	0.001	0.001	-

Table 4. Frequency of changes in total bilirubinemia in Clofibrate and placebo groups

Groups	Admission N (%)	Patients 24 hours after treatment N (%)	Patients 48 hours after treatment N (%)	Patients 72 hours after treatment N (%)
Clofibrate	47 (100.0)	47 (100.0)	32 (68.0)	1 (2.1)
placebo	50 (100.0)	50 (100.0)	45 (90.0)	16 (32.0)

Discussion

The present study indicated that prescription of an oral dose of Clofibrate (25mg/Kg) with phototherapy in preterm neonates suffering from non-hemolytic hyperbilirubinemia significantly reduced total serum bilirubin levels at 24 and 48 hours after treatment compared with phototherapy alone. All neonates in the Clofibrate group except one were discharged 72 hours after treatment. Also, the prescription of Clofibrate significantly reduced the duration of hospitalization and phototherapy. The findings of this study showed the efficacy of Clofibrate in treating hyperbilirubinemia of preterm neonates.

Clofibrate acts as a peroxisome proliferator-activated receptor (PPAR) and thus disrupts lipid metabolism. It works by reducing serum lipids and low-density lipoprotein fraction rich in triglycerides (5). However, side effects of long-term use include diarrhea, vomiting, drowsiness, liver failure, increased cholestasis, increased prevalence of gallbladder, pancreatitis, renal failure, and peripheral neuropathy (8, 9). No side effects have been reported with an oral dose in the present study.

Eghbalian et al. reported that a single dose of Clofibrate (100 mg/Kg) with phototherapy is more effective than phototherapy alone in treating non-hemolytic hyperbilirubinemia in term newborn (7). Kumar et al. also stated that neonates with bilirubin in the range of 15–25 mg/dl were randomized to receive an oral dose of 50 mg/kg of Clofibrate or no dose at the beginning of phototherapy. There was a significant association of 7 mg/dl in bilirubin and about 24 h in the duration of phototherapy in the Clofibrate group (8). Another study compared the effects of low-dose oral Clofibrate (25 mg/kg) with moderate-dose (50 mg/kg) in treating non-hemolytic hyperbilirubinemia in 132 healthy term neonates. The results showed that there was no statistically significant difference between different doses of Clofibrate and the mean total bilirubin 12, 24, 36, and 48 hours after treatment (10). These studies were consistent with our findings on the efficacy of Clobibrate in treating hyperbilirubinemia.

Zahed et al. reported that prophylactic treatment of Clofibrate (50 mg/kg in the first hours after birth and the first periods of breastfeeding) reduced neonatal hyperbilirubinemia, but was not significant (11).

Lindenbaum et al. reported in a double-blind therapeutic trial that Clofibrate was a preventive treatment of hyperbilirubinemia in preterm neonates between 31 and 36 weeks. In this study, an oral dose of 100 mg/kg of ethyl Clofibrate was prescribed between 24 and 48 hours after birth (12). The results of this study confirmed our findings.

The limitation of the present study is the unclear long-term effect of Clofibrate which requires further studies.

Conclusion

The findings of this study showed the effect of Clofibrate in treating hyperbilirubinemia of preterm neonates. In addition, the prescription of Clofibrate significantly reduced the duration of hospitalization and phototherapy.

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Conflict of interest

The authors declare that there is no conflict of interest.

References

1. Torabi Z, Eskandarzadeh A, Ahmadiafshar A. The effect of clofibrate with phototherapy on full-term newborns with non-hemolytic jaundice. Iran Red Crescent Med J. 2013; 15(4):285-6.
2. Bhutani VK, Zipursky A, Blencowe H, Khanna R, Sgro M, Ebbesen F, et al. Neonatal hyperbilirubinemia and Rhesus disease of the newborn: incidence and impairment estimates for 2010 at regional and global levels. Pediatr Res. 2013; 74(S1):86-100.
3. Méndez-Sánchez N, Vítek L, Aguilar-Olivos NE, Uribe M. Bilirubin as 13. Biomarkers in Liver Disease. Berlin, Germany: Springer; 2017. P. 281.
4. Shapiro SM, Riordan SM. Review of bilirubin neurotoxicity II: preventing and treating acute bilirubin encephalopathy and kernicterus spectrum disorders. Pediatr Res. 2020; 87(2):332-7.
5. Gholitabar M, McGuire H, Rennie J, Manning D, Lai R. Clofibrate in combination with phototherapy for unconjugated neonatal hyperbilirubinaemia. Cochrane Database Syst Rev. 2012; 12(12): CD009017.
6. Hamidi M, Zamanzad B, Mesripour A. Comparing the effect of clofibrate and phenobarbital on the newborns with hyperbilirubinemia. Excli J. 2013; 12:75-8.
7. Eghbalian F, Pourhossein A, Zandevakili H. Effect of clofibrate in non-hemolytic indirect hyperbilirubinemia in full term neonates. Indian J Pediatr. 2007; 74(11):1003-6.
8. Kumar P, Adhisivam B, Bhat BV. Clofibrate as an adjunct to phototherapy for unconjugated hyperbilirubinemia in term neonates. Indian J Pediatr. 2017; 84(10):763-7.
9. Fallah R, Islami Z, Lotfi SR. Single dose of 50 mg/kg clofibrate in jaundice of healthy term neonates: randomised clinical trial of efficacy and safety. Indian J Pediatr. 2012; 79(2):194-7.
10. Eghbalian F, Monsef F, Alam Ghomi N, Monsef A. Effect of low versus moderate dose of clofibrate on serum bilirubin in healthy term neonates with indirect hyperbilirubinemia. Iran J Med Sci. 2013; 38(4):349-50.
11. Zahed Pasha Y, Alizadeh-Tabari S, Zahed Pasha E, Zamani M. Etiology and therapeutic management of neonatal jaundice in Iran: a systematic review and meta-analysis. World J Pediatr. 2020; 16(5):480-93.
12. Lindenbaum A, Delaporte B, Benattar C, Dehan M, Magny JF, Gerbet D, et al. Preventive treatment of jaundice in premature newborn infants with clofibrate. Double-blind controlled therapeutic trial. Arch Fr Pediatr. 1985; 42(9):759-63.