The Effect of Clofibrate and Phototherapy on Prolonged Jaundice due to Breast Milk in Full-Term Neonates

Clinical Medicine Insights: Pediatrics
Volume 17: 1–4
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DOI: 10.1177/11795565231177987

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ABSTRACT

INTRODUCTION: Jaundice is one of the most common problems during infancy. It is believed that breast milk jaundice is one of the reasons for the persistence of jaundice after 14 days of prolonged jaundice. This study evaluates the effect of Clofibrate and phototherapy on prolonged jaundice originating from breast milk in term and healthy neonates.

MATERIALS AND METHODS: This double-blind clinical trial study was performed on 100 randomly divided neonates in the neonatal ward of Besat Hospital. In addition to phototherapy, the case group received a single dose of edible Clofibrate (50 mg/kg) dissolved in 2 CCs of distilled water. The control group received the same amount of distilled water as the phototherapy group. After treatment, bilirubin change rate, duration of hospitalization, and any association with gender, gestational age, hemoglobin, blood type, and Rh of neonates were determined and compared throughout the 2 groups.

RESULTS: Data analysis showed that the bilirubin reduction rate was statistically significantly higher in the case group than in the control group ($P < .05$). The mean duration of hospitalization and phototherapy in the case group was significantly lower than in the control group ($P = .005$). The bilirubin reduction rate was not affected significantly by gestational age, blood type, or Rh.

CONCLUSION: This study's results demonstrated that Clofibrate effectively decreased bilirubin levels and shortened the duration of phototherapy and hospitalization in infants with probable breast milk jaundice.

REGISTRATION: IRCT2012092910933N1

KEYWORDS: Prolonged, jaundice, neonatal, hyperbilirubinemia, Clofibrate

RECEIVED: March 12, 2022. **ACCEPTED:** May 5, 2023.

TYPE ORIGINAL RESEARCH

FUNDING: The author(s) disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: This study was partly supported by grant 9306182867 from Hamadan University of Medical Sciences.

COMPETING INTERESTS: The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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Introduction

Hyperbilirubinemia is one of the most common and typically causes benign problems in neonates.[1] Bilirubin is one of the biliary pigments obtained from the breakdown of hemoglobin that is conjugated by the liver. In the indirect hyperbilirubinemia condition, unconjugated bilirubin increases.[1-3] Stable indirect hyperbilirubinemia after the second week of birth is called prolonged Jaundice.Som of the causes of prolonged jaundice is urinary tract infection, hypothyroidism, intestinal obstruction, hemolysis, Crigler-Najjar, galactosemia, and breast milk jaundice. The cause of breast milk jaundice is the presence of glucuronidase in some mothers' milk.[1-4]

When the pathological causes of Prolonged Jaundice are ruled out, breast milk jaundice is believed to be the primary cause of Prolonged Jaundice. Twelve percent of breastfeeding neonates develop indirect hyperbilirubinemia beginning late in the first week; hyperbilirubinemia forms following physiological jaundice. A maximum concentration of 10 to 30 mg/dl in the second and third weeks persists. If breastfeeding continues, bilirubin may rise for about 3 months and then gradually reduce. The exact cause is unknown; some researchers feel that the cause of breast milk jaundice may be glucuronidase of breast milk.

There are several approaches to treating prolonged breast milk jaundice.[1,2] One recommended treatment is discontinuing breastfeeding for 48 hours and using alternate milk, which may lead to the mother permanently stopping breastfeeding.

Regardless of the origin of the acquisition of jaundice, the objective of treatment is to prevent indirect bilirubin concentration from to cause neurotoxicity (kernicterus). Phototherapy has been the standard treatment for hyperbilirubinemia for the last 4 decades. Blood transfusions are also applicable in severe jaundice individuals, in which phototherapy is ineffective.[1,2] Although phototherapy and blood transfusions have been considered the most critical suggested treatments for hyperbilirubinemia, recent advances have allotted drug therapy as a viable alternative. Regarding the enzymatic mechanisms for bilirubin uptake and excretion, pharmaceuticals such as phenobarbital, oral charcoal, D-penicillamine, metalloporphyrin, and Clofibrate have been shown to be effective. However, their use

in the treatment or prevention of jaundice has not yet been confirmed. Furthermore, additional investigation is needed.[3-11] Drugs with various mechanisms of action, similar to the ones previously stated, have been used for the following purposes: (1) stimulation of enzymes to increase conjugation such as phenobarbital and nicotinamide, (2) bilirubin reuptake block in substances such as active charcoal and cholestyramine, (3) inhibition of bilirubin production that can be observed in elements such as copper, zinc, and metalloporphyrin compounds.[12-14]

Clofibrate activates peroxisome proliferator-activated receptors (PPARs) that lower cholesterol and triglycerides.[6,7] Additionally, Clofibrate stimulates glucuronyl transferase, thus causing an increase in bilirubin conjugation along with its excretion. Administration of Clofibrate along with phototherapy shortens the duration of jaundice.

The prescription of Clofibrate as an anti-lipidemic drug in adults is associated with nausea and diarrhea. However, a 100 mg/kg dosage in neonates with non-hemolytic jaundice was not associated with any side effects.[6] Studies have shown that the impact of Clofibrate in low and medium doses effectively reduces neonatal jaundice. Just saw increasing the amount did not help significantly.[7] Administration of this drug at maximum dosage (100 mg/kg), while administered at the beginning of hospitalization, has the most favorable therapeutic effect that can be achieved with negligible adverse effects.[5,6,8-10]

The recent studies on Clofibrate administration as an adjunct to phototherapy for prolonged jaundice caused by breast milk were limited due to a lack of trials from different geological regions and a lack of data on mortality of kernicterus and long-term safety.

Therefore, the present study aimed to evaluate the effect of Clofibrate on reducing total serum bilirubin (TSB) and prolonged jaundice caused by breast milk.

Methodology

The study was a double-blind clinical trial in the framework of a research project approved by the Vice-Chancellor of Research and Technology of Hamadan University of Medical Sciences with project number 9306182867. The study was conducted for 2 years on 100 term infants over 14 days old, weighing 4000 to 2500 g, who were admitted to the neonatal ward of Besat Hospital in the city of Hamedan due to prolonged jaundice (December 2013 to December 2015). The study included healthy-term neonates with 14 days of jaundice and indirect bilirubin reading higher than 10 mg who were exclusively breastfed.

Individuals excluded from the study are as follows: (1) Those who received phenobarbital and/or traditional herbal medicine; (2) Those who had clinical and laboratory evidence in favor of liver disease, hemolysis, a direct bilirubin value greater than 1.5 mg/dl, positive culture, the presence of reducing substances in ruin, and a TSH value higher than 5, electrolyte disturbance, a high bilirubin value is leading to blood transfusion, and formula feeding. The neonates were randomly divided into 2 groups of 50. After receiving written consent from the neonates' legal guardian, the experimental case group received a single dose of edible Clofibrate (50 mg/kg) dissolved in 2 CCs of distilled water combined with phototherapy (the devices available in Iran deliver 4 lamps from above to the baby). In addition to phototherapy, the control group received the same amount of distilled water as the experimental group.

In both groups, total and indirect bilirubin were measured on admission as well as at 12 and 36 hours later. After treatment, bilirubin change rate, duration of hospitalization, and relationship to gender, gestational age, hemoglobin, blood type, and Rh of neonates in the 2 groups were determined and compared. Serum bilirubin was measured with the Technica RA1000 device. A phototherapy device constructed by Parsa company with 5 specific blue lamps ranging from 450 to 420 nm wavelengths was placed 30 cm above all of the neonates; all subject neonates were checked for jaundice, general condition, and possible complications of Clofibrate such as diarrhea or dehydration up to 72 hours after discharge in Besat Hospital's outpatient clinic. Data were analyzed by SPSS software, version 19. A paired *t*-test was constructed in both the control and experimental group to compare the differences in bilirubin concentration at 0, 12, and 36 hours. To compare a Mann-Whitney test was used to calculate the mean total bilirubin between the 2 groups was compared at 0, 12, 36 hours. The *P*-value was $<.5$; therefore, there was considerable significance found. We have de-identified the details such that the identity of the patient may not be ascertained in any way.

Results

Total serum bilirubin levels were determined at 0, 12, and 36 hours after phototherapy was begun and were 18.13, 15.27, and 11.65 mg/dl in the control group and were 19.49, 14.34, and 8. 51 mg/dl in the case group. Data analysis depicted that the bilirubin reduction rate was significantly increased in the case group than in the control group ($P<.05$) (Table 1).

The mean duration of hospitalization and phototherapy in the control group was 2.37 ± 0.77 days, while in case group,[2] it was 1.75 ± 0.52 days. The decision to discharge the patients was made by the research doctor according to Nelson Texts icteric neonatal discharge protocol. The mean hospitalization duration and phototherapy in the case group were significantly lower than in the control group (005/0 = *P*).

It was found that there was no statistically significant difference between the 2 groups in terms of age and gender, distribution of type of delivery, and hemoglobin level ($P>.05$), and ($P=0/427$). A comparison of the 2 groups in terms of blood type and Rh showed that the 2 groups were similar ($P=0/753$ and $P=0/806$). Comparing bilirubin reduction in the control and case groups based on gestational age, blood

Table 1. Mean, minimum, and maximum bilirubin levels in 0, 12, and 36 hours after phototherapy in control and case neonates.

P VALUE	HOUR 36 (MG/DL)	HOUR 12 (MG/DL)	ON ADMISSION (HOUR 0, MG/DL)	GROUP	
<.05	8	12.2	14.2	Min	Control
<.05	16.9	20.5	24.2	Max	
<.05	11.64	15.27	18.13	Mean	
<.05	4.1	8.4	14.8	Min	Case
<.05	16.7	22.4	26.2	Max	
<.05	8.51	14.34	19.49	mean	

type, and Rh showed that these factors did not play an influential role in reducing bilirubin and did not significantly affect test results.

No side effects from Clofibrate were reported in patients during hospitalization and 72 hours after discharge.

Out of 100 neonates in the 2 treatment groups, 49 neonates were boys (male) and 51 were girls (female). In the control group (50 neonates), the ratio of boys to girls was 26 to 24, and in the case group, it was 23 to 27, which was determined by data analysis using the Chi-Square test. The distribution of gender frequency of patients in the 2 groups was not different, and there was no statistically significant difference ($P < .05$) (Table 2).

Table 2. Distribution of gender frequency of neonates admitted to Besat Hospital in the city of Hamadan due to prolonged neonatal jaundice.

CASE	CONTROL	GROUP / GENDER
23, 46.9%	26, 50.1%	M
27, 52.9%	24, 47.1%	F

Discussion

The study evaluated a high dose of Clofibrate with phototherapy effect on prolonged breast milk jaundice in term and healthy neonates. In the present study, there was no significant difference between age, gender, type of delivery, hemoglobin level, and mean total bilirubin at baseline between study groups. Additionally, comparing the 2 groups in terms of blood type and Rh showed similarities in the 2 study groups. These factors indicate the appropriate match of the designed study groups.

The study indicated that the bilirubin reduction rate was statistically and significantly higher in the case group compared to the control group. In other words, and compared to placebo, Clofibrate further decreased bilirubin levels in prolonged jaundice. This finding is consistent with similar studies.

The mean length of hospital stay and duration of phototherapy in the case group was significantly lower than in the control group. This finding is consistent with similar studies.[5-7]

Few studies have been performed on the effect of Clofibrate on prolonged breast milk jaundice. For example, Pasha et al conducted a survey on 56 term neonates with prolonged breast milk jaundice at the University of Babol. The mean plasma total bilirubin levels at 12th, 24th, and 48th hours of treatment were significantly lower in the Clofibrate-treated group as compared with the control group, along with a shorter duration of jaundice and decreased need of phototherapy. The results of this study is in agreement with our study, demonstrating that Clofibrate can significantly reduce serum bilirubin level. In the present study, 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 to 100 mg/kg of Clofibrate was well tolerated with no side effects

In a study by Eghbalian et al,[6] to evaluate the therapeutic effects of Clofibrate in non-hemolytic indirect jaundice of term neonates, the control group received only phototherapy, and the case group received a single dose of 100 mg/kg edible Clofibrate with phototherapy. The total and indirect bilirubin reduction rate in neonates receiving Clofibrate with phototherapy was statistically and significantly higher than in patients who only received phototherapy.

Another study conducted by Eghbalian et al sought to investigate the effect of low (25 mg/kg) and moderate (50 mg/kg) Clofibrate doses in reducing bilirubin in term and healthy neonates confirmed the effectiveness of edible Clofibrate in neonates bilirubin reduction. Since there is no difference in low or moderate dose of edible Clofibrate in reducing bilirubin, duration of phototherapy, and hospitalization, the use of lower doses of the drug to prevent possible side effects has been suggested.[7,13]

In the study conducted by Mohammadzadeh et al,[8] the case group received 1 dose of edible Clofibrate at the beginning of phototherapy, and the control group was treated only with

phototherapy. The results indicated that total serum bilirubin at 12, 24, and 48 hours in the case group was significantly lower than in the control group, similar to the present study.

In the Gabilan study, in France, Clofibrate (50 mg/kg) was given as a single edible dose to 47 neonates. In contrast, the other 46 neonates only received phototherapy. It was observed that the severity and duration of jaundice decreased in the Clofibrate group.[14]

Bourget et al,[15] who studied the pharmacological effects of Clofibrate in neonates, concluded that a single dose of this drug is an appropriate method of treating neonatal jaundice.[15]

In comparison to other studies, we found that Clofibrate is an effective drug in reducing bilirubin levels and can be used in cases of prolonged jaundice that is seen in a significant percentage of breastfed infants.

Contrary to what many believe, breast milk jaundice treatment is to stop breastfeeding for 1 to 2 days and to use formula milk; use of Clofibrate in neonates with breast milk jaundice may prevent unnecessary stoppage of breast milk and decrease the incidence of early discontinuation of breastfeeding in these infants.

Due to its edibility, ease of use, and absence of side effects proven in this study, this drug can be recommended in prolonged breast milk jaundice cases. Although, the large-scale use of Clofibrate in prolonged jaundice requires more prominent and more robust studies.

Conclusion

This study's results demonstrated that Clofibrate effectively decreased bilirubin levels and shortened the duration of phototherapy and hospitalization in infants with probable breast milk jaundice.

This eliminated the need to stop breast milk use in these infants temporarily

Because the number of cases in this study is too low to give a certainty level using Clofibrate as an effective treatment for jaundice.

Suppose these results are replicated in larger studies. In that case, it could be an effective, powerful tool to both promote breastfeeding and prevent prolonged jaundice and its possible sequel.

Limitations of the Study

The small number of patients is a major limitation. The number of cases in this study is too small to provide a level of certainty regarding the use of Clofibrate as an effective treatment for jaundice.

Declarations

Ethics approval and consent to participate

This study was approved by the Institutional Review Board of Hamadan University of Medical Sciences (پ/16/35/9/4113) and was performed in accordance with the principles of the Declaration of Helsinki. All parents of the infants provided a written informed consent for study participation. The study was registered at Iranian Registry of Clinical Trials with the code IRCT2012092910933N1.

Consent for publication

Not applicable.

Author contribution(s)

FE: Writing—original draft; RR: Writing—original draft; JF: Data curation and methodology; AA: Supervision.

Acknowledgements

The authors would like to thank the Vice-Chancellor of Research and Technology at the Medical Sciences University of Hamadan and Dr. Javad Fardmal for cooperating in conducting this research.

This article was extracted from the MD thesis of Mr Amin Asgharzadeh, which was approved by the Research Council of Hamadan University of Medical Sciences Hamadan at this university (Thesis COD : 9306182867).

Availability of data and materials

Not applicable.

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