Effect of clofibrate on reducing neonatal jaundice: a systematic review and meta-analysis

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ABSTRACT

In neonates, bilirubin tends to be deposited in body tissues, especially the skin and mucous membranes. Jaundice is an early symptom of bilirubin excretion disorders. Therefore, the aim of this study was to investigate the effect of clofibrate on reducing neonatal jaundice. In this systematic review, international databases, including PubMed, Scopus, Web of Science, Embase, Cochrane, and Google Scholar, were searched without time and language restrictions. The reference lists of all studies ultimately included were manually searched. In the 17 articles reviewed, with a sample size of 665 people published between 2005 and 2019, the average weight of the neonates varied from 2,186 g to 4,000 g. Furthermore, the average age of neonates varied from 2 days to 9 days. Four doses of clofibrate (25, 30, 50, 100 mg/kg of neonatal body weight) were used. The bilirubin level of neonates significantly decreased in the intervention group 24, 36, 48, and 72 hours after the start of treatment. Clofibrate administration decreased total serum bilirubin, especially from the second day onwards, and also reduced hospitalization time, hospital costs, and side effects from hospitalization.

Keywords: Clofibrate; Hyperbilirubinemia; Jaundice; Neonatal jaundice

Introduction

Bilirubin is a compound produced by the catabolism of hemoglobin that tends to be deposited in the body tissues of neonates, especially the skin and mucous membranes. Jaundice is an early symptom of bilirubin excretion disorders. If bilirubin is not excreted from the body in time, it will reside in the brain tissue and cause temporary and permanent neurological disorders by damaging the brainstem, in a condition known as kernicterus [1]. Elevated bilirubin levels (hyperbilirubinemia) are among the most common disorders in infancy.
Clofibrate is an activator of peroxisome proliferator-activated receptors (PPARs) that effectively lowers cholesterol and triglyceride levels in adults. It also induces glucuronyl transferase and causes the accumulation and excretion of bilirubin. Some studies have also suggested reducing neonates’ need for phototherapy and shortening their hospitalization course [11,17–21]. Clofibrate is a practical drug recommended for the treatment of neonatal hyperbilirubinemia. Research results have shown that clofibrate effectively reduces neonatal jaundice, with an effect appearing 24 hours after treatment [16,19–21]. A single dose of 50 mg/kg of clofibrate to treat neonatal hyperbilirubinemia shortens the hospitalization course, which is also economically advantageous [6]. Clofibrate may have short-term benefits for neonates with hyperbilirubinemia, especially for term neonates and neonates without hemolytic diseases [19–22]. Clofibrate results in a faster reduction of total serum bilirubin (TSB) and a shorter hospitalization course, and no side effects have been observed in full-term neonates with jaundice [7,16,19–21].

A recent Cochrane review on clofibrate administration as an adjunct to phototherapy for neonatal unconjugated hyperbilirubinemia was limited due to a high degree of heterogeneity among the trials, a lack of trials from different geographical regions, and a lack of data on mortality from kernicterus and long-term safety [23]. Therefore, the present study aimed to evaluate the effect of clofibrate on the reduction of TSB and neonatal jaundice.

Materials and Methods

Study Protocol
This systematic review and meta-analysis investigated the effect of clofibrate on reducing neonatal jaundice. This study was written based on the PRISMA protocol for systematic review and meta-analysis studies.

Statistical Population
Studies in which neonates were treated with clofibrate to reduce their blood bilirubin levels in addition to phototherapy were evaluated. In selecting these people, no restrictions were imposed on sex, age, race, and weight at birth.

Study Outcome
The main outcome considered was a reduction in bilirubin levels.

Search Strategy
In this systematic review, the international databases, including PubMed, Scopus, Web of Science, Embase, Cochrane, and Google Scholar, were searched without time and language restrictions. If an article was published in a language other than English, the full text of the article was translated into Persian to extract the relevant information. The search was performed using the standard keywords “jaundice,” “icterus,” “hyperbilirubinemia,” “neonatal,” “infant,” “clofibrate,” “meta-analysis,” and “systematic review,” as well as their equivalent MeSH terms (updated through May 15, 2021). Their compounds were also searched in the abovementioned databases using the (AND, OR) operators. The reference lists of all studies that were ultimately included were also manually searched. Table 1 shows the search strategy in some databases and Table 2 presents the results for the evaluation of quality of studies [1,2,6–8,11,12,16–18,23–29].
Inclusion and Exclusion Criteria

PICO (patient, intervention, comparison, outcome) components
The study population was all neonates who received clofibrate to reduce bilirubin levels in addition to phototherapy. The intervention was clofibrate administration. The comparison was neonates who used placebo in addition to phototherapy or received no treatment other than phototherapy. The study outcome was bilirubin.

Inclusion criteria for preliminary studies
In this meta-analysis, the preliminary studies included randomized clinical trials with or without blinding. The intervention groups in the included trials were neonates who had received clofibrate in addition to phototherapy, and the control groups received no intervention or placebo.

Exclusion criteria
Exclusion criteria included failure to report the required information, case reports, low-quality studies based on the Cochrane Institute’s clinical quality assessment checklist, lack of access to the full texts of studies, studies examining the effect of clofibrate on neonatal jaundice based on measurements of bilirubin levels in the umbilical cord of neonates, and those investigating the effect of clofibrate combined with another drug on neonatal jaundice.

Quality evaluation of studies
After identifying the initial studies, 2 authors independently evaluated all the initial studies using the Cochrane Institute’s clinical quality assessment checklist. This checklist includes 7 items, each evaluating 1 of the dimensions or types of essential biases in clinical trials. Each item in this checklist has 3 options: a high risk of bias, a low risk of bias, and unclear. After completing the bias risk assessment in all

Table 1. Search strategy in selected databases

| Database     | Search strategy                                                                                                                                 |
|--------------|-----------------------------------------------------------------------------------------------------------------------------------------------|
| Scopus       | (TITLE-ABS-KEY (Clofibrate) AND TITLE-ABS-KEY (hyperbilirubinemia OR jaundice) AND TITLE-ABS-KEY (infant OR neonatal))                       |
| PubMed       | (((Clofibrate [Title/Abstract]) AND (Hyperbilirubinemia [Title/Abstract] OR Jaundice [Title/Abstract])) AND (Infant [Title/Abstract] OR neonatal [Title/Abstract])) |
| Web of Science | You searched for: TOPIC: (Clofibrate AND TOPIC: (Hyperbilirubinemia OR Jaundice) AND TOPIC: (Infant OR neonatal)                              |
| Cochrane     | Clofibrate in Title Abstract Keyword AND Hyperbilirubinemia OR Jaundice in Title Abstract Keyword AND Infant OR neonatal in Title Abstract Keyword |

Table 2. Quality evaluation of studies

| Study                  | Q1 | Q2 | Q3 | Q4 | Q5 | Q6 | Q7          |
|------------------------|----|----|----|----|----|----|-------------|
| Ahadi et al. [2]       | Low| Low| Low| Low| Low| High| Unclear     |
| Gholami et al. [25]    | Low| High| Low| Low| Low| Low| Low         |
| Mahyar et al. [12]     | Low| Low| Low| Low| Low| Low| Low         |
| Kumar et al. [23]      | Low| Low| Low| Low| Unclear| Low| Low         |
| NouriShadkam et al. [18]| Low| Low| Low| Low| Low| Low| Low         |
| Fallah et al. [6]      | Low| Low| Low| Low| Unclear| Low| Low         |
| Habibi et al. [16]     | Low| Low| Low| High| Low| Low| Low         |
| Alosy [24]             | High| Low| Low| Low| Low| Low| Low         |
| Kandharkar [27]        | High| Low| Low| Low| Low| Low| Low         |
| Sakha et al. [26]      | Low| Low| Low| Low| Low| Low| Low         |
| Zahedpasha et al. [7]  | Low| Low| Unclear| High| Low| Low| Low         |
| Moslehi and Pishva [17]| Low| High| Low| Low| Low| Low| Low         |
| Badeli et al. [1]      | Low| Low| Low| Unclear| Low| Low| Low         |
| Zahedpasha et al. [28] | Low| Unclear| Low| Low| High| Low| Low         |
| Sharafi et al. [8]     | Low| Low| Low| Unclear| Low| Low| Low         |
| Mohammadzadeh et al. [29]| Low| Unclear| Low| Low| Low| Low| High         |
| Mohammadzadeh et al. [11]| Low| High| Low| Low| Low| Low| High         |

Q1, random sequence generation; Q2, allocation concealment; Q3, blinding of participants; Q4, Blinding of outcome assessment; Q5, incomplete outcome data; Q6, selective reporting; Q7, anything else, ideally prespecified.
studies, disagreements about the item options in each study were evaluated and resolved through consensus. Table 2 shows the quality evaluation of studies.

**Data Extraction**
Two researchers independently extracted data from studies to minimize reporting bias and data collection errors. The researchers entered the extracted data onto a checklist, including the first author’s name, the year of study publication, study title, the number of samples, the mean and standard deviation of neonatal bilirubin levels before and after the intervention, age, sex, and neonatal weight, clofibrate dosage, and follow-up duration. A third researcher reviewed the data extracted by the 2 previous researchers to correct any discrepancies. If the required data were not reported in an article, a request for the data was sent through correspondence with the article’s author.

**Statistical Analysis**
Due to the quantitative nature of the outcome of interest, the effect size of the intervention was calculated based on the mean difference in serum bilirubin levels before and after the intervention compared to the mean difference outside the experimental group.

Data from studies were combined for the meta-analysis according to the number of samples, mean, and standard deviation. In order to evaluate the heterogeneity of the studies, the Cochrane Q test and the $I^2$ index were used. Since a fixed-effects model is used when heterogeneity is low and a stochastic-effects model is used when a high degree of heterogeneity is present, the present study used a stochastic-effects model. Data analysis was performed using Stata ver. 14.0 (StataCorp., College Station, TX, USA). A $p$-value $<0.05$ was considered to indicate statistical significance.

**Results**
Initially, 980 articles were found in the above databases. After reviewing the titles, 385 duplicate studies were excluded. The remaining 595 abstracts were reviewed, and 487 articles were eliminated according to the exclusion criteria. Ninety-one of the remaining 108 articles were removed due to incomplete information or the lack of a full text. Finally, the remaining 17 articles entered the quality evaluation stage; all of these articles were deemed to be of good quality and included in the meta-analysis. Figure 1 presents a flow chart of the inclusion of studies in the systematic review and meta-analysis.

**Characteristics of Studies Included in the Systematic Review**
Table 3 presents information on the articles entered into the systematic review and meta-analysis. In the 17 articles reviewed, with a sample size of 665 people published between 2005 and 2019, the average weight of the neonates varied from 2,186 g to 4,000 g. The average age of the neonates ranged from 2.09 days to 9.8 days. Four doses of clofibrate (25, 30, 50, 100 mg/kg of neonatal body weight) were used in the studies. All studies were conducted in Iraq, Iran, and India. Table 3 shows the characteristics of studies included in this systematic review [1,2,6–8,11,12,16–18,23–29].

Since the study phases were different (6, 12, 16, 24, 36, 48, and 72 hours after the intervention), we could not conduct a subgroup analysis based on clofibrate dose, age, weight, or the countries studied.

Figure 2 shows a comparison of neonatal bilirubin levels between the control and case groups before the intervention. There was no statistically significant difference between the control and case groups with respect to the mean scores of neonatal bilirubin levels. No statistically significant difference was observed between both groups in terms of neonatal bilirubin levels 6 hours after the intervention.

Figure 3 shows a comparison of neonatal bilirubin levels between both groups 12 hours after the intervention. Clofibrate use significantly decreased the
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Table 3. Characteristics of the studies included in the systematic review

| Study | Year of publication | Type of study | Country | Sample size | Age (d) | Dosage of clofibrate (mg/kg) | Weight (kg) | No. of girls | No. of boys | No. of intervention and 4.86 at 72 hours after the intervention in 36 hours after the intervention, 4.01 at 48 hours after the intervention, 1.81 at 24 hours after the intervention, 3.88 at 12 hours after the intervention, 2.79 at 16 hours after the intervention, and by 1.81 at 16 hours after the intervention. Two days after treatment, the neonatal bilirubin levels in the intervention group significantly decreased by 3.88 compared to the beginning of the study, and by 36 hours after the intervention, a significant decrease (by 4.01) in neonatal bilirubin levels was observed in the intervention group. By 48 hours, the neonatal bilirubin levels in the intervention group significantly decreased by 4.86 compared to before clofibrate consumption, and a 3.87 decrease was observed at 72 hours. In all phases, neonatal bilirubin levels decreased significantly in the intervention group compared to before the intervention.

Discussion

No statistically significant difference was observed between the control and intervention groups with respect to the mean neonatal TSB values before the intervention. Until 6 and 12 hours after the intervention, neonatal TSB levels decreased in both groups, without statistically significant between-group differences.

Twelve hours after the intervention, neonatal TSB levels in the intervention group were 0.71 lower than those in the control group, which was not a statistically significant difference. The neonatal TSB levels in the intervention group were 0.54, 1.20, 2.39, 1.52, and 0.71 lower than those in the control group at 16, 18, 24, 36, 48, and 72 hours after the intervention, respectively, and these differences were statistically significant.

The mean TSB level was significantly decreased by 1.64 at 12 hours after the intervention, 2.79 at 16 hours after the intervention, 1.81 at 24 hours after the intervention, 3.88 at 36 hours after the intervention, 4.01 at 48 hours after the intervention and 4.86 at 72 hours after the intervention.
the intervention group. The neonatal TSB levels significantly decreased in the intervention group in all phases compared to before the intervention.

The results reported by Caballero-Noguez et al. [30] regarding changes in total and indirect bilirubin levels in 2 groups (phenobarbital and clofibrate) compared to the control group showed that TSB levels significantly decreased 24 and 72 hours after the intervention. Alosy [24] showed that 12 hours, 24 hours, and 4 days after the intervention, TSB levels decreased in the clofibrate group and the control group, but this drop was more significant in the clofibrate group, which is consistent with our study. This may be due to the effect of clofibrate on enhancing glucuronyl transferase activity, as a result of which clofibrate raises hepatic bilirubin clearance in 6 hours. Unlike sodium phenobarbital, clofibrate does not cause sleepiness or respiratory depression. It also
| Author (year of publication) | Effect (95% CI) | Weight |
|-----------------------------|-----------------|--------|
| Ahadi A (2013)              | −1.25 (−1.81, −0.70) | 6.32   |
| Mahyar A (2019)             | −0.38 (−1.01, 0.24)  | 6.19   |
| Kumar P (2017)              | −1.88 (−2.38, −1.38) | 6.41   |
| NouriShadkam M (2016)       | 0.13 (−0.34, 0.59)   | 6.46   |
| Fallah R (2012)             | −1.95 (−2.56, −1.33) | 6.21   |
| Habibi M (2012)             | −0.67 (−1.23, −0.11) | 6.31   |
| Alosy BD (2017)             | −0.37 (−0.65, −0.09) | 6.67   |
| Sakha SH (2009)             | −0.18 (−0.66, 0.29)  | 6.44   |
| Zahedpasha Y (2007)         | −0.43 (−0.94, 0.08)  | 6.38   |
| Moslehi MA (2007)           | −4.35 (−5.29, −3.41) | 5.57   |
| Moslehi MA (2007)           | −4.77 (−5.78, −3.77) | 5.43   |
| Badel HR (2008)             | −1.89 (−2.39, −1.39) | 6.40   |
| Zahedpasha Y (2008)         | −0.30 (−0.93, 0.32)  | 6.20   |
| Sharafi R (2010)            | −1.05 (−1.59, −0.51) | 6.34   |
| Mohammadzadeh A (2009)      | 0.52 (0.00, 1.03)    | 6.38   |
| Mohammadzadeh A (2005)      | −1.34 (−1.90, −0.78) | 6.30   |
| Overall, DL (I²=93.6%, p=0.000) | −1.20 (−1.72, −0.68) | 100.00 |

**Figure 4.** Comparison of neonatal bilirubin levels between both groups 24 hours after the intervention. Weights are from random-effects model.

CI, confidence interval; DL, DerSimonian-Laird.

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| Author (year of publication) | Effect (95% CI) | Weight |
|-----------------------------|-----------------|--------|
| Mahyar A (2019)             | −0.10 (−0.72, 0.52)  | 8.34   |
| Kumar P (2017)              | −4.43 (−5.21, −3.66) | 8.07   |
| NouriShadkam M (2016)       | −0.53 (−1.00, 0.06)  | 8.56   |
| Fallah R (2012)             | −2.07 (−2.70, −1.44) | 8.32   |
| Habibi M (2012)             | −1.10 (−1.68, −0.51) | 8.40   |
| Kandharkar V (2019)         | −4.07 (−4.94, −3.21) | 7.89   |
| Sakha SH (2009)             | −1.30 (−1.82, −0.77) | 8.49   |
| Zahedpasha Y (2007)         | −0.56 (−1.08, −0.04) | 8.50   |
| Zahedpasha Y (2008)         | −0.54 (−1.17, 0.09)  | 8.32   |
| Sharafi R (2010)            | −2.84 (−3.56, −2.11) | 8.17   |
| Mohammadzadeh A (2009)      | 0.28 (−0.22, 0.79)  | 5.51   |
| Mohammadzadeh A (2005)      | −1.30 (−1.85, −0.74) | 8.44   |
| Overall, DL (I²=94.5%, p=0.000) | −1.52 (−2.25, −0.79) | 100.00 |

**Figure 5.** Comparison of neonatal bilirubin levels between both groups 48 hours after the intervention. Weights are from random-effects model.

CI, confidence interval; DL, DerSimonian-Laird.

Results in liver bilirubin clearance [16]. Fallah et al. [6] showed that 12 and 48 hours after the intervention, 27 neonates in the clofibrate group (90%) and 15 neonates in the control group (56.7%) had TSB levels less than 14 mg/dL (p = 0.02). The mean length of hospitalization (mean ± standard deviation: 1.7 ± 0.7 days vs. 1.2 ± 3.2 days, p = 0.03) and the duration of phototherapy (mean ± standard deviation: 30.2 ± 13.99 hours vs. 46.2 ± 58.5 hours; p = 0.001) were significantly lower in the clofibrate group. Loose stool was only observed in 2 clofibrate patients. There was no significant difference in the safety of the treatments, and they showed that a dose of 50 mg/kg of clofibrate was effective in treating neonatal jaundice.
hyperbilirubinemia and reducing hospitalization duration and cost.

TSB levels in the clofibrate group and phototherapy at 12, 24, 36, and 48 hours after the intervention were significantly lower than those in the phototherapy group. Significantly less phototherapy was needed in the clofibrate group than in the phototherapy-only group [1,19].

Long-term administration of clofibrate in adults has several side effects, such as nausea and vomiting, loose stool, muscle cramps, and pruritus; however, no such effects have been reported in neonates who receive high doses of clofibrate [1,11,25].

Studies have shown that both clofibrate and phenobarbital reduce TSB levels in a single dose, but phenobarbital is more effective; therefore, phenobarbital reduces TSB levels more rapidly than clofibrate, thereby reducing hospitalization time and costs [24].

Studies have shown that in addition to reducing TSB levels, clofibrate also shortens the duration of phototherapy. Clofibrate may have short-term benefits in full-term infants who do not have a hemolytic disease; however, long-term follow-up is required to evaluate its safety and long-term effects. At present, there is no evidence suggesting that clofibrate can alter the likelihood of death and kernicterus [25].

Habibi et al. [16] showed that clofibrate reduced TSB 24 hours after administration, while in other studies, it was effective 12 and 16 hours after clofibrate administration. Clofibrate activates PPARs and regulates plasma lipid levels by lowering very-low-density lipoproteins. The drug is absorbed from the gastrointestinal tract and rapidly hydrolyzed to an active metabolite (clofibric acid). This active metabolite is ultimately excreted through urine as conjugated glucuronide. Sakha et al. [26] also showed that clofibrate is an effective supplementary drug in neonatal hyperbilirubinemia, leading to a decrease in TSB levels and a reduction in the phototherapy duration in full-term and premature neonates. Kumar et al. [23] and Kandharkar [27] observed that clofibrate administration significantly reduced serum TSB levels at 48 hours after the intervention. Mahyar et al. [12] showed that purgative manna and clofibrate did not reduce TSB levels in unconjugated hyperbilirubinemia neonates, which is inconsistent with our study and previous studies.

Eghbalian et al. [31] showed that the prescription of 25 mg/kg clofibrate as a single dose, just as the dose of 50 mg/kg as a single dose, could significantly reduce serum bilirubin levels. These researchers recommended using a low dose of clofibrate to treat neonatal unconjugated hyperbilirubinemia.

Gholitabar et al. [32] argued that the existing data have been insufficient to absolutely confirm the effect of clofibrate on neonatal jaundice, and more studies are needed to be conducted on this issue. Clofibrate is an available drug that can effectively treat neonatal hyperbilirubinemia without any side effects. However, the general administration of this drug in high-risk neonates, such as premature infants and those with hemolytic jaundice should be further investigated [11].

Moslehi and Pishva [17] showed no statistically significant difference between a low dose (25 mg/kg) and a moderate dose (50 mg/kg) of clofibrate. Six hours after clofibrate administration, indirect TSB levels decreased compared with the control group. Clofibrate also reduces the need for phototherapy in healthy individuals. NouriShadkam et al. [18] showed that clofibrate was ineffective on TSB on the first day, but on the second day, it was effective in decreasing TSB. Eghbalian et al. [21] reported that clofibrate was an effective supplementary drug in neonatal hyperbilirubinemia, leading to decreased TSB levels and a shortened phototherapy duration in premature neonates. Sharafi et al. [8] showed that clofibrate was effective for outpatients with neonatal hyperbilirubinemia undergoing phototherapy at home.

Conclusion

According to the results of this study, administration of clofibrate decreased TSB, especially from the second day onwards, and also reduced hospitalization time, hospital costs, and hospitalization-associated complications.

Larger randomized controlled trials (complying with all principles of study design) along with longer follow-up and consideration of hemolytic diseases and blood transfusion are needed to further elucidate this issue.

The reviewed studies showed that doses of 25–100 mg/kg and short-term administration of clofibrate did not lead to any complications during the treatment and follow-up periods. Lipids and unconjugated bilirubin can conjoin with each other and bind to albumin. Therefore, changes in bilirubin levels must be adjusted with consideration of alterations in the lipid profile. In this regard, lipids are among the most important macronutrients, playing necessary roles in cell growth and development in newborns; therefore, the long-term administration of clofibrate could impair organ development and growth.

In the reviewed studies, complications were mostly evaluated by clinical observations, which could be considered as a limitation of clinical studies. Thus, it is recommended to perform laboratory tests and biochemistry examinations (according to the side effects) in future studies to obtain more useful results.
Limitations of the Study
The full text of some studies was not available, and some information required for data analysis was incomplete.

Notes

Ethics Approval
This study was approved by the Institutional Review Board of Hamadan University of Medical Sciences (IR.UMSHA.REC. 1400.364) and performed in accordance with the principles of the Declaration of Helsinki. The requirement for informed consent was waived because of the retrospective nature of this study.

Conflicts of Interest
The authors have no conflicts of interest to declare.

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None.

Availability of Data
All data generated or analyzed during this study are included in this published article. Other data may be requested through the corresponding author.

Authors’ Contributions
Conceptualization: RR; Data curation: FE; Formal analysis: RR; Investigation: AHD; Methodology: RR; Project administration: RR; Resources: FE; Software: Conceptualization: RR; Data curation: FE; Formal analysis: RR; Methodology: RR; Project administration: RR; Resources: FE; Writing-original draft: RR; Writing-review & editing: all authors.

Additional Contributions
Lotfollah Karimi (Hamedan University of Technology, Hamedan, Iran) provided statistical support.

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