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Review Article

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

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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,

observed in 60% of infants, of whom 10% have the severe form for which treatment is needed [2]. The rate of hyperbilirubinemia in premature neonates is 80% [3], and neonatal jaundice is observed in up to 85% of all live births. If there is no hemolysis, sepsis, trauma at birth, or prematurity, it usually resolves within 3 to 5 days without significant complications. However, evidence suggests that severe neonatal jaundice (SNJ) leads to substantial morbidity and mortality. SNJ is also an important cause of neurological disorders and other long-term consequences, including cerebral palsy, non-syndromic auditory neuropathy, deafness, and learning difficulties. A recent report by Slusher et al. [4] noted that at least 481,000 term/near-term neonates are affected by SNJ/hyperbilirubinemia each year, of whom 114,000 die and more than 63,000 survive with kernicterus. In the USA, jaundice is seen in 15.6% of hospitalized neonates. The incidence of SNJ is 667.8 per 10,000 live births in Africa and 3.7 per 10,000 live births in Europe [5]. Although this disorder generally resolves, an appropriate intervention to avoid bilirubin neurotoxicity should be seriously considered [6]. There are 3 ways to treat hyperbilirubinemia: phototherapy, blood transfusion, and medication. The most common of these methods is phototherapy, and transfusion of the baby's blood in conditions of excessive bilirubin [7–10]. Although blood transfusion is one of the main treatments for hyperbilirubinemia, it has some side effects [11,12]. These detrimental side effects suggest that an alternative drug treatment strategy should be developed to address this disorder. Drug interventions include D-penicillamine, phenobarbital, clofibrate, bile salts, metalloporphyrins, laxatives, and bilirubin oxidases [6,13–15]. Clofibrate is a glucuronosyltransferase inducer suggested to reduce bilirubin levels in neonates with hyperbilirubinemia [16–21]. 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].

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	High
Kumar et al. [23]	Low	Low	Low	Low	Unclear	Low	Low
NouriShadkam et al. [18]	Low	Low	Low	Low	Low	Low	Unclear
Fallah et al. [6]	Low	Low	Low	Unclear	Low	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	High
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	High	Low
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.

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

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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.

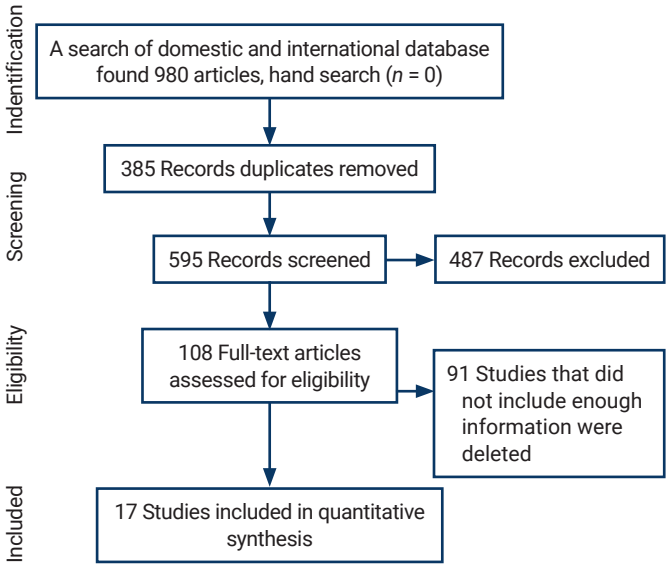

Figure 1. Flow chart of the inclusion of studies in the systematic review and meta-analysis.

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 conducted 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. Neonatal bilirubin levels in the intervention group were 0.71 mg/dL lower than those in controls, but the difference was not statistically significant. Figure 4 shows a comparison of neonatal bilirubin levels between both groups 24 hours after the intervention. Clofibrate use significantly decreased the

Table 3. Characteristics of the studies included in the systematic review

Study	Year of publication	Type of study	Country	Sample size	No. of girls	No. of boys	Age (d)	Weight (kg)	Dosage of clofibrate (mg/kg)
Ahadi et al. [2]	2013	Double-blind clinical trial	Iran	30	16	14	2.09	2.5–4	100
Gholami et al. [25]	2019	Randomized controlled clinical trial	Iran	30			4.45	3.193–3.460	50
Gholami et al. [25]	2019	Randomized controlled clinical trial	Iran	30			4.45	3.193–3.460	100
Mahyar et al. [12]	2019	Randomized clinical trial	Iran	20	11	9	5	3.196	30
Kumar et al. [23]	2017	Randomized controlled trial	India	45	24	21	4	2.760	50
NouriShadkam et al. [18]	2016	Double-blind randomized clinical trial	Iran	41	21	20	6.41	3.490	100
Fallah et al. [6]	2012	Parallel single-blind randomized clinical trial	Iran	30	14	16	4.73	3.202	50
Habibi et al. [16]	2012	Single-blind clinical trial	Iran	26	11	15	3.31	3.057	100
Alosy [24]	2017	Case-control study	Iraq	100					100
Kandharkar [27]	2019	Randomized controlled trial	India	32	16	16	3.1	2.845	100
Sakha et al. [26]	2009	Double-blind, placebo-controlled, randomized trial	Iran	35	15	20	6.2	2.330	100
Zahedpasha et al. [7]	2007	Randomized clinical trial	Iran	30	16	14	5.67	3.083–3.300	100
Moslehi and Pishva [17]	2007	Clinical randomized controlled trial	Iran	30	13	17	5.25	2.564	25
Moslehi and Pishva [17]	2007	Clinical randomized controlled trial	Iran	30	16	14	5.18	2.525	50
Badeli et al. [1]	2008	Clinical trial	Iran	45	19	26	5	3.190	100
Zahedpasha et al. [28]	2008	Randomized clinical trial	Iran	21			5.81	3.195–5.200	100
Sharafi et al. [8]	2010	Clinical trial	Iran	30	18	12	6.8	3.107	50
Mohammadzadeh et al. [29]	2009	Randomized double-blind placebo-controlled trial	Iran	30	18	12	8.7	2.186	100
Mohammadzadeh et al. [11]	2005	Clinical controlled study	Iran	30	10	20	9.8	3.257	100

neonatal bilirubin levels in the intervention group by 1.20 mg/dL compared to the control group. A significant difference was observed between the control and intervention groups with respect to the mean neonatal bilirubin levels. The neonatal bilirubin levels in the intervention group were 2.39 mg/dL lower than those in the control group.

Figure 5 shows a comparison of neonatal bilirubin levels between both groups 48 hours after the intervention. Neonatal bilirubin levels in the intervention group were 1.52 mg/dL lower than those of the control group, and this difference was statistically significant. At 72 hours after the intervention, neonatal bilirubin levels in the intervention group were 0.75 mg/dL lower than those in the control group, but this difference was not statistically significant.

Neonatal bilirubin levels in the intervention group significantly decreased by 1.64 at 6 hours after the intervention, by 2.79 at 12 hours after the intervention, and by 1.81 at 16 hours after 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 in

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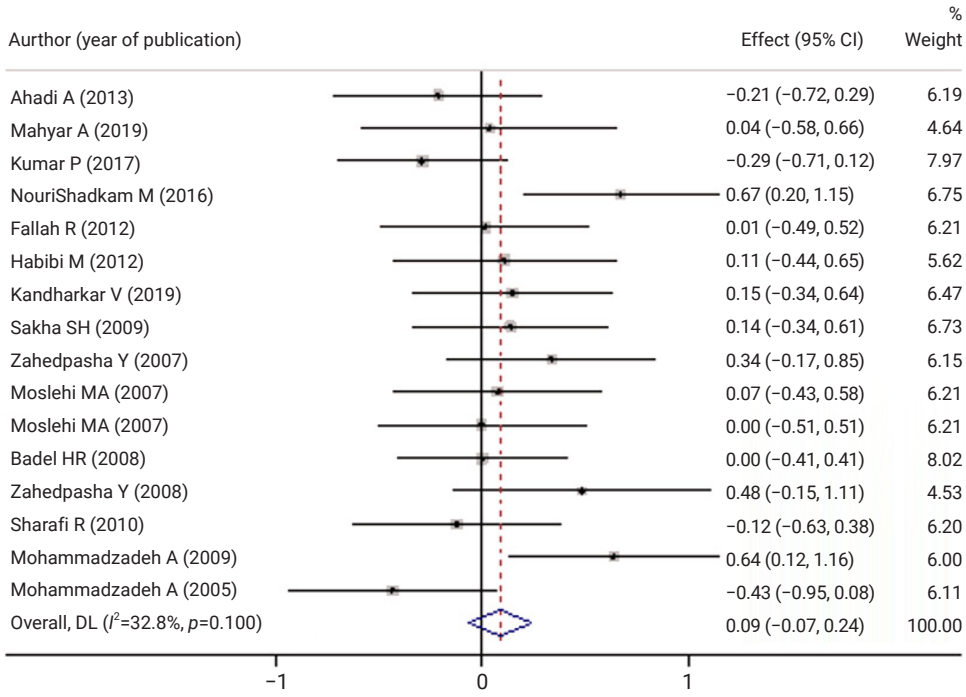

Figure 2. Comparison of neonatal bilirubin levels between the control and case groups before the intervention. Weights are from random-effects model.
CI, confidence interval; DL, DerSimonian-Laird.

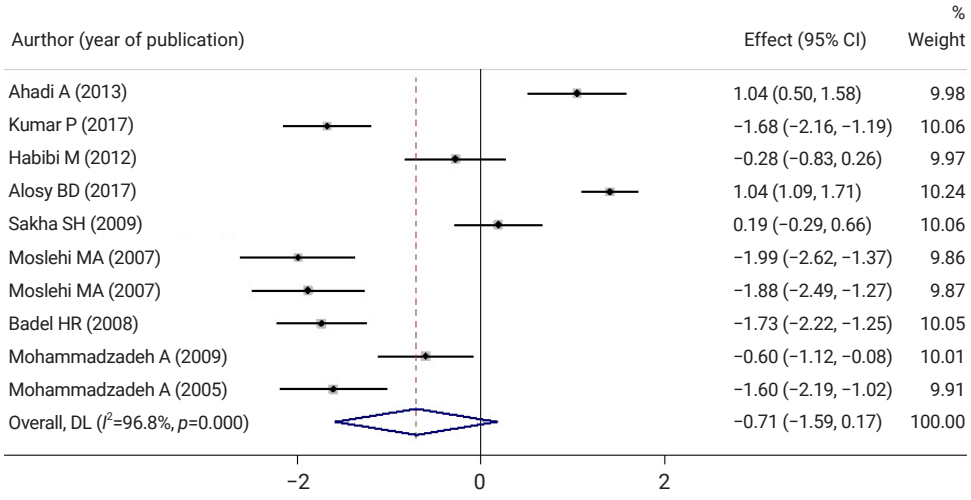

Figure 3. Comparison of neonatal bilirubin levels between both groups 12 hours after the intervention. Weights are from random-effects model.
CI, confidence interval; DL, DerSimonian-Laird.

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

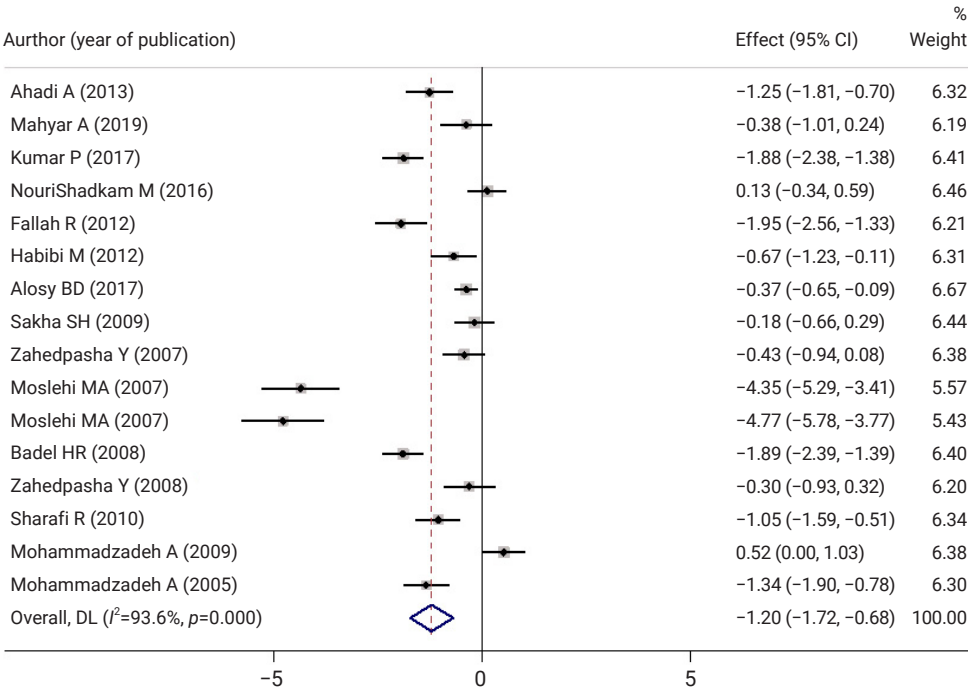

Figure 4. Comparison of neonatal bilirubin levels between both groups 24 hours after the intervention. Weights are from random-effects model.
CI, confidence interval; DL, DerSimonian-Laird.

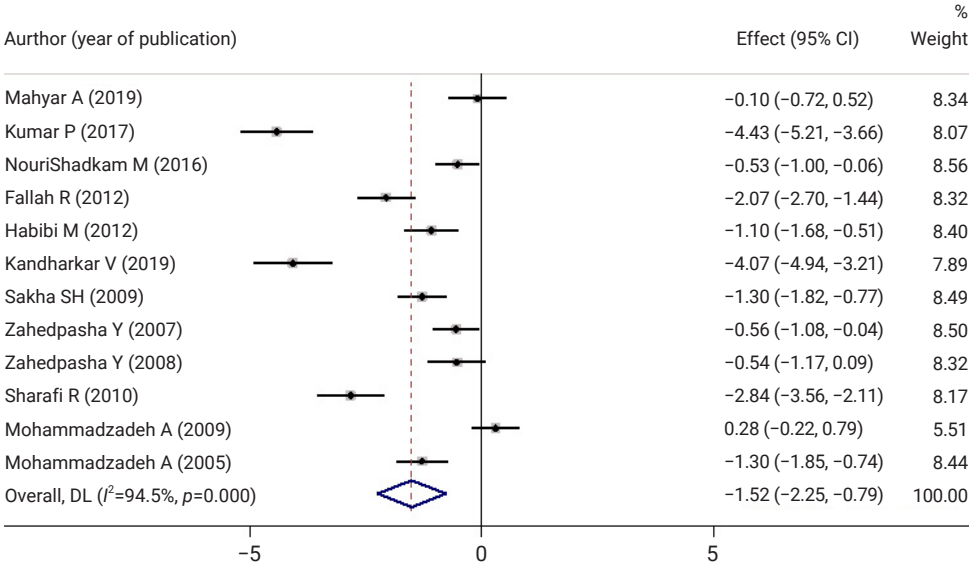

Figure 5. Comparison of neonatal bilirubin levels between both groups 48 hours after the intervention. Weights are from random-effects model.
CI, confidence interval; DL, DerSimonian-Laird.

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

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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 neonate. 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.

Funding

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: LK; Supervision: RR; Validation: LK; Visualization: HB; 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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