IJN
Iranian Journal of Neonatology
http://ijn.mums.ac.ir

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Systematic Review

Effect of Fenofibrate on Neonatal Hyperbilirubinemia: A Systematic Review and Meta-analysis

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ABSTRACT

Background: Jaundice is one of the most common neonatal complications. Therefore, promptly diagnosing and treating it is vital. This study aimed to determine the effect of Fenofibrate and phototherapy compared to the phototherapy alone on total serum bilirubin (TSB) at 24 and 48 h (primary outcome) and side effects (secondary outcome).

Methods: English (Cochrane Library, Web of Science, Medline, CINAHL, PsycINFO, PubMed, and Google Scholar) and Persian (SID and Magiran) databases were searched using verified keywords (MeSH library) without time constraint. The risk of bias was assessed using the Cochrane Handbook. RevMan software (version 5.3) was used for meta-analysis and the mean difference was calculated as effect size. In heterogeneous cases, the random effect was reported instead of the fixed one.

Results: The total number of studies found in all databases was 5482. Six articles were included in the present study. The results of the meta-analysis showed no statistically significant difference in TSB levels within 24 (Mean difference: -5.56; 95% Confidence Interval (95% CI): 4.53 to -16.05; P = 0.27) and 48 h (-4.77; 2.57 to -12.10; P= 0.20) between Fenofibrate with phototherapy group and the phototherapy alone group. No side effects have been reported in included studies.

Conclusion: Although the results of the five studies showed the significant effect of Fenofibrate as adjuvant therapy on reducing TSB level, the meta-analysis failed to show the same result in the study groups. It is recommended to perform more trials following all principles of randomized controlled trials to find an effective treatment for hyperbilirubinemia.

Keywords: Fenofibrate, Jaundice, Neonatal hyperbilirubinemia

Introduction

Neonatal jaundice or icterus was discovered years ago which refers to a bilirubin level > 5 mg/dL. The term kernicterus was first introduced in 1900 (1). Neonatal jaundice is very common among term infants. Sixty percent of term infants and 80% of preterm infants develop jaundice, which usually appears one week after birth. The normal bilirubin level of the umbilical cord is 1-3 mg/dL, which increases to 5-6 mg/dL on the second to fourth days after birth and decreases to less than 2 mg/dL on the 5th to 7th days after birth (2).

Hyperbilirubinemia is caused by an accumulation of bilirubin in the blood due to increased degradation of red blood cells and decreased excretion of unconjugated bilirubin (3). Normally, circulating red blood cells are destroyed and heme moiety is converted to the water-soluble form of bilirubin and excreted in the intestine through the bile. Neonates cannot convert the red blood cell bilirubin to a soluble form and excrete it from the body. Therefore, unconjugated bilirubin accumulates in the skin and mucous membranes and causes

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Please cite this paper as:
Zamiri-Miandoab N, Montazeri R, Hassanpour SH, Mirghafourvand M. Effect of Fenofibrate on Neonatal Hyperbilirubinemia: A Systematic Review and Meta-analysis. Iranian Journal of Neonatology. 2021 Jul: 12(3). DOI: 10.22038/ijn.2021.53483.1977

hyperbilirubinemia (4).

Various studies have shown that risk factors for hyperbilirubinemia include low birth weight, breastfeeding, neonatal infection, premature rupture of membrane, male gender, East Asian race, and bleeding during the first trimester of pregnancy. Linn et al. indicated that administration of oxytocin and epidural anesthesia during labor do not affect the incidence of hyperbilirubinemia (5). There are two main categories of direct and indirect hyperbilirubinemia in infants. Indirect hyperbilirubinemia is dangerous and can cause kernicterus. Indirect hyperbilirubinemia leads to ABO and Rh incompatibility, sepsis, breast milk, hypothyroidism, deficiency of a particular enzyme (e.g., glucose-6-phosphate dehydrogenase [G6PD], Gilbert's syndrome, and hypertrophic pyloric stenosis (6). Conjugated or direct hyperbilirubinemia occurs when more than 20% of total bilirubin or 2 mg/dL is conjugated two weeks after birth (7).

Assessment of blood bilirubin level, CBC, maternal and infant RH and blood type, blood glucose, and G6PD or G6PDH levels, blood and urine cultures, and direct Coombs test are essential in neonates with jaundice (8). Visual inspection (touching the infant's skin and assessing skin color) is one of the simplest ways to diagnose neonatal jaundice; however, it is not enough (9). Bilirubin level should be measured in all infants with jaundice using a transcutaneous bilirubin meter, which is a non-invasive method in infants with a gestational age of > 35 weeks within 24 h after birth. Serum bilirubin level can be measured in cases that transcutaneous bilirubin is not measurable. Serum bilirubin level should be measured if the TCB level > 250μMOL/L. TSB can also be measured in premature infants with gestational age < 35 weeks and less than 24 h after birth (10).

Several methods are used to treat hyperbilirubinemia. Phototherapy is a non-pharmacological method for treating hyperbilirubinemia. However, it has some side effects such as retinal damage, bronze baby syndrome, and loose stools (11). Probiotics were also used to treat jaundice. Deshmukh et al. in a systematic review showed that probiotics reduced the duration of phototherapy; however, they could not significantly reduce the incidence of jaundice (12).

Drugs such as phenobarbitone, Metalloprphyrins, D-penicillamine, and Gemfibrozil have been used to treat hyperbilirubinemia; however, they are not very effective and safe. Newer drugs (e.g., Fenofibrate and Clofibrate) have also been used to treat hyperbilirubinemia. Fibrates induce bilirubin conjugation more effectively, and converts unconjugated bilirubin to conjugated one, and increase its clearance by activating Glucuronosyltransferase (13). Researchers have also assessed the effect of Fenofibrate on neonatal jaundice in several studies; however, no systematic evidence was found. The research team decided to conduct a systematic study regarding the effect of Fenofibrate on total serum bilirubin due to the increasing prevalence of jaundice (2) and its complications (14).

Methods

Eligibility Criteria

All Persian and English articles on the effect of Fenofibrate on neonatal hyperbilirubinemia were included in this study. The PICO referred to participants (neonates with hyperbilirubinemia), intervention (Fenofibrate with phototherapy), comparison group (receiving placebo with phototherapy or phototherapy alone), and outcome (measuring TSB at 24 and 48 h as the primary outcome and side effects as secondary outcome). Finally, six randomized controlled trials were included. We excluded other types of studies, such as case-control studies. Two authors independently conducted the searching and resource review process. Inclusion criteria included neonates with gestational age > 35 weeks with symptoms of neonatal hyperbilirubinemia, TSB > 15 mg/dl, and healthy in other respects. Infants with underlying diseases who received any medication were excluded from the study.

Information Sources

In this review paper, English (Cochrane Library, Web of Science, Medline, CINAHL, PsycINFO, PubMed, Google Scholar) and Persian (SID, MagIran) databases were searched using verified keywords (Mesh library) without time constraint. Both single-database and cross-database search techniques were used to ensure that all keywords were searched.

Search Strategy

The authors searched English and Persian databases using approved keywords (MeSH library). Keywords Hyperbilirubinemia, neonatal hyperbilirubinemia, and jaundice were searched through the databases. No systematic study was found on the effect of Fenofibrate on neonatal hyperbilirubinemia.

For instance, the search strategy for PubMed was as following:

(((((("fenofibrate") OR AND ("hyperbilirubinemia" OR)) OR ("hyperbilirubinemia, neonatal" OR ("hyperbilirubinemia" AND "neonatal") OR "neonatal hyperbilirubinemia" OR ("hyperbilirubinemia, hereditary" OR "hyperbilirubinemia, hereditary")) OR ("jaundice, chronic idiopathic" OR ("jaundice" AND "chronic" AND "idiopathic") OR "chronic idiopathic jaundice" OR ("jaundice" AND "chronic" AND "idiopathic") OR "jaundice, chronic idiopathic")) AND ("jaundice, neonatal" OR ("jaundice" AND "neonatal") OR ("neonatal "AND "jaundice)).

Data Collection Process

Two authors independently extracted data on study design, sample size, inclusion criteria, type of intervention, outcomes, and results (Table 1). The length of stay, the time of administration of Fenofibrate, the duration of phototherapy, and the time of the effect of Fenofibrate were also assessed.

Table 1. Characteristics of included studies

Kumar et al. 2012 [13]		
Country	India	
Study design	Randomized Controlled Trial	
Sample size	40	
Study population	Term neonates	
Intervention /treatment	10 mg/kg Fenofibrate with phototherapy	
Comparator	Phototherapy without Fenofibrate	
Outcomes	Total Serum Bilirubin (TSB) level, duration of phototherapy, and length of stay	
Results	Decrease of the TSB level, duration of phototherapy, and hospital stay.	
	Risk of bias table	
Item	Authors' judgment	Support for judgment
Random sequence generation (selection bias)	Low risk	Neonates were randomly allocated into two groups; however, the method was not mentioned.
Allocation concealment (selection bias)	Unclear risk	No specific information has been given regarding allocation concealment.
Blinding of participants and staff (performance bias)	Unclear risk	No specific information has been given regarding the blinding of participants and staff.
Blinding of outcome assessment (detection bias)	Unclear risk	No specific information has been given regarding assessor blinding.
Incomplete outcome data (attrition bias)	Low risk	All participants completed the study.
Selective reporting (reporting bias)	Low risk	It seems that all the outcomes have been reported.
Gowda et al. 2014 [16]		
Country	India	
Study design	Prospective study	
Sample size	100	
Study population	Infants weighing more than 2000 g and TSB level between 15 to 25 mg%.	
Intervention /treatment	5 mg/kg Fenofibrate with phototherapy	
Comparator	Phototherapy without Fenofibrate	
Outcomes	TSB level	
Results	There was no significant difference between groups.	
	Risk of bias table	
Item	Authors' judgment	Support for judgment
Random sequence generation (selection bias)	High risk	No randomization method has been used for random sequence generation.
Allocation concealment (selection bias)	High risk	There was no evidence for allocation concealment.
Blinding of participants and staff (performance bias)	High risk	There was no evidence for blinding of participants and staff.
Blinding of outcome assessment (detection bias)	High risk	There was no evidence for blinding of the outcome assessor.
Incomplete outcome data (attrition bias)	Low risk	All participants have been followed up.
Selective reporting (reporting bias)	Low risk	The protocol is unavailable; however, it seems that all outcomes have been reported.
Al-Asy et al. 2015 [17]		
Country	Egypt	
Study design	Randomized Controlled Trial	
Sample size	60	
Study population	1- 6 days old term infants weighing 2500- 3500 g with symptoms of hyperbilirubinemia and TSB 15-20.	
Intervention /treatment	10 mg/kg Fenofibrate with phototherapy	
Comparator	Phototherapy without Fenofibrate	
Outcomes	Length of stay, TSB level	
Results	Reduction of hospital stay and TSB level in the intervention group compared to that of the control group.	
	Risk of bias table	
Item	Authors' judgment	Support for judgment
Random sequence generation (selection bias)	Low risk	The newborns have been randomly allocated into two groups; however, the method was not mentioned.
Allocation concealment (selection bias)	Unclear risk	No specific information has been given regarding allocation concealment.
Blinding of participants and staff (performance bias)	Unclear risk	No specific information has been given regarding the blinding of participants and staff.

Table 1. Continued

Blinding of outcome assessment (detection bias)	Unclear risk	No specific information has been given regarding assessor blinding.
Incomplete outcome data (attrition bias)	Low risk	All participants completed the study.
Selective reporting (reporting bias)	Low risk	The protocol is unavailable; however, it seems that all outcomes have been reported.
Chaudhary et al. 2016 [20]		
Country	India	
Study design	Randomized Controlled Trial	
Sample size	50	
Study population	The term neonates weighing 1500-3500 g with jaundice on days 3-11 and TSB 15-21.	
Intervention /treatment	10 mg/kg Fenofibrate with phototherapy	
Comparator	The control group received a placebo (glucose solution) and phototherapy.	
Outcomes	Duration of phototherapy and TSB level.	
Results	Decrease the duration of phototherapy and TSB level.	
Risk of bias table		
Item	Authors' judgment	Support for judgment
Random sequence generation (selection bias)	Low risk	The computer program of random tables has been used for random allocation.
Allocation concealment (selection bias)	Unclear risk	No specific information has been given regarding allocation concealment.
Blinding of participants and personnel (performance bias)	Low risk	It is a double-blind study.
Blinding of outcome assessment (detection bias)	Low risk	It is a double-blind study.
Incomplete outcome data (attrition bias)	Low risk	The study reported that two participants were excluded.
Selective reporting (reporting bias)	Low risk	It seems that all of the outcomes have been reported.
Dabour et al. 2016 [19]		
Country	Egypt	
Study design	Randomized Controlled Trial	
Sample size	40	
Study population	Full-term neonate with indirect hyperbilirubinemia admitted to the NICU	
Intervention /treatment	10 mg/kg Fenofibrate with phototherapy	
Comparator	Phototherapy without Fenofibrate	
Outcomes	Length of stay, TSB level	
Results	Decrease of hospital stay and TSB level in the intervention group compared to that of the control group.	
Risk of bias table		
Item	Authors' judgment	Support for judgment
Random sequence generation (selection bias)	Low risk	Neonates were randomly allocated into two groups; however, the method was not mentioned.
Allocation concealment (selection bias)	Unclear risk	No specific information has been given regarding allocation concealment.
Blinding of participants and staff (performance bias)	Unclear risk	No specific information has been given regarding the blinding of participants and personnel.
Blinding of outcome assessment (detection bias)	Unclear risk	No specific information has been given regarding assessor blinding.
Incomplete outcome data (attrition bias)	Low risk	All neonates have been followed up.
Selective reporting (reporting bias)	Low risk	It seems that all of the outcomes have been reported.
Ahmadpour et al. 2018 [18]		
Country	Iran	
Study design	Randomized Controlled Trial	
Sample size	80	
Study population	Infants with TSB up to 15	
Intervention /treatment	10 mg/kg Fenofibrate with phototherapy	
Comparator	Phototherapy without Fenofibrate	
Outcomes	TSB serum level	
Results	Decrease of TSB serum level in the intervention group compared to that of the control group.	
Risk of bias table		
Item	Authors' judgment	Support for judgment
Random sequence generation (selection bias)	Low risk	A random number table has been used for random sequence generation.
Allocation concealment(selection bias)	Unclear risk	No specific information has been given regarding allocation concealment.
Blinding of participants and staff (performance bias)	Unclear risk	No specific information has been given regarding the blinding of participants and staff.
Blinding of outcome assessment (detection bias)	Unclear risk	No specific information has been given regarding assessor blinding.
Incomplete outcome data (attrition bias)	Low risk	All participants completed the study.
Selective reporting (reporting bias)	Low risk	All outcomes have been reported.

Risk of Bias Across Studies

The risk of bias was assessed using the Cochrane Handbook. The authors independently determined the risk of bias. Any disagreement was resolved through consultation with a third party. The risk of bias was assessed according to six criteria (randomization, allocation concealment, blinding of participants, blinding of the assessor, incomplete outcome data, and selective reporting) in each study (Figures 2 and 3). Graphical or statistical methods were not used to determine the publication bias due to the number of included studies was less than 10 in the meta-analysis (15).

Statistical Analysis

RevMan software (version 5.3) was used to demonstrate the risk of bias plot in the meta-analysis. The authors were contacted but they did not respond since standard deviation was not reported in two studies after the intervention and there was no additional data including standard error or 95% confidence interval to calculate the standard deviation (16, 17). Meta-analysis was performed on four studies and the mean difference was calculated as the effect size. The heterogeneity of the studies was evaluated based on I^2 and the random effect was reported instead of the fixed effect in heterogeneous cases.

Results

Study Selection

The total number of studies found in all databases was 5482. Seven studies were inserted in this paper by reviewing the titles of all found articles. One article was excluded after reviewing the method because it was a case-control study. Finally, six randomized controlled trials were included in the present study (Figure 1)

Characteristics of Included Study

One study was conducted in Iran (18), two studies in Egypt (17, 19), and three studies in India (13, 16, 20). The minimum number of participants was 40 (13, 19) and the maximum was 100 (16). Glucose solution was used as a placebo in the control group only in one study (20). The control group received routine care (phototherapy) in the rest of the studies. The dose of Fenofibrate was 10 mg/kg in intervention groups of all studies except that of Chaudhary et al. (5 mg/kg). TSB > 15 mg was one of the inclusion criteria in all studies except one (19).

Risk of Biases

The randomization method was not mentioned in the studies by Al-Asy et al. (16) and Gowda et al. (16). No study has mentioned allocation concealment. Only Chaudhary et al. (19) used the blinded experiment. Gowda et al. (16), Dabour et al. (19), and Al-Asy et al. (17) failed to report accurate sample loss. No bias was reported in any of the studies (Figures 2 and 3; Table1).

Results of Included Study

Ahmadpour *et al.* (18) evaluated the efficacy of oral Fenofibrate on TSB in 80 neonates with hyperbilirubinemia. The results of this study revealed that administrating oral Fenofibrate with phototherapy reduced serum bilirubin level as well as the duration of phototherapy and hospitalization.

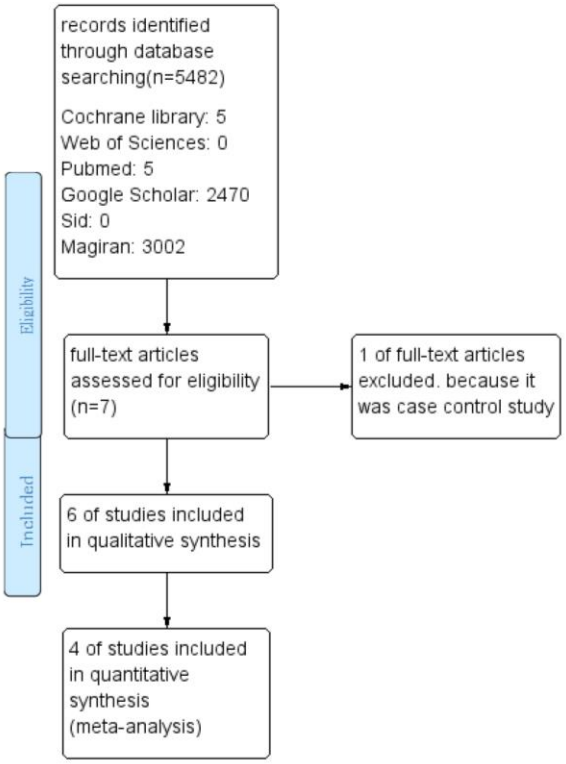

Figure 1. PRISMA flowchart for the study screening and

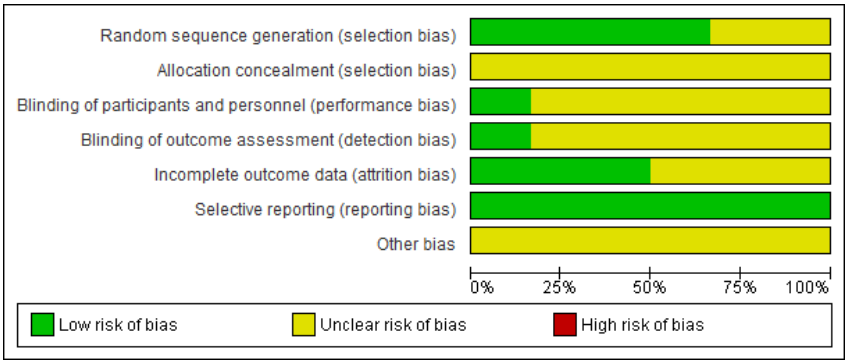

Figure 2. Risk of bias graph: Authors' judgments about each case of risk of bias presented as a percentage across all included studies

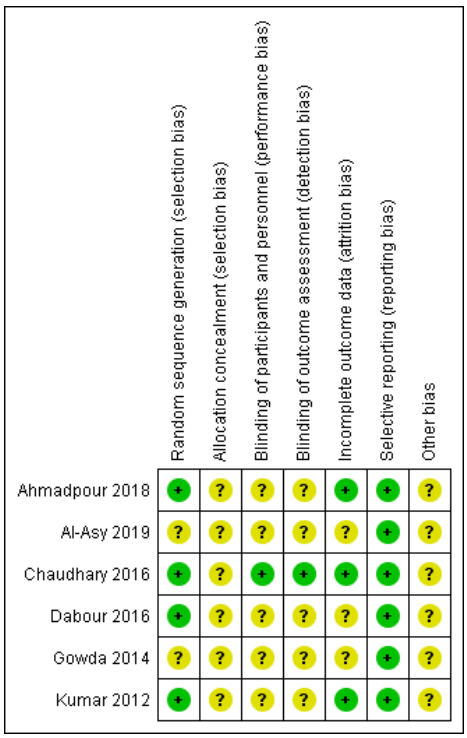

Figure 3. Risk of bias summary: Authors' judgments about each case of risk of bias for each included study

Kumar et al. (13) assessed the effect of Fenofibrate on the duration of phototherapy and hospitalization in 40 neonates with hyperbilirubinemia. The mean TSB level in the intervention group was significantly lower than in the control group. No side effect of Fenofibrate was reported in the intervention group. The results of this study showed that Fenofibrate reduced the duration of phototherapy and hospitalization.

Chaudhary et al. (20) estimated the effect of Fenofibrate on neonatal hyperbilirubinemia. Serum bilirubin level was significantly lower than the intervention group. Phototherapy duration was shorter in the Fenofibrate group than in the control group. No side effects were reported. The results showed that oral Fenofibrate reduced serum bilirubin level and duration of phototherapy in neonates with hyperbilirubinemia. The results showed that Fenofibrate is a safe and effective drug.

Al-Asy et al. (17) evaluated the effect of Fenofibrate on indirect hyperbilirubinemia in infants admitted to the NICU of Tanta University Hospital. The results of this study showed that TSB level and length of stay were lower in the intervention group than in the control group. Phototherapy with Fenofibrate reduced the level of conjugated bilirubin. Fenofibrate was also reported to be cost-effective with no side effects.

Gowda *et al.* (16) evaluated the effect of 5 mg/kg oral Fenofibrate on non-conjugated Hyperbilirubinemia in a prospective study at a hospital in India. The results showed that Fenofibrate failed to reduce bilirubin levels.

Dabour *et al.* (19) assessed the effect of Fenofibrate on the control of indirect hyperbilirubinemia in infants. The results of this study showed that Fenofibrate combined with phototherapy was effective in reducing the length of stay and bilirubin levels.

Of six reviewed studies, Gowda *et al.* found out that Fenofibrate was ineffective. However, they prescribed 10 mg/kg Fenofibrate compared to 5 mg/kg in the other five studies.

Meta-analysis Results

The results of the meta-analysis showed no statistically significant difference between Fenofibrate with phototherapy group and the control group in TSB levels within 24 h (Mean difference (MD): -5.56; 95% confidence interval (95% CI): 4.53 to -16.05 with a high level of heterogeneity (I^2=100%, P= 0.27) and 48 h (MD: -4.77; 95% CI: 2.57 to -12.10), with a high level of Heterogeneity (I^2=100%, P= 0.20) after birth. The studies by Al-Asy et al. and Gowda et al. were excluded from the meta-analysis because they did not report a standard deviation, although an email was sent to both authors (Figures 4 and 5).

Quality of Evidence

GRADE approach (Grading of Recommendations Assessment, Development, and Evaluation) (15)

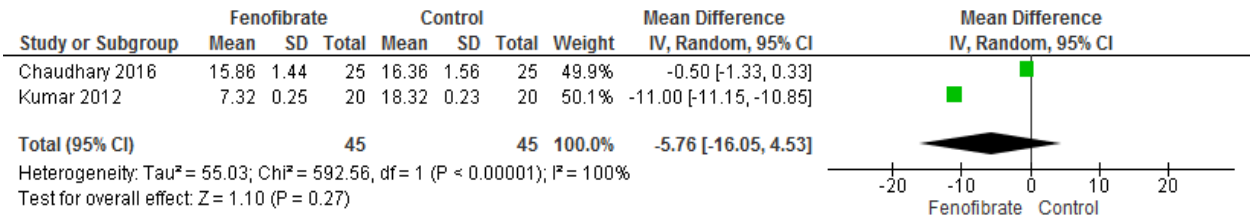

Figure 4. Forest plot of comparison: Effect of Fenofibrate versus control on TSB after 24 hours

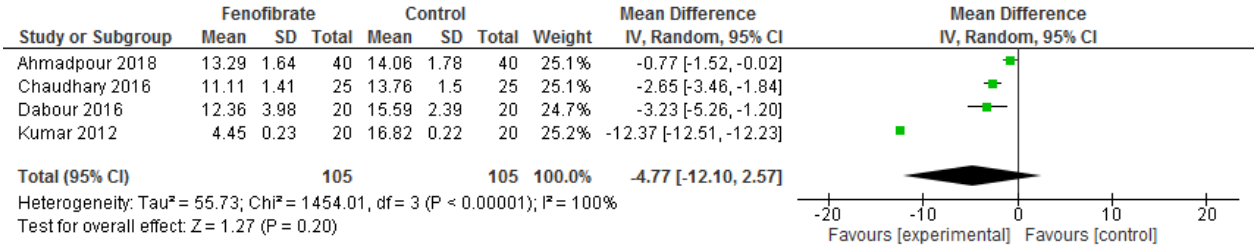

Figure 5. Forest plot of comparison: Effect of Fenofibrate versus control on TSB after 48 hours

Table 2. Fenofibrate and phototherapy compared to the phototherapy alone on total serum bilirubin (TSB)

No. of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Fenofibrate and phototherapy	Phototherapy alone	Pooled effect size (95% CI)	Final judgment
TSB after 24 hours										
2	Randomized trials	No Serious	Very serious inconsistency*	No serious indirectness	Very Serious imprecision**	No serious	12.06/45	17.16/45	-5.76 (-16.05 to 4.53)	⨁◯◯◯ Very low
TSB after 48 hours										
4	Randomized trials	No Serious	Very serious inconsistency*	No serious indirectness	Very Serious imprecision**	No serious	10.91/105	14.8/105	-4.77 (-12.10 to 2.57)	⨁◯◯◯ Very low

* I^2 is higher than 50%, ** Not met optimal information size/ CI is very wide

was applied to determine the quality of evidence. The evidence level decreased due to high heterogeneity, relatively small sample size, and was used to evaluate the quality of the evidence. The level of evidence has decreased due to high heterogeneity, lack of optimal information size, and wide confidence intervals (Table 2).

Discussion

Treatment should begin after a definitive diagnosis of neonatal jaundice, however there is a big difference between time and treatment methods (8). One of the most effective treatments for neonatal jaundice is phototherapy, which is started based on gestational age and risk factors. Some neonates need a wide variety of treatments based on gender, gestational age, and delivery time (21). Very few pharmacological interventions are used to clinically treat neonatal jaundice (22). The effect of Fenofibrate as adjuvant therapy on neonatal jaundice was investigated in this study.

Although out of six reviewed studies, the results of the five studies showed the effect of Fenofibrate on reducing serum bilirubin level, the results of the meta-analysis indicated that Fenofibrate has no significant effect on bilirubin level.

Fenofibrate, one of the most commonly prescribed fibrates, has been widely used since 1975 (23). Fenofibrate is a pro-drug that is hydrolyzed by tissue and plasma esterases to its main active metabolite (Fenofibric acid) immediately after absorption. It lowers cholesterol and triglycerides in healthy people and people with hyperlipidemia. Fenofibrate also reduces Uric acid (24). Although fibers are used to treat hypolipidemia, they boost glucuronosyltransferase activity, which increases bilirubin production and excretion. Therefore, these drugs reduce infant jaundice by affecting bilirubin metabolism (20).

Fenofibrate has many interesting medicinal properties including a short half-life (20 h) and rapid excretion (25). Therefore, they do not accumulate in the tissue due to their relatively short half-life, efficient absorption, and rapid excretion (26). Fibrates are easily tolerated and have very few side effects. The most important side effect is myositis in patients with kidney failure (27). Long-term use of Fenofibrate causes some unpleasant side effects, including gastrointestinal disorder and muscle cramps in adults (17). However, no adverse effects have been reported with single-dose administration in infants. Common side effects of Fenofibrate are headache and abnormal pulmonary function test results (e.g., AST and ALT). Other rare side effects are hypertension, dizziness, itching, nausea, gastrointestinal disorders, and urinary tract infections (28).

Given that phototherapy was used alongside Fenofibrate in all the studies, the effect of Fenofibrate alone cannot be determined here. No studies, to the best of our knowledge, have evaluated the long-term administration of Fenofibrate. One of the limitations is that none of the studies was low risk in terms of bias. Also, there was high heterogeneity in both meta-analyses and the quality of evidence was low. The high heterogeneity indicated that the results

should be cautiously interpreted. There is no certainty about coverage of all research articles by this study due to language limitations.

Conclusion

Although of six reviewed studies, the results of the five studies indicated the effect of Fenofibrate as adjuvant therapy for phototherapy on reducing serum bilirubin level, the results of the meta-analysis showed no significant effect of Fenofibrate on bilirubin level. Therefore, it is recommended to conduct more clinical trials with adaptive designs and adhere to all principles of randomized controlled clinical trials to find an effective treatment for hyperbilirubinemia.

Acknowledgments

No acknowledgments.

Conflicts of interest

The authors declare that there is no conflict of interest.

Ethics approval

Not applicable.

Funding

The authors received no financial, authorship, and/or publication support for this article.

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