Review Article

The Effects of Clofibrate on Neonatal Jaundice: A Systematic Review

Abstract

Background: Neonatal jaundice is a prevalent disease that causes many complications, including kernicterus and even death. Previous studies have shown that clofibrate as an aryloxy isobutyric acid derivate can be effectively applied for the treatment of neonatal jaundice. Thus, this review was carried out to investigate the effects and mechanism of action of clofibrate on neonatal jaundice. **Methods:** The keywords such as "Clofibrate" in combination with "Neonatal jaundice" or "Neonatal hyperbilirubinemia" or "Newborn Jaundice" were used to search for relevant publications indexed in the Institute for Scientific Information (ISI), Scopus, PubMed, and Google Scholar databases. Finally, after reviewing the studies, 24 papers were included in this study. **Results:** Results showed that the processes of albumin-bound bilirubin transfer to the hepatocytes, hepatic uptake, and storage via ligandin, hepatic conjugation via uridine diphosphate glucuronosyltransferase 1A1 (UGT1A1), conjugation into the bile via MRP2 represent the main action mechanism of clofibrate that turns it into the bilirubin conjugates and expels it from the bile. Besides, clofibrate has been shown to reduce the level of Total Serum Bilirubin (TSB) in infants even at a dosage of 25 mg/kg without leaving side effects. **Conclusions:** The results of this review revealed that clofibrate effectively reduces TSB in short-term usage and can even have a promising effect at the dosage of 25 mg/kg in full-term infants. Most studies have shown this property over a short period in term infants, and there is no evidence about long-term usage in this regard.

Keywords: *Clofibrate, hyperbilirubinemia, neonatal jaundice, newborn jaundice*

Fathemeh Eghbalian, Ali Hasanpour-Dehkordi[1], Roya Raeisi

Department of Pediatric, Hamadan University of Medical Sciences, Hamadan, Iran, [1]Social Determinants of Health Research Center, School of Allied Medical Sciences, Shahrekord University of Medical Sciences, Shahrekord, Iran

Introduction

Neonatal jaundice is one of the prevalent and life-threatening disorders in neonates.[1] Neonatal jaundice is prevalent among up to 80% of premature infants and 60% of term infants.[2,3] This disease develops during the first few days of birth and is caused by several factors such as uridine diphosphate glucuronosyltransferase 1A1 (UGT1A1), polymorphism, low birth weight, small for gestational age, neonatal sepsis, hematoma absorption, maternal-fetal ABO blood group incompatibility, metabolic diseases, liver diseases, etc.[4] If it isn't treated in due time, it will result in dangerous and sometimes permanent complications such as neurological disorders, cerebral palsy, auditory nerve damage, chore athetoid, and bilirubin encephalopathy,[5,6] and interferes with maternal-infant emotional interaction and breastfeeding.[7] Additionally, this multi-risk factor disease is considered as a reason for most cases of newborn hospitalization imposing significant health burdens in low-income and middle-income countries.[8]

The main mechanism of jaundice is based on the imbalance between bilirubin production and conjugation. Bilirubin in the form of unconjugated bilirubin is transferred in the blood. The liver changes bilirubin into a conjugated form which is expelled from the body along with bile.[9] Very high levels of unconjugated bilirubin can cause kernicterus and consequently neurotoxic complications like cerebral palsy and deafness.[10,11] So if the jaundice is not treated properly as soon as possible, then it causes a lot of complications.[1] Currently, various treatments are applied for the treatment of neonatal jaundice in medical settings among which phototherapy is the mainstay of these methods.[12] Although, phototherapy has low complications in short-term treatment, it causes squints and abnormal developmental performance in newborns,[13] interference with maternal-infant interaction, imbalance in thermal environment and water loss, electrolyte disturbance hypocalcemia, the

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Address for correspondence:
Dr. Roya Raeisi,
Pediatric Department, Hamadan University of Medical Sciences, Hamadan, Iran.
E-mail: r_reisi2@yahoo.com

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disorder of circadian rhythms, as well as the development of the bronze baby syndrome.[14-16] Besides, the health care providers must consider a set of items such as different wavelengths, total doses, intensities, and commencement threshold for achieving the best effectiveness and safety.[17] Therefore, in addition to the phototherapy administered, as the current treatment to reduce the complications and treatment duration, other treatments, such as medication therapy should be considered. Therefore, the increasing desire to use drugs has been developed as an adjunct therapy. On the other hand, there is limited strong evidence about the use of pharmacotherapy such as clofibrate, human albumin, intravenous immunoglobulin, herbal therapy, ursodeoxycholic acid, and phenobarbital treatment in neonatal jaundice.[12,18-21] Clofibrate is an aryloxyisobutyric acid derivative used in the treatment of hypertriglyceridemia and dyslipidemia.[13] However, previous studies showed that clofibrate is effective in the treatment of neonatal jaundice.[14,22] Therefore, this study was conducted to investigate the effects and mechanism of clofibrate action on neonatal jaundice.

Materials and Methods

To conduct this study, the keywords of interest were searched using EndNote software. The keywords included "Clofibrate" in combination with "Neonatal jaundice" or "Neonatal hyperbilirubinemia" or "Newborn Jaundice" that were used to search for relevant publications indexed in the Institute for Scientific Information (ISI), Scopus, and PubMed databases. (For ISI and PubMed databases, keywords were searched by EndNote software.)

Given the insufficiency of the studies in the ISI and PubMed databases, the Google scholar database was searched. Among 862 results obtained concerning the mentioned keywords, 6 papers (except duplications) were added to the bank of the study. A standard form was designed consisting of items such as author, the title or purpose of the study, intervention, gestational age, birth weight, age at enrolment (day), Total Serum Bilirubin (TSB) at admission, clofibrate dosage (mg/kg), side effects (at hospitalization period and follow-up), outcomes (including the mean TSB, duration of phototherapy, and duration of hospitalization), journal name and article number. The full text of the papers matched the purpose of the study was recorded in the form and entered into the study with agreement of co-authors. A search was conducted by two separate researchers. The inclusion criteria were clinical trials performed on neonatal jaundice, as well as the studies that showed positive effects on neonatal jaundice. The papers which had non-positive effects, full texts of which were not accessible, review papers, non-English or non-Persian language papers, and those which were not related to the aim of this study were excluded after all the authors reached an agreement. Finally, 24 papers were included in the study [Figure 1].

For quality assessment, the protocol of RCTs was considered and the methodological quality of the primary

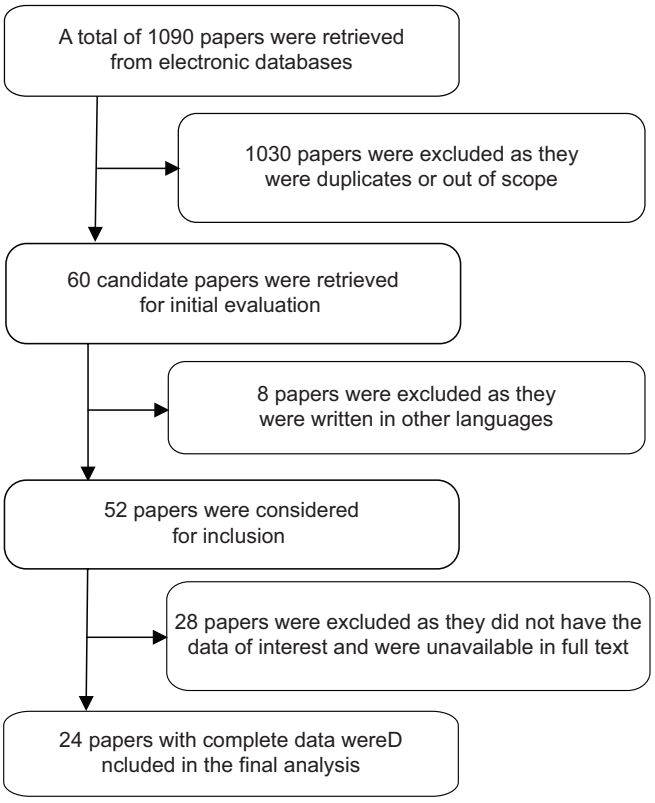

Figure 1: Flowchart of the study design (This flowchart illustrates how the papers were selected for final analysis.)

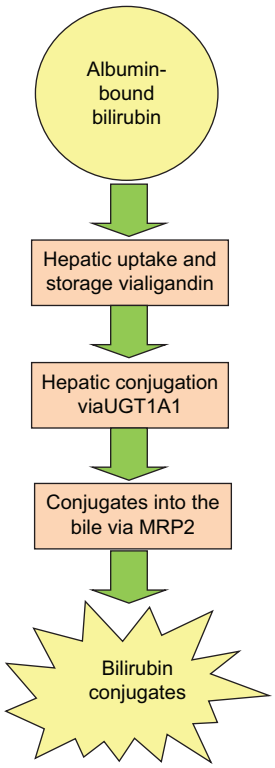

Figure 2: Bilirubin clearance mechanism of clofibrate in the liver

Table 1: The effects of clofibrate treatment on neonatal jaundice

References	Gestational age	Birth weight (kg)	Age at enrolment (day)	TSB at admission (mg/dl)	Direct and indirect bilirubin (mg/dl)	Clofibrate dose (mg/kg)	Side effects	Outcome*			
								TSB level (mg/dl)	Direct and indirect bilirubin (mg/dl)	Duration of phototherapy	Duration of hospitalization
Mohammadzadeh *et al.*[23]	Full-term (37-41 weeks of gestation)	3260±481	9±4	23.33±3.36	0.92±0.52 (Direct)	100	No	Reduced (After 12, 24, and 48 h)	No change reported for direct bilirubin	Reduced	-
Zahedpasha *et al.*[24]	Not reported	3110.8±453.9	6.02±2.09	17/85±2.09	0.79±0.12 (Direct)	100	No	Reduced (After 48 and 72 h)	No change reported for direct bilirubin	-	Reduced
Eghbalian *et al.*[14]	Full-term	>2500	Majority 2-3	20.85±3.6	20.35±3.5 (Indirect)	100	No	Reduced (After 12 and 24 h)	Reduced for indirect bilirubin (After 12 and 24h)	Reduced	Reduced
Moslehi *et al.*[25]	Full-term	2543±548	5.2±1.9	17.63±1.4	0.46±0.20 (Direct)	25/50	No	Reduced (After 12 and 24 h)	-	Reduced	-
Zahedpasha *et al.*[26]	Full-term	3133±456	6.0±2.9	17.85±2.09	0.79±0.11 (Direct)	100	No	Reduced (After 48 and 72 h)	No change reported for direct bilirubin	-	Reduced
Badeli *et al.*[27]	Full-term	3171±278	5.3±1.8	18.4±1.6	-	100	No	Reduced (After 12, 24, and 36 h)	-	Reduced	Reduced
Mohammadzadeh *et al.*[28]	Preterm (31.5±1.5 weeks of gestation)	1369±201	31.48±1.52	5.9±2.4	-	100	No	Reduced (After 24 h)	-	Reduced	-
Zahedpasha *et al.*[29]**	Full-term	3258±479	18.0±1.9	5.1±2.3	0.78±0.18 (Direct)	100	No	Reduced (After 16, 24, and 48 h)	No change for direct bilirubin	Reduced	Reduced
Ghotbi *et al.*[30]	Full-term	3211.5±425	4.2±0.15	17.4±0.93	-	100	No	Reduced (After 12, 24, and 48 h)	-	-	Reduced
Mohammadzadeh *et al.*[31]	Preterm (31.5±1.5 weeks of gestation)	2114±328 (Low birth weight)	9.2±5.4	21.1±5.2	0.51±0.26 (Direct)	100	No	No change	No change	Reduced	-
Sakha *et al.*[32]	Preterm (34-37 weeks of gestation)	2359±535	6.1±2.9	19.8±2.4	0.82±0.41 (Direct)	100	No	Reduced (After 48 h)	-	Reduced	-
Sharafi *et al.*[33]	Full-term	3129±431	6.7±2.9	17.3±1.5	-	50	No	Reduced (After 24 and 48 h)	-	Reduced	-
Alipour *et al.*[34]	Full-term	3245±189	6±2.56	-	-	100	No	Reduced (After 24 h)	-	Reduced	-
Eghbalian *et al.*[35]	-	-	-	3.31±1.84	-	50/25	No	Reduced (After 12, 24, and 36 h)	-	Reduced	Reduced
Fallah *et al.*[36]	Full-term	3197±370	4.85±1.96	19.52±2.64	-	50	No	Reduced (After 12, 24, and 48h)	-	Reduced	Reduced
Habibi *et al.*[22]	Full-term	3081±319	3.25±1.04	20.65±2.41	0.45±0.48 (Direct)	100	-	Reduced (After 24 and 48 h)	-	Reduced	-

Contd...

Table 1: Contd...

References	Gestational age	Birth weight (kg)	Age at enrolment (day)	TSB at admission (mg/dl)	Direct and indirect bilirubin (mg/dl)	Clofibrate dose (mg/kg)	Side effects	Outcome*			
								TSB level (mg/dl)	Direct and indirect bilirubin (mg/dl)	Duration of phototherapy	Duration of hospitalization
Ahadi *et al*.[37]	Full-term	2500-4000	4.06±4.04	17.9 4±1.01	-	100	No	Reduced (After 24 and 72 h)	-	-	Reduced
Hamidi *et al*.[38]	Full-term	-	-	17.5±1.4	-	100	No	Reduced (After 12, 24, 48, and 72 h)	-	Reduced	Reduced
Poursakha *et al*.[39]	Near term (35 weeks of gestation)	2360±0.53	6.11±2.88	19.88±2.30	-	100	No	Reduced (After 48 h)	-	Reduced	-
Zahed Pasha *et al*.[40]	Full-term	2500-4000	-	2.05±0.06 (Umbilical cord bilirubin)	-	50	-	No change	-	-	-
Nourishadkam *et al*.[41]	Full-term	3240±380	6.12±2.48	16.49±2.64	-	100	No	Reduced (After 24 h)	-	-	-
Alosy[42]	Full-term	2500-4000	-	-	-	100	No	Reduced (After 24 and 69 h)	-	Reduced	Reduced
Kumar *et al*.[43]	Full-term	2780±253.5	4.05±1.48	18.3±2.05	-	50	No	Reduced (After 48 h)	-	Reduced	-

*Outcomes considered based on comparing the *P* between control and treatment groups. **Neonates were affected by glucose-6-phosphate dehydrogenase (G6PD) deficiency

studies was assessed including research design, study sample, participation rates, sources of bias, data collection, follow-up or attrition rates, and data analysis. The studies with the minimum clinical trials requirements were included in the study.

Results

Finally, 24 papers were found to meet the inclusion criteria and were selected for the study. Most important variables influencing the outcome of the studies and clofibrate treatment are presented in Table 1.

Discussion

This study was conducted to investigate the effects and action mechanism of clofibrate on neonatal jaundice. Clofibrate modulates the gene involved in lipid homeostasis[44] and as an aryloxyisobutyric acid derivate can stimulate peroxisomeproliferator-activated receptors, as a result of which the conjugation with glucuronic acid is catalyzed by UGT1A1.[45,46] Eventually, bilirubin conjugates are excreted into the bile through the canalicular ATP-dependent transporter MRP2. Taken together, clofibrate increases the excretion of albumin-bound bilirubin through enhancing the enzymatic steps in hepatocytes[47] [Figure 2].

Besides, clofibrate increases the stimulation of glucuronosyltransferase and augments bilirubin conjugation and excretion, causing a significant increase in the bilirubin clearance and reduction of unconjugated hyperbilirubinemia.[48] Therefore, these changes also reduce the duration of phototherapy and hospitalization in neonates and diminish the complications attributed to them. Although clofibrate acts as an antilipidemic drug and causes several complications (such as vomiting, nausea, gastrointestinal problems, loose stools, leucopenia, transient cholestasis, muscle cramping, fatigue, pruritus, alopecia, renal failure, abnormal liver function)[16,49-54] the reviewed studies showed that, the dose of 25-100 mg/kg and short-time administration of clofibrate has not exerted any complication during the treatment and follow-up periods. Lipid and unconjugated bilirubin can conjoint each other and bond to the albumin. Therefore, changes in bilirubin amounts must be adjusted by considering the lipid profile alteration. In this regard, lipids are one of the most important macronutrients, which are necessary for cell growth and development in newborns, so the long-term administration of clofibrate can impair organ development and growth.[55,56]

In the reviewed studies, complications were mostly evaluated by clinical observations which could be considered as a limitation of the clinical studies. Thus, it is recommended to perform laboratory tests and biochemistry examinations (according to the side effects) in future studies to obtain more valuable results. A high degree of heterogeneity among the trials resulted from different TSB levels at baseline,

limitation in geological regions (the majority of the trials were carried out in Asia which conceals the effects of genetic factors), lack of using the placebo, and consequently lack of blinding in the control group and unclear allocation was among other limitations of the reviewed studies. On the other hand, hemolytic disease (ABO incompatibility of Rh) and congenital anomaly of infants were considered as exclusion criteria or there was rare number of studies conducted in this area. Therefore, conducting such studies can indicate clear results and address its optimal therapeutic dose in infants with hemolytic diseases.[57]

Conclusion

The results of this review revealed that clofibrate effectively reduces TSB in short-term usage and can even have a promising effect at the dosage of 25 mg/kg in full-term infants. Larger RCTs (complying with all principles of the design) along with longer follow-up and considering hemolytic disease and blood transfusion are needed to elaborate more on the issue.

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Conflicts of interest

There are no conflicts of interest.

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