REVIEW ARTICLE

Clofibrate for Unconjugated Hyperbilirubinemia in Neonates: *A Systematic Review*

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Objective: To evaluate the effect of clofibrate for unconjugated hyperbilirubinemia in neonates.

Methods: A systematic review with meta-analysis of randomized controlled trials or quasi-randomized controlled trials was conducted to evaluate the clofibrate treatment in neonates with unconjugated hyperbilirubinemia. We followed the guidelines from the Cochrane review group and the PRISMA statement.

Results: Of 148 studies identified, a total of 13 studies on 867 infants were included. A single oral administration of clofibrate was associated with decreased need of phototherapy (RR:.38, 95% CI: 0.21 to 0.68), shortened duration of phototherapy (mean duration: 23.88 h, 95% CI: 33.03 to -14.72 h) and reduced peak total serum bilirubin (mean duration: -1.62 mg/dL, 95% CI: 2.13 to -1.11 mg/dL). These effects were especially obvious in term infants and infants without hemolytic diseases. Data regarding mortality or kernicterus were not available from included studies.

Conclusions: Clofibrate may have short-term benefits for the infants with hyperbilirubinaemia, especially for population of term infants and infants without hemolytic diseases. Large RCTs with long-term followup are required to verify the safety of clofibrate and assess its long-term effects.

Key words: *Clofibrate, Jaundice, Management, Meta-analysis, Newborn, Phototherapy.*

Neonatal jaundice is one of the most common conditions confronting neonatologists. Epidemiologic studies show that about 60% of term and 80% of preterm babies develop jaundice in the first week of life [1]. The goal of the management of unconjugated hyperbilirubinemia is to avoid bilirubin toxicity [2]. Exchange transfusion and phototherapy are two leading treatments for severe jaundice. Although the need for exchange transfusion has markedly decreased after the availability of effective phototherapy, a small proportion of infants with severe hyperbilirubinemia need exchange transfusion, which leads to increased risk of infections and death [3,4].

Clofibrate, an activator of peroxisome receptors, increases the hepatic conjugation of unconjugated bilirubin by inducing activity of glucuronyl transferase [5,6]. In 1981, Lindenbaum, *et al*. [7] published the first randomized controlled trial (RCT) for the use of clofibrate in neonates with jaundice. Since then, a series of clinical trails have reported that clofibrate could decrease the need of phototherapy and exchange transfusion by decreasing the peak serum bilirubin and duration of hyperbilirubinemia. We therefore conducted this systematic review and meta-analysis to evaluate the effect of clofibrate in neonates with unconjugated hyperbilirubinemia.

METHODS

Data sources

We followed the guidelines from the Cochrane review group for undertaking and reporting this systematic review and meta-analysis [8]. The published medical literature in the Medline, Embase, Cochrane Central Register of Controlled Trials (CCTR) and ISI Web of Knowledge (SCI) databases were searched in October, 2010. The reference lists of identified studies and key review articles were also searched. Abstracts of the National and International American Pediatric Society/Pediatric Academic Societies, The European Paediatric Research Societies and the Effective Care of the Newborn Infant were hand searched for unpublished articles (up to 2010). No language restriction was applied. Two authors independently searched these databases by using the subject headings terms "clofibrate", "hyperbiliru-binemia", "hyperbiliru-binemia, neonatal", "jaundice", "jaundice, neonates" and the key words "clofibrate",

"jaundice", "hyperbiliru-binemia". Studies with titles or abstracts that discussed clofibrate for jaundice were retrieved.

Study selection

Inclusion criteria for trials included (*i*) age <28 days; (*ii*) unconjugated hyperbilirubinemia (irrespective of etiology and defined as conjugated bilirubin less than 2 mg/dL); (*iii*) clofibrate administration for prevention or treatment of unconjugated hyperbilirubinemia; (*iv*) RCT or quasi-RCT (parallel group /crossover); (*v*) trials with at least one of the outcome parameters in this review (see below). All articles were initially screened by title, abstract, and keywords. When appropriateness of the article could not be determined, the full article was obtained. Two authors independently screened the studies for eligibility. Any disagreement was resolved through discussion to reach a consensus.

Data extraction

The following data were extracted and put into the standardized forms: author, publication year, characteristics of neonates (gestational age, birth weight, causes of jaundice, postnatal age and level of total serum bilirubin (TSB) at admission), dose of clofibrate, criteria for phototherapy and exchange transfusion, and follow-up periods. Outcomes included the need of phototherapy (for the trials which started phototherapy on admission, the need of phototherapy was assessed at 48-72 h after clofibrate administration and for prophylactic administration, it was assessed at the end of study), the need of exchange transfusion, duration of phototherapy, peak TSB (the highest TSB level after clofibrate administration), morbidity of kernicterus, and side effects of treatment (vomiting, loose stools, leucopenia, renal failure, abnormal liver function tests, etc).

Quality assessment of studies

The quality of the studies was assessed according to the standardized criteria of the Cochrane Database of Systematic Reviews. The methodological quality of each trial was assessed independently by two authors. For each trial, information was sought regarding the method of randomization, allocation concealment, blinding of intervention, blinding of outcome assessment and reporting of the complete outcome. The unstated details were acquired through communication with the authors of the trials.

Statistical analysis

Meta-analysis of the included trials was performed using RevMan 5. For categorical outcomes, the relative risk (RR), the risk difference (RD) and 95% confidence intervals (CIs) were calculated. For continuous outcomes, mean difference (MD) and 95% CIs were calculated. Heterogeneity was measured by using the I^2 test [9]. Data without heterogeneity (I^2 <50%) were combined by fixed-effects model [10]. When there was unexplained heterogeneity, we incorporated it into a random-effects model [11]. Subgroup analyses were conducted according to causes of jaundice (with/without hemolytic diseases) and term/preterm status of neonates. Potential publication bias was assessed by funnel plot [12]. A *P* value of <0.05 was considered statistically significant.

RESULTS

Studies and participants

148 articles were retrieved on the basis of the general search strategy. Of them, two authors reached a complete consensus that 13 RCTs with 867 neonates met the inclusion criteria and were selected for analyses (***Fig.* 1**). The trial dates ranged from 1981 to 2010; two of 13 trials were published in French [7, 13], one in Spanish [14] and ten in English [15-24].

***Table* I** presents the characteristic of subjects in included trials. Eight of the 13 trials included only term infants, four trials only preterm infants, and one trial included both. The average birth weight ranged from 1879 g to 3370 g. The average TSB levels at admission were from 5.9 to 23.1 mg/dL.

Intervention

The average age at admission varied from 2 to 9.2 days. Neonates in all trials received a single oral dose of clofibrate within the first 14 days after birth. Clofibrate was dissolved in solution (corn oil or water), and was given orally with/without orogastric tubes. The dose of clofibrate ranged from 25 mg/kg to 100mg/kg. Phototherapy was given on admission [15-19, 21-24] or when TSB was over certain threshold respectively [7,14,20]. Exchange transfusion was given when TSB was not well controlled by clofibrate and phototherapy in four trials [7, 13-14, 22]. The main characteristics of these interventions are described in ***Table* II**.

Methodologic quality

For most of the studies, both evaluators reached a high degree of agreement for study-quality assessment. Disagreements existed in three studies where there were no details regarding allocation concealment and blinding [15,20,22]. However, these disagreements were resolved after contacting the authors. All were randomized/quasi-randomized trials, although the methods of randomization

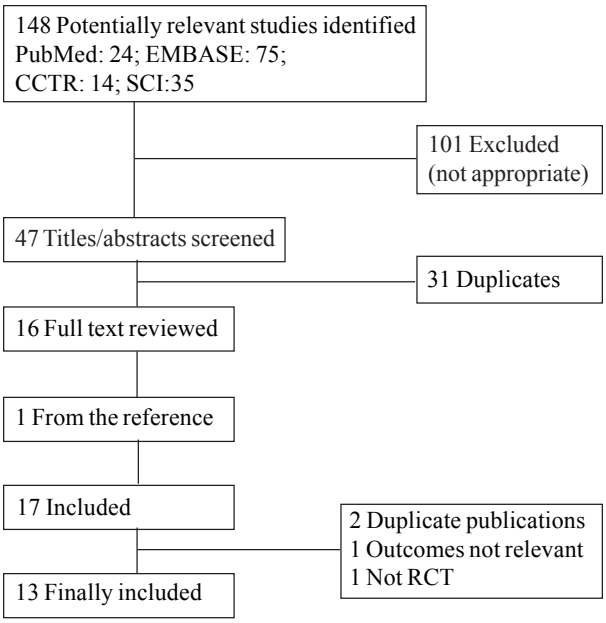

FIG. 1 *Results of search strategy of systematic review.*

in two studies were not clearly stated [18,21]. In six trials, randomized allocation was concealed from the physicians [7,13,15,20,22-23]. In six studies, intervention was blinded to the physicians, nurses and parents by use of placebos, and blinded outcome assessments were concealed from physicians and clinical technologists [7, 13,15,20,22-23]. One trial had incomplete outcome reporting [14]. Other twelve trials had complete reporting of in-hospital outcomes for infants, without possible attrition bias through withdrawals and dropouts [***Web Table* I**].

The funnel plot for the primary outcome of peak TSB did not show any publication bias in this review (***Web Fig.* 1**).

Outcomes

Phototherapy: Need for phototherapy was significantly reduced in the clofibrate treated infants in meta-ten trials (**Fig. 2**). Subgroup analysis showed that the reduction in RR for the need of phototherapy was prominent in infants without hemolytic diseases rather than with hemolytic diseases, and in term infants rather than in preterm infants.

Duration of phototherapy was reported in 7 out of the 13 trials. Clofibrate treatment resulted in a shorter duration of phototherapy than that in control group (***Fig.* 4**). The subgroup meta-analysis revealed a significant decrease in the duration of phototherapy for infants without hemolytic disease, and for term or preterm infants. There was no information about phototherapy duration in infants with hemolytic disease (***Table* III)**.

Need of exchange transfusion: Meta-analysis of four trials reporting the need of exchange transfusion did not reveal a statistically significant difference in need for exchange transfusion (***Fig.* 3**). Clofibrate treatment did not significantly decrease the need of exchange transfusion in

TABLE I CHARACTERISTICS OF SUBJECTS IN TRIALS

Author, Year [Ref.]	*N clofibrate/ control*	*Gestational age*	*Birth Weight (g)*	*TSB levels at admission (mg/dL)*	*Hemolytic disease*
Lindenbaum,1981 [7]	9347/46	Term	3370±105	14.3±0.4	22 with ABO incompatibility
Lindenbaum,1985 [13]	8946/43	Preterm (31-36)	1879±221	unclear	Without
Flores Nava,1996 [14]	4522/23	Preterm/ term (34 -42)	2754±803	unclear	Included ABO and Rh incompatibility*
Mohammadzadeh, 2005 [15]	6030/30	Term	3260±481	23.1±3.4	Without
Moslehi, 2007 [16]	9060/30	Term	2543±548	17.6±1.4	Without
Eghbalian, 2007 [17]	6030/30	Term	>2500	20.9±3.6	Without
Zahedpasha,2007 [18]	6030/30	Term	3133±456	17.9±2.1	Without
Badeli, 2008 [19]	9045/45	Term	3171±278	18.4±1.6	Without
Mohammadzadeh, 2008 [20]	5226/26	Preterm (31.5±1.5)	1369±201	5.9±2.4	Without
Zahedpasha, 2008 [21]	4021/19	Term	3258±479	18.0±1.9	G6PD deficient
Mohammadzadeh, 2009 [22]	6030/30	Preterm (31.5±1.5)	2114±328	21.1±5.2	Without
Sakha, 2009 [23]	6835/33	Preterm (34 -37)	2359±535	19.8±2.4	Without
Sharafi, 2010 [24]	6030/30	Term	3129±431	17.3±1.5	Without

**11 cases with ABO incompatibility, 1with Rh incompatibility; TSB: total serum bilirubin.*

TABLE II CHARACTERISTICS OF INTERVENTIONS IN TRIALS

Author, Year [Ref]	*Age at admission (days)*	*clofibrate dose* (mg / kg)*	*Threshold of phototherapy (mg/dL TSB)*		*Threshold of exchange transfusion*	*Follow-up for side effects (after discharge)*
			Start	*end*		
Lindenbaum,1981 [7]	2-3	50	>17.5	unclear	unclear	Without
Lindenbaum,1985 [13]	2-3	100	Unclear	unclear	unclear	12 days
Flores Nava, 1996 [14]	< 1.5	100	Indirect bilirubin†	Indirect bilirubin‡	Jasso's Standard	unclear
Mohammadzadeh, 2005 [15]	9±4	100	on admission	<14mg/dL	>30 or 25 mg/dL	2 days
Moslehi, 2007 [16]	5.2±1.9	50 /25	on admission	unclear	unclear	2 days
Eghbalian, 2007 [17]	Most 2-3	100	on admission	<12mg/dL	>30 or 25 mg/dL	1 week
Zahedpasha, 2007 [18]	6.0±2.9	100	on admission	<10mg/dL	TSB >25 mg/dL	1 week
Badeli, 2008 [19]	5.3±1.8	100	on admission	unclear	unclear	1 month
Mohammadzadeh, 2008 [20]	unclear	100	5 or 7mg/dL§	≤50% of photo-therapy level	unclear	unclear
Zahedpasha, 2008 [21]	5.1±2.3	100	on admission	< 10mg/dL	unclear	1 week
Mohammadzadeh, 2009 [22]	9.2±5.4	100	on admission	unclear	unclear	1 week
Sakha, 2009 [23]	6.1±2.9	100	on admission	2004 AAP guidelines‖	unclear	1 week
Sharafi, 2010 [24]	6.7±2.9	50	on admission	<10mg/dL	unclear	2 months

**All studied used a single oral dose; † Indirect bilirubin >4 mg/dL in umbilical cord blood, >6 mg/dL within 12 h of life; >10 mg/ dL within 24 h, >13 mg/dL within 48 h, and >15 mg/dL at any time; ‡Indirect bilirubin <10mg/dL or <admission level-2mg/dL; §Reach to 5mg/dL in birth weight in birth weight less than 1,000 g, 7mg/dL in birth weight 1,000~1,500 g; ‖ American Academy of Pediatrics Subcommittee on Hyperbilirubinemia.*

infants with or without hemolytic disease, and in term infants or preterm infants.

Peak TSB concentration: Peak TSB was significantly lower in clofibrate group (***Fig.* 5**). Significantly reduced TSB levels were seen in infants without hemolytic diseases and in term infants. In infants with hemolytic diseases and in preterm infants, effect was not significant. *Mortality and Kernicterus*: No study reported outcome of death or Kernicterus.

Side effects: In the included studies, side effects were assessed through clinical observation and laboratory tests [complete blood count, total serum bilirubin, blood urea nitrogen, blood creatinine, liver function tests (SGOT, SGPT)] during the follow-up periods ranging between 2 days to 2 months. Only one infant had cholestasis with direct bilirubin 3.9 mg/dL after three days of clofibrate. No other side effects were reported.

DISCUSSION

In this systematic review, we found that clofibrate-treatment reduced the need of phototherapy, shortened duration of phototherapy, and resulted in a lower peak TSB. These beneficial effects were prominent in subgroups of infants without hemolytic diseases and in term infants. Clofibrate treatment did not show prominent effects in infants with hemolytic diseases. However, the number of infants with hemolytic diseases included in the review was too small to draw any meaningful conclusion.

The absence of significant therapeutic effect of clofibrate in preterm infants could be because of insufficient sample size, and also due to its different metabolism in preterm infants. The main metabolite of clofibrate is clofibric acid, which has the effective plasma concentration of 140µg/mL for jaundiced neonates [13]. In humans, most of the plasma clofibric acid is bound to albumin. Thus, decreased level of albumin in preterm infants could lead to increased free form of clofibric acid, which facilitates the clearance of clofibric acid and results in lower plasma levels of clofibric acid. Because preterm infants have lower level of albumin, the dose of clofibrate needs to be adjusted according to the gestational age: 100 mg / kg for 34 to 36 weeks of gestational age, and >100 mg / kg for 31 to 33 weeks [13]. Lower dose of clofibrate for preterm infants in some studies may explain the lack of a significant effect.

Short-term safety of clofibrate treatment was good in

TABLE III META-ANALYSES OF OUTCOMES

Outcome	*No of studies*	*No of cases*	*Measure (95% CI)*[†]
Need of phototherapy			
All infants	10	685	RR: 0.38 [0.21, 0.68]; RD: -0.38 [-0.57, -0.18]
infants without HD[*]	8	578	RR: 0.17 [0.06, 0.48]; RD: -0.42 [-0.64, -0.19]
infants with HD	2	62	RR: 1.00 [0.35, 2.86]; RD: -0.06 [-0.56, 0.44]
term infants	8	553	RR: 0.20 [0.07, 0.54]; RD: -0.42 [-0.64, -0.20]
preterm infants	1	87	RR: 0.81 [0.58, 1.14]; RD: -0.13 [-0.33, 0.07]
Need of exchange transfusion			
All infants	4	285	RR: 0.27 [0.07, 1.05]‡; RD: -0.05 [-0.09,-0.00]‡
infants without HD	2	147	RR: 0.59 [0.08, 4.37]‡; RD: -0.01 [-0.07, 0.04]‡
infants with HD	1	22	RR:0.47 [0.02, 10.32]‡; RD: -0.08 [-0.29, 0.13]‡
term infants	1	93	RR:0.33 [0.01, 7.81]‡; RD: -0.02 [-0.08, 0.04]‡
preterm infants	2	147	RR: 0.59 [0.08, 4.37]‡; RD: -0.01 [-0.07, 0.04]‡
Duration of phototherapy (hs)			
All infants	7	465	MD: -23.88 [-33.03, -14.72]
infants without HD[*]	6	420	MD: -21.50 [-30.68, -12.32]
infants with HD	0	0	
term infants	4	300	MD: -19.95 [-31.22, -8.67]
preterm infants	2	120	MD: -25.00 [-33.75, -16.25]‡
Peak TSB (mg/dL)			
All infants	12	790	MD: -1.62 [-2.13, -1.11]
infants without HD	11	728	MD: -1.69 [-2.17, -1.21]
infants with HD	2	62	MD: -0.48 [-2.04, 1.08]
term infants	8	553	MD: -1.89 [-2.56, -1.22]
preterm infants	4	237	MD: -0.97 [-2.23, 0.28]

[*] *HD represents hemolytic disease;* [†] *Most of following outcome using randomized-effects model because of statistical heterogeneity;* ‡ *Given without statistical heterogeneity fix-effects model used.*

the included studies, except for a single case of transient cholestasis. Clofibrate has been found to be carcinogenic in rodents but epidemiological and observational studies have not found any such evidence in adult humans [25-27]. It is not known whether long-term carcinogenesis could occur in neonates with clofibrate treatment. However, in most of the studies, tests for liver or muscle enzymes were not done, and the follow-up periods were too short (<2 month).

The methodological quality varied among studies. In some trials, allocation concealment was unclear or inappropriate which might have resulted in overestimation of the intervention effect. Due to the lack of blinding of intervention in several trials, treatment bias could have occurred. Moreover, sample sizes in included trials were generally small.

A major limitation of this meta-analysis is the statistical heterogeneity. Although subgroup analyses (cause of jaundice, gestational age) and the sensitivity analyses (dose of clofibrate, publication year or location) were done, the heterogeneity remains unsolved. This heterogeneity resulted from the difference of baseline TSB at admission, the varied causes of jaundice, the thresholds for phototherapy and exchange transfusion, the different methods of TSB measurement, and the genetic factors between different nations.

This meta-analysis shows that clofibrate may have short-term benefits for the infants with hyperbilirubinemia, especially in term infants and infants without hemolytic diseases. At present, there is no evidence to show whether clofibrate treatment modifies the risk of death, kernicterus or long-term neurodevelopmental impairment due to bilirubin encephalopathy.

Long-term developmental follow-up is required to assess the safety of clofibrate treatment, confirm its long-term benefits in different settings, and address its optimal

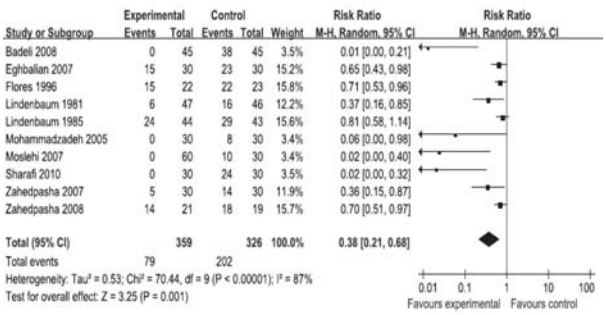

FIG. 2 *Need of phototherapy.*

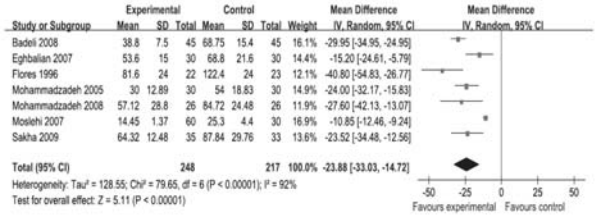

FIG. 4 *Duration of phototherapy.*

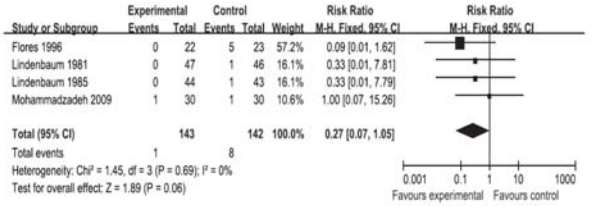

FIG. 3 *Need of exchange transfusion*

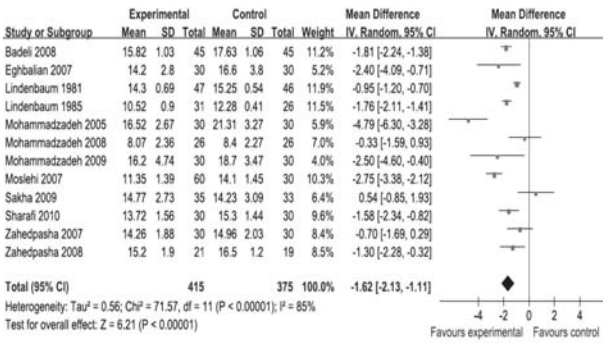

FIG. 5 *Peak TSB.*

therapeutic dose in preterm neonates and infants with hemolytic diseases.

Contributors: TX: writing the review; DC: data collection and writing the draft; ZD: responsible for data collection and study-quality assessment; YQ: provide support for the analysis of the data; and, DM: designing the review and supporting the publication.

Funding: National Natural Science Foundation of China (No. 31171020, No. 30825039 and No. 30973236). Ministry of Education of China (No.IRT0935, No.20070610092). Science and Technology Department of Sichuan Province (No.2010SZ0280).

Competing interests: None stated.

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