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ORIGINAL ARTICLE

Single Dose of 50 mg/kg Clofibrate in Jaundice of Healthy Term Neonates: Randomised Clinical Trial of Efficacy and Safety

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Abstract
Objective To evaluate the effect of single oral dose of 50 mg/kg clofibrate in hyperbilirubinemia of term healthy neonates in Yazd, Iran.
Methods A parallel single- blinded randomized clinical trial, conducted on 60 healthy term neonates admitted between July and December 2007 to Shahid Sadoughi Hospital. Inclusion criteria were neonates with gestation age of 38–42 wk, birth weight of 2500–4000 g, product of normal vaginal delivery, breast-fed and total serum bilirubin (TSB) level of 17–29.9 mg/dL. Neonates with sepsis, anemia, severe asphyxia, hemolytic diseases, major congenital anomalies, indirect hyperbilirubinemia and underlying hepatic disorders were excluded. Selection of patients was based on random allocation *via* table of random numbers and the patients distributed into two groups. In group one, 30 neonates were treated with phototherapy alone and in 30 of other group treatment done with single dose of 50 mg/kg clofibrate and phototherapy. The primary endpoint with respect to efficacy in reducing of TSB was achieving TSB to less than 14 mg/dL as measured at the beginning, 12, 24 and 48 h after the start of phototherapy. Secondary outcomes were hospital stay days, duration of phototherapy and side effects of treatments during hospital stay and on the second day after discharge.
Results No significant differences were seen from the viewpoint of rout of delivery, gender, gestational age, birth weight, hemoglobin and bilirubin level at time of admission and weight in discharge time in the two groups. After 48 h of intervention, 27 (90%) neonates in clofibrate group and 15 (56.7%) in control group had TSB of less than 14 mg/dL (p 0.02). Mean TSB 12 h after treatment (mean ± SD: 14.82±1.7 mg/dL *vs.* 16.67±1.77 mg/dL, P 0.001), 24 h after treatment (mean ± SD: 11.97±2.92 mg/dL *vs.* 14.61± 2.52 mg/dL, P 0.001) and 48 h after treatment (mean ± SD: 7.91±2.45 mg/dL *vs.*12.74±2.21 mg/dL, P 0.0001), mean of hospital stay days (mean ± SD: 1.7±0.7 days *vs.*3.2± 1.2 days, P 0.03) and duration of phototherapy (mean ± SD: 30.2±13.99 h *vs.*46.2±15.58 h, P 0.001] were significantly lower in clofibrate group. Only loose stool was seen in two patients of clofibrate group and no significant difference was seen from view of safety of the treatments.
Conclusions A single dose of 50 mg/kg clofibrate in treatment of neonatal hyperbilirubinemia is effective, safe and cost effective in view of reducing hospital stay days.

Keywords Clofibrate · Hyperbilirubinemia · Jaundice · Neonate

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Introduction

Jaundice is seen in over half of all full term and most preterm newborns in the first week of their life [1]. Unconjugated bilirubin in toxic level crosses blood brain

barrier and classical kernicterus or subtle neurodevelopmental disabilities [2]. Kernicterus is rare in healthy term and late preterm infants in total serum bilirubin (TSB) level of less than 25 mg/dL [3].

Regardless of etiology, appropriate intervention should be considered in severe hyperbilirubinemia of newborns to prevent bilirubin neurotoxicity. Phototherapy and if unsuccessful, exchange transfusion is the most common intervention to treat and prevent severe hyperbilirubinemia [4]. "Phototherapy, however, has several known disadvantages while exchange transfusion is associated with a significant morbidity, and even mortality. These harmful effects indicate the need to develop alternative pharmacological treatment strategies for unconjugated hyperbilirubinemia [5]."

Pharmacological intervention such as D-penicillamine, phenobarbital, clofibrate, bile salts, metalloporhyrins, laxatives and bilirubin oxidase may be used in the treatment of neonatal jaundice [5, 6].

Clofibrate is an antilipidemic drug that lowers serum very-low density lipoproteins and may lower cholesterol. The drug activates peroxisome proliferator -activated receptors and also increases bilirubin conjugation and excretion [6]. In most of researches, 100 mg/kg/dose of clofibrate has been administered [7–15]. Pharmacokinetic profiles of oral single dose of 100 mg/kg and 50 mg/kg of clofibrate in term neonates were similar in both dosages of the drug and low dose of 50 mg/kg of it seems to be a suitable dose [16]. Little is known about the usefulness of such low amount dose of the drug in healthy term neonates.

The purpose of this study was to evaluate effect of single oral dose of 50 mg/kg clofibrate in hyperbilirubinemia of term healthy neonates in Yazd—central city of I.R.Iran.

In the present study the authors tested the hypothesis that low dose clofibrate treatment of hyperbilirubinemia would: reduce the total serum bilirubin level, reduce the hospital stay days and not have serious side effects.

Material and Methods

A randomized single—blind clinical, open-label, parallel group study conducted on healthy term neonates with hyperbilirubinemia referred and admitted between July and December 2007 to Shahid Sadoughi Hospital in Yazd, Iran. Sample size based on Z formula and confidence interval of 95% with 80% power, type one error of 5%, case group variance of 1.75, control group variance of 1.5 and an effect size (difference in mean bilirubin levels between the two groups) of 1.2 mg/dL [17] was assessed on 30 patients per group.

Eligible participants were neonates with:

- Gestation age of 38–42 wk
- Birth weight of 2500–4000 g
- Product of normal vaginal delivery
- Bilirubin level of 17–29.9 mg/dL
- Breast-fed

Neonates with sepsis, anemia, severe asphyxia, hemolytic diseases, indirect hyperbilirubinemia, major congenital anomalies and underlying hepatic disorders were excluded. The trial used equal randomization and allocation ratio was 1:1 for two groups. Simple randomisation was by a computer generated random number list prepared by an investigator with no clinical involvement in the trial and no restriction was used. The authors stratified by admission for treatment of hyperbilirubinemia. After the research resident had obtained the parents' consent, he telephoned a contact who was independent of the recruitment process for allocation consignment.

Whereas patients and physicians allocated to the intervention group were aware of the allocated arm, outcome assessors and data analysts were kept blinded to the allocation.

The patients were distributed into two groups. In group one, 30 of neonates were treated with phototherapy alone and other 30 with single dose of 50 mg/kg clofibrate and phototherapy (group 2). Each phototherapy unit had four special blue lamps (Philips Co of Germany), replaced after 800 h and adjusted to 20 cm above the neonate's cot. Phototherapy was started immediately on admission for all neonates in both the groups until TSB decreased to less than 10 mg/dL. In bilirubin level of 25–30 mg/dL, if intensive phototherapy was not effective, exchange transfusion was performed in the neonates. Total and direct serum bilirubin level of peripheral vein blood samples were determined by Jendrassik-Grof method.

The primary endpoint with respect to efficacy in reducing of TSB was the achieving of TSB to less than 14 mg/dL as measured at the beginning, 12, 24 and 48 h after the start of phototherapy. Then TSB was measured daily and when TSB declined to less than 10 mg/dL, the patients were discharged. Duration of phototherapy was recorded by a nurse who was not involved in drug administration.

All neonates were evaluated for clinical side-effects of treatments during their stay days in hospital and on the second day after discharge in the hospital clinic.

Secondary outcomes were hospital stay days, duration of phototherapy in hours and side effects of treatments. Variables such as sex, gestational age, birth weight, on admission, hemoglobin level, bilirubin levels, weight in discharge time, duration of phototherapy and hospital stay days were carefully recorded.

Table 1 Comparison of clinical and paraclinical characteristics of patients in two groups

Data	Phototherapy alone Mean ± SD	Phototherapy and clofibrate Mean ± SD	*P*
Gestational age (wk)	37.87±1.07	38.23±0.971	0.171
Age in admission (days)	4.97±2.16	4.73±1.76	0.648
Birth weight (g)	3193.67±369.2	3202.3±371.1	0.928
weight in discharge time	3201.67±374.4	3255.5±370.1	0.465
Admission hemoglobin level	16.9±1.78	16.19±1.55	0.105
Admission bilirubin level	19.5±2.21	19.54±3.07	0.954

Statistical Analysis

The data were analyzed using SPSS: 15 statistical software. Chi-square test or Fisher exact test was used for data analysis of qualitative variables and mean values were compared using independent *t*-test. Differences were considered significant at $P<0.05$.

Informed consent was taken from parents of neonates and this study has been approved by the Ethics Committee of Shahid Sadoughi University of Medical Sciences, Yazd, Iran. The design and conduct of this trial was straightforward, and the authors' did not have any losses to follow-up or exclusions.

Results

To evaluate the efficacy of clofibrate in hyperbilirubinemia of healthy term neonates, data of 60 infants who were randomly distributed into two groups was analyzed.

Sixteen patients (54%) in group 1 and fourteen (46%) in group 2 were female and sex distribution was not different in the two groups (*P* 1). Table 1 shows baseline demographic and clinical characteristics of patients for each group which indicates no significant differences in respect of gestational age, birth weight, hemoglobin and bilirubin level at the time of admission and weight at the time of discharge in the two groups with *t*- test. After 48 h of intervention, 27 (90%) neonates in clofibrate group and 15 (56.7%) in control group had TSB of less than 14 mg/dL (*p* 0.02).Comparison of TSB level after beginning of treatment in two groups is shown in Table 2 which indicates that mean TSB 12, 24 and 48 h after treatment were significantly lower in clofibrate group.Comparison of hospital stay days and duration of phototherapy in hours is presented in Table 3. *T*- test showed that means of these two parameters were statistically significant, lower in clofibrate group.

One neonate in phototherapy alone group and none in clofibrate group needed exchange transfusion. No serious adverse events were seen in the two groups and only loose stool was seen in two patients of clofibrate group. No significant difference was seen in side effects frequency between the two drugs (*p* 0.76).None of patients needed re-hospitalization.

Discussion

In the present study, effect of hyperbilirubinemia treatment during the first week of birth in term healthy neonates who were product of normal vaginal delivery, with single oral dose of 50 mg/kg clofibrate with phototherapy and phototherapy alone, were compared. In group of clofibrate with phototherapy, number of neonates who after 48 h of intervention had TSB of less than 14 mg/dLwas more than phototherapy alone. Means of TSB 12, 24 and 48 h after treatment, hospital stay days and duration of phototherapy were significantly lower in clofibrate-treated group. No serious side effects were seen in the two groups.

Results of the present study indicated that clofibrate can significantly reduce TSB level and it was effective in treatment of neonatal jaundice which is in compliance with other studies. (7–15) However, in other researches, the drug

Table 2 Comparison of bilirubin levels in 12, 24 and 48 h after treatment in case and control groups

Bilirubin level	Phototherapy alone Mean ± SD	Phototherapy and clofibrate Mean ± SD	*P*
in 12 h	16.67±1.77	14.82±1.7	0.001
in 24 h	14.61±2.52	11.97±2.92	0.001
in 48 h	12.74±2.21	7.91±2.45	0.0001

Table 3 Comparison of hospital stay days and phototherapy duration in two groups

Data	Phototherapy Mean ± SD	Phototherapy and clofibrate Mean ± SD	*P*
Hospital stay (days)	3.2±1.2	1.7±0.7	0.03
Phototherapy duration (in h)	46.2±15.58	30.2±13.99	0.001

with 100 mg/kg/dose was administered [7–15] and in Sakha et al. study in Tabriz—Iran in late pre-term neonates with non-hemolytic jaundice, only the mean TSB 48 h after phototherapy was significantly lower in clofibrate group [7] and in other two Iranian studies in full term neonates with nonhemolytic jaundice, similar to present study, means of TSB 12, 24 and 48 h after treatment were significantly lower in the group treated with clofibrate [9, 11]. However, in Mohammadzadeh et al study, neonates beyond the first wk of life were evaluated [11]. Also in a study in Babol-Iran, means of TSB 48 and 72 h after treatment were significantly lower in clofibrate group [10]. In a study in Rasht—Iran, means of TSB 12, 24, 36 and 48 h after treatment were significantly lower in clofibrate-treated group [12].

Results of present study showed that single low dose of 50 mg/kg of clofibrate was effective and safe in treatment of nonhemolytic neonatal hyperbilirubinemia and in agreement with the results of Moslehi et al study in Shiraz-Iran [18] and recommendation of two researchers [16, 19].

In the present study, days of hospital stay and duration of phototherapy were lower in clofibrate group which supports those of other studies [7–15]

Side effects of long term use of clofibrate in adults are nausea, vomiting, loose stool, muscle cramping, fatigue, pruritus, alopecia and leukopenia [20]. Transient loose stool was seen in two of the present patients. No life-threatening and serious side effects were seen in the present patients and this is what found in other researches [7–15, 18].

The limitations of this study were its small sample size, short duration of follow up and lack of placebo group. The strengths of present study were use of low dose and enrollment of neonates in first wk of birth. Therefore, it is suggested that further studies be conducted with a larger sample size, longer follow up periods and different dosage of drug and placebo.

Conclusions

A single low dose of 50 mg/kg clofibrate is effective and safe in treatment of jaundice in term healthy neonates during the first wk of birth. Since other new pharmacological interventions such as metalloporphyrins are not available in developing countries, clofibrate therapy is safe and cost effective in view of reducing hospital stay days.

Conflict of Interest None.

Role of Funding Source None.

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