The Effect of Oral Fenofibrate on Serum Bilirubin Level in Term Neonates with Hyperbilirubinemia: A Randomized Clinical Trial

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Abstract

Background
Several agents have been used for the treatment of neonatal hyperbilirubinemia, but the effect of oral fenofibrate on serum bilirubin level was not evaluated so much. The aim of this study was to assess the effect of oral fenofibrate on a total serum bilirubin (TSB) in term neonates with hyperbilirubinemia.

Materials and Methods: This clinical trial was done on 80 term neonate with a TSB higher than 15 mg/dl in two equal groups of control and intervention. Both groups received conventional phototherapy with the same condition. The intervention group received a single dose of oral Fenofibrate (Sobhan-Darou Company, Iran) 10 mg/kg. The TSB was measured in both groups, at admission, second day, and third day and also at the time of discharge. The serum bilirubin level, the duration of phototherapy and need to exchange transfusion were compared in two groups.

Results: Results showed that of 80 neonates studied, the TSB at the second day of hospitalization in the intervention group was 13.29±1.64 mg/dl and in control group 14.06±1.78 mg/dl (p=0.04), and at the third day in intervention group it was decreased to 9.99±1.53 (p=0.04), and in control group to 11.01±1.68 mg/dl, (p=0.006). The duration of phototherapy in the intervention group was 2.5±0.71 days and in control group 3.35±0.97 days (p=0.003).

Conclusion
According to the result of this study administration of oral Fenofibrate in a term neonate with hyperbilirubinemia under the phototherapy lead to faster decline in serum bilirubin levels, shorten the duration of hospital stay and earlier discharge from hospital.

Key Words: Bilirubin, Hyperbilirubinemia, Fenofibrate, Jaundice, Neonate.


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1- INTRODUCTION

Although phototherapy and exchange transfusion (EXT) are the most important proposed treatments for hyperbilirubinemia (1, 2), but the use of several drugs has become more common with recent advances (3, 4). There are little agents for the treatment of hyperbilirubinemia, including intravenous immunoglobulin (IVIG), D-penicillamine, metalloporphyrin, phenobarbital, zinc sulfate and colofibrate (5-7). Fibrates have been used as a hypolipidemic drug for several years (8); it also enhances the bilirubin conjugation and excretion through induction of glucuronyl transferase activity (9). Most studies focused on the effect of fibrates on hyperbilirubinemia have been done with clofibrate(10). Clofibrate has been used for prophylaxis and treatment of hyperbilirubinemia in neonates at a dose of 100 mg/kg (11-14).

The common side effect of clofibrate is nausea. Other side effects include vomiting, loose stools, muscle cramping, fatigue, pruritus, alopecia, leukopenia, renal failure and peripheral neuropathy. Therefore, clofibrate is an uncommon drug, today (8, 9). Although fenofibrate is as the same as clofibrate in terms of the mechanism of action, it has fewer side effects than clofibrate so it is much safer than clofibrate in the pediatric group. However, no side effects of fenofibrate have been observed by a single dose administration in the neonatal period (9, 15). Several side effects have been found in prolonged use of fenofibrate in adults, such as gastrointestinal discomfort and muscle cramps, but no side effects of fenofibrate have been observed by a single-dose administration in the neonatal period (6). In adult population fenofibrate, which has better safety than clofibrate is widely used in the treatment of hyperlipidemia (3, 16). In a neonatal period one study, oral administration of fenofibrate at 10 mg/kg dose reduced the total serum bilirubin (TSB), and duration of hospitalization (17), but in another study, with a dose of 5 mg/kg fenofibrate accompanied with phototherapy had no effect on the serum bilirubin level compared to the control group (18). Considering the limited studies on the therapeutic effect of fenofibrate on hyperbilirubinemia and its equivocal effects this study was carried out to determine the effect of oral fenofibrate on a serum bilirubin level in term newborns hospitalized due to the neonatal hyperbilirubinemia.

2- MATERIALS AND METHODS

2-1. Patients

This clinical trial was conducted on newborn infants, referred and admitted to the Amirkola Children's Hospital (ACH); affiliated to the Babol University of Medical Sciences, Northern Iran, because of the neonatal hyperbilirubinemia according to the local protocol of phototherapy (19). The inclusion criteria were the term neonates (37-41 weeks and 6 days): a. older than 72 hours, b. admitted due to the jaundice with a total serum bilirubin (TSB) level higher than 15 mg/dl, c. healthy in other ways and d. who only received phototherapy. Exclusion criteria included infants with congenital anomalies, infants who received drugs such as maternal phenobarbital, Cotoneaster and Descurainia sophia before or during hospitalization as well as infants who required sepsis work-up or had respiratory symptoms like respiratory distress during phototherapy.

2-2. Phototherapy protocol

In both groups, phototherapy was typically performed according to the Amirkola Children's Hospital (ACH) guideline for the treatment of hyperbilirubinemia (19) (Table.1). The entered newborns were randomly divided into two intervention
and control groups (n=40 in each group) using a table of random numbers. The two groups were matched in terms of birth weight, age, gender and cause of hyperbilirubinemia. In the control group, 40 hyperbilirubinemia newborns with matching birth weight, gender, age and other demographic information were selected. If the neonates had a total serum bilirubin (TSB) >20 mg/dl during phototherapy, they have been considered as a severe hyperbilirubinemia and defined as no response to phototherapy(20). Exchange transfusion was done for these neonates if their TSB reached the exchange level.

**Table 1:** Amirkola Children's Hospital (ACH) guideline for the treatment of neonatal hyperbilirubinemia in term neonates after 72 hours of age (14).

<table>
<thead>
<tr>
<th>Treatment protocol based on TSB (mg/dl)</th>
<th>EXT</th>
<th>Phototherapy stop and discharge</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phototherapy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Without risk factor*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥15</td>
<td>&gt;20</td>
<td>&gt;25</td>
</tr>
</tbody>
</table>

*Risk factors were asphyxia, intraventricular hemorrhage, hemolysis, hypoxia, sepsis, hypalbuminemia, G6PD deficiency, mismatch of blood groups and hypothermia.

TSB: Total Serum Bilirubin; EXT: Exchange Transfusion.

2-3. Intervention

In the intervention group, a single dose of 10 mg/kg fenofibrate (Sobhan- Darou Company, Iran) was orally administered since entry to the study. The control group did not receive any medications other than the phototherapy. Serum bilirubin level of the two groups was measured during hospitalization, and the neonates were discharged from the hospital after the serum bilirubin level was decreased to <10 mg/dl. Serum bilirubin levels were measured, recorded, and compared at admission, second day, third day, and discharge time in control and intervention groups. Confounding factors, including, gender, mother's age, and causes of jaundice were matched together. The TSB was measured using the photometric method in the Amirkola Hospital laboratory with the kit (Darman Faraz Kav. Co., Iran). Gestational age was determined using pre-natal sonography parameters, physical examination and new Ballard score. The intervention group received a single dose of 10 mg/kg fenofibrate (Sobhan Darou Company) (100 mg of fenofibrate, dissolved in 5 ml of distilled water, 1 ml of this solution was equivalent to 20 mg of Fenofibrate) since entry to the study. The control group did not receive any medications other than the phototherapy.

2-4. Sample size

Considering the impact of at least 0.6 mg difference on TSB, based on similar articles (15), the sample size for each group was 40 neonates at α = 0.05 and 80% power. The primary outcomes included the serum bilirubin levels, and the secondary outcomes were the duration of phototherapy, the lack of response to phototherapy, the incidence of severe hyperbilirubinemia and the need for exchange transfusion in two groups. Neonatal demographic information was collected using a checklist that was created by the researcher. Then, the outcomes were compared in two groups. Flow Diagram of the study protocol was illustrated in Figure.1.

2-5. Ethics

The protocol of the trial study was approved by the Ethics Committee of Babol University of Medical Sciences with the approval code of MUBABOL.HRI.REC.1396.36. This study was also registered in the Iranian registry of clinical trials (WWW.IRCT.IR) with registration number-ID: IRCT.2017081635732N1. Written informed
consent was taken from the parents before inclusion into the study.

2-6. Data analysis
Data were analyzed using SPSS software version 18.0 through T-test, Chi-square test ($\chi^2$), Mann-Whitney, correlation coefficients and retest were used to compare the group and $P<0.05$ were considered significant.

![Flow Diagram of the study protocol](image)

Fig1: Flow Diagram of the study protocol.

3- RESULTS
Totally, 80 newborn infants were studied. The intervention group consisted of 20 girls and 20 boys and the control group had 15 (37.5%) males and 25 (62.5%) females ($P=0.26$). In the intervention group, 26 (65%) and 14 (35%) neonates were born by cesarean and vaginally, respectively. In the control group, 25 (62.5%) and 15 infants (37.5%) were born by cesarean and vaginally, respectively ($p = 0.81$). Concerning the cause of jaundice in the intervention group, 24 (60%), 4 (10%), 8 (20%) and 4 (10%) neonates had unknown cause,
Glucose6-Phosphate Dehydrogenase (G6PD) deficiency, ABO incompatibility, Rh incompatibility, respectively, but in the control group 29 (72.5%), 3 (7.5%) and 7 (17.5%) infants had unknown cause, G6PD deficiency, ABO incompatibility, respectively and only 1 (2.5%) newborn suffered from combination of G6PD deficiency and ABO incompatibility, (p=0.22). In the present study, no sever hyperbilirubinemia leading to exchange transfusion and no drug complications were observed in both groups. Comparison of neonatal demographic variables in the control and intervention groups is illustrated in Table.2. As shown in Table.2, the demographic variables had no significant difference in both intervention and control groups. The mean age of jaundice onset was not significantly different in the two groups (intervention group=3.3±1.36 days, control group=3.55±1.55 days, p=0.40). The mean age of hospitalization was 6 ± 3.07 days and 5.88±1.26 days in the intervention and control groups, respectively (p=0.77). The mean age of the phototherapy initiation was 6 ± 3.07 and 5.88 ± 1.26 days in the intervention and control groups, respectively (p=0.77). The variables related to hyperbilirubinemia in both intervention and control groups are represented in Table.3. The results of Table.3 indicated that there was no statistically significant difference in terms of gestational age, weight, jaundice onset, hospitalization age and the age of the phototherapy initiation between two groups. The primary and secondary outcomes of the study were evaluated in this section.

Table-2: Baseline demographic variables of the jaundiced neonates hospitalized for phototherapy in the control and intervention groups.

<table>
<thead>
<tr>
<th>Variables</th>
<th>Classification</th>
<th>Intervention Group</th>
<th>Control Group</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td>Male</td>
<td>20 (50)</td>
<td>15 (37.5)</td>
<td>0.26</td>
</tr>
<tr>
<td>Number (%)</td>
<td>Female</td>
<td>20 (50)</td>
<td>25 (62.5)</td>
<td></td>
</tr>
<tr>
<td>Gestational age (week), Mean ± SD</td>
<td>-</td>
<td>38.53±0.75</td>
<td>38.43±0.84</td>
<td>0.57</td>
</tr>
<tr>
<td>Birth weight (gr), Mean ± SD</td>
<td>-</td>
<td>3260±452</td>
<td>3086±531</td>
<td>0.11</td>
</tr>
<tr>
<td>Type of delivery, Number (%)</td>
<td>By cesarean</td>
<td>26 (65)</td>
<td>25 (62.5)</td>
<td>0.81</td>
</tr>
<tr>
<td></td>
<td>Vaginally</td>
<td>14 (35)</td>
<td>15 (37.5)</td>
<td></td>
</tr>
</tbody>
</table>

SD: Standard deviation.

Table-3: Comparison of variables related to hyperbilirubinemia in the intervention and control groups of the jaundiced neonates hospitalized for phototherapy.

<table>
<thead>
<tr>
<th>Variables</th>
<th>Intervention group</th>
<th>Control group</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age of jaundice onset (day); Mean ± SD</td>
<td>3.3±1.36</td>
<td>3.5±1.55</td>
<td>0.40</td>
</tr>
<tr>
<td>Age of hospitalization (day); Mean ± SD</td>
<td>6±3.07</td>
<td>5.88±1.26</td>
<td>0.77</td>
</tr>
<tr>
<td>Age of the phototherapy initiation(day); Mean ± SD</td>
<td>6±3.07</td>
<td>5.88±1.26</td>
<td>0.77</td>
</tr>
<tr>
<td>Severe hyperbilirubinemia at phototherapy initiation; Number (%)</td>
<td>7 (17)</td>
<td>8 (20)</td>
<td>0.31</td>
</tr>
<tr>
<td>Cause of jaundice; Number (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unknown</td>
<td>24 (60)</td>
<td>29 (72.5)</td>
<td></td>
</tr>
<tr>
<td>ABO incompatibility</td>
<td>8 (20)</td>
<td>7 (17.5)</td>
<td></td>
</tr>
<tr>
<td>Rh incompatibility</td>
<td>4 (10)</td>
<td>0 (0)</td>
<td></td>
</tr>
<tr>
<td>G6PD</td>
<td>4 (10)</td>
<td>3 (7.5)</td>
<td></td>
</tr>
<tr>
<td>G6PD+ABO</td>
<td>0 (0)</td>
<td>1 (2.5)</td>
<td></td>
</tr>
</tbody>
</table>

ABO: ABO incompatibility; G6PD: Glucose6-Phosphate Dehydrogenase deficiency; SD: Standard deviation.
Effect of Oral Fenofibrate on Serum Bilirubin Level

Table 4: Mean SBL (mg/dl) at different times of hospitalization and discharge in intervention and control groups of the jaundiced neonates hospitalized owing hyperbilirubinemia

<table>
<thead>
<tr>
<th>Time of bilirubin measurement</th>
<th>Intervention group</th>
<th>Control group</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>At admission</td>
<td>1.45±16.93</td>
<td>2.14±16.90</td>
<td>0.95</td>
</tr>
<tr>
<td>Second time (2nd day)</td>
<td>1.64±13.29</td>
<td>1.78±14.06</td>
<td>0.04</td>
</tr>
<tr>
<td>Third time (3rd day)</td>
<td>1.53±9.99</td>
<td>1.68±11.01</td>
<td>0.006</td>
</tr>
<tr>
<td>At discharge</td>
<td>0.88±8.96</td>
<td>0.81±8.78</td>
<td>0.35</td>
</tr>
<tr>
<td>P-value</td>
<td>&lt; 0.001</td>
<td>&lt; 0.001</td>
<td></td>
</tr>
</tbody>
</table>

Fig. 2: Trend of bilirubin changes after fenofibrate administration in the term newborns with jaundice in Amirkola Children's Hospital.

3-1. Serum bilirubin level

The serum bilirubin level was not significantly different between the two groups at admission (p = 0.95), but it had a significant decrease in the intervention group compared to the control group during the second and third days and at the discharge day. The mean bilirubin levels measured in the different periods are illustrated in Table 4. The result of repeated measurements displayed that the trend of changes in bilirubin level was statistically significant between two groups (p = 0.01). As illustrated in Figure 2, the mean bilirubin level at baseline was approximately the same for the intervention and control groups, and in
next times, a more tangible decrease was observed in the intervention group due to the use of Fenofibrate. This trend had been drawn up to the third time, according to the recorded results. On the fourth day, a significant number of newborns in the intervention group and a number of newborns in the control group were discharged; therefore, there was no equal population in both groups to obtain a correct mean for comparing the TSB between two groups. Thus, in order to predict the decrease of bilirubin levels in two groups, the depicted trend was shown with dashed line, extending the bilirubin level reduction and maintaining the gradient can be expected.

3-2. Duration of phototherapy (day)
The duration of phototherapy was 2.5 ± 0.71 and 3.35 ± 0.97 days in the intervention and control groups, respectively, which shows a statistically significant difference (p=0.003).

3-3. Incidence of severe hyperbilirubinemia during phototherapy
No severe hyperbilirubinemia was observed in both groups during phototherapy.

3-4. Need for exchange transfusion
There was no need for exchange transfusion in the intervention and control groups.

3-5. Adverse drug reaction
No complication attributed to the fenofibrate has been reported in the intervention group.

4- DISCUSSION
The results of this study demonstrated that the oral administration of fenofibrate with phototherapy rapidly reduces the serum bilirubin level; shorten the duration of phototherapy and accelerating the discharge of newborns from hospital. The result of this study confirms the findings of the El-Frargy et al.’s study (21). El-Frargy et al. compared different treatment modalities of jaundice in newborns. Totally, 120 neonates were divided into two groups who received phototherapy, all neonates of the first group received phenobarbital, but all neonates of the second group received fenofibrate. In this study the serum bilirubin level in the fenofibrate group was significantly lower than the phenobarbital group 24 and 48 hours after the start of phototherapy and at the discharge time. They concluded that a single oral dose of fenofibrate (10 mg/kg) with phototherapy was much more effective than oral phenobarbital in a dose of 3 mg/kg/day for 3 days. Their method was the same as ours.

In addition, the need for phototherapy in the intervention group was less than the control group in our study. In the El-Frargy et al.’s study (21), oral fenofibrate administration and phototherapy were simultaneously used. Moreover, the effect of fenofibrate and phototherapy was compared with phenobarbital. In the present study, 100 mg of fenofibrate was dissolved in 5 ml of distilled water, 1 ml of this solution was equivalent to 20 mg of fenofibrate, but in their study, 300 mg tablet was dissolved in 10 ml distilled water to get concentrated 30 mg of fenofibrate in 1 ml, which slightly differ with ours. However, neither in the study of El-frargy et al. nor in the current study, the gastrointestinal complication that could be attributed to the drug was observed. The present study, also confirmed the findings of Chaudhary et al. in India (8), who evaluated the effect of 10 mg/kg oral fenofibrate in 50 newborns with neonatal hyperbilirubinemia and divided the neonates into two controls (received an oral glucose solution), and intervention (received a single dose of 10 mg/kg fenofibrate) groups. In their study, the
serum bilirubin level in the fenofibrate group at 36 and 48 hours after starting the phototherapy and the mean time needed for phototherapy were significantly lower in the fenofibrate group than in control group which are consistent with those of the present study. Most studies have used a dose of 10 mg/kg. The results of this study (8) have indicated a reduction in the duration of phototherapy after administration of fenofibrate, which can be economically cost-effective and reduce the costs. This similarity can be due to the similarity of inclusion criteria of both studies: a. newborns with serum bilirubin >15 mg/dl, b. newborns at more than three days of age and c. newborns received fenofibrate with phototherapy.

Kumar et al. (2010) in India evaluated the effect of fenofibrate on hyperbilirubinemia of 40 neonates (15). The mean serum bilirubin level was 19.06 mg/dl and 19.25 mg/dl in the control and intervention groups, respectively. It was significantly reduced in the third, fourth, and fifth times at 24, 36 and 48 hours after administration of fenofibrate. Mean TSB level decreased from 19.25 mg/dl at admission to 14.45 mg/dl after 48 hours, indicating a significant difference. The administration of fenofibrate reduced the duration and number of sessions of phototherapy. However, in the control group after 48 hours, 50% of newborns needed to continue their phototherapy. The mean weight of newborns was 2808, which did not represent a significant relationship between weight and mean TSB level, and the mean age of neonates was 5.15 days. The results of the current study on the significant reduction of bilirubin level are the same as those of Kumar et al.’s study (15). This consistency can be due to the similar demographic variables of newborns such as age, gender, weight, which had no significant differences in both studies, as well as the dose of fenofibrate, was similar in both studies. In our study, the most common cause of jaundice was unknown in the intervention and control group, but in Kumar et al.'s study (15), the cause of jaundice was not studied, which could be one of the limitations of their study. According to the results of the study, rapid diagnosis in neonates with risk factors is important. Besides, an increase in the incidence of unknown causes of jaundice in newborns needs further investigation and improved diagnosis using new knowledge and resources. Al-Asy et al. (2013) in Egypt evaluated the effect of fenofibrate on 60 neonates with indirect neonatal hyperbilirubinemia (17). There was a significant relationship between fenofibrate and control groups in terms of the TSB and duration of hospital stay, which illustrated a significant decrease in the intervention groups in their study. In their study, the TSB was decreased from 16.59 mg/dl to 13.88 mg/dl after 24 hours, to 12.28 mg/dl after 48 hours, and to 9.74 mg/dl after 72 hours. No exchange transfusion was required in both groups in their study. In Al-Asy et al.’s study, the serum bilirubin level, mean duration of phototherapy and duration of hospitalization were significantly lower in the fenofibrate group (a single oral dose of 10 mg/kg) than in the control group. They concluded that the use of fenofibrate with phototherapy accelerated the rate of reduction of bilirubin in neonates. The mean serum bilirubin level was lower in the study of Al-Asy et al. (17) than that of Kumar et al.’s study (15). In addition, the mean serum bilirubin level at admission was higher in Kumar et al's study (19.25 mg/dl) (15) than in Al-Asy et al.’s (16.25 mg/dl) (17). In our study, the mean serum bilirubin level at admission (16.93 mg/dl) was 16.93 mg/dl, which are closer to the study of Al-Asy et al. study (17). Moreover, Al-Asy et al. (17) showed that the intervention group receiving fenofibrate had a lower duration of stay in hospital than the control group and this
difference was significant. In our study, the age of admission and the age of phototherapy initiation in the intervention group were clinically slightly higher. The effectiveness of oral fenofibrate in the management of unconjugated hyperbilirubinemia on 100 neonates with jaundice was evaluated by Gowda et al. (18). Neonates were divided into two groups. The first group received a single dose of 5 mg/kg fenofibrate with phototherapy and the second group received only phototherapy. The direct and indirect bilirubin levels were measured at 12, 24 and 48 hours and no significant difference was found in bilirubin levels at 12, 24 and 48 hours between the two groups, respectively. Their results demonstrated that a single oral dose of fenofibrate (5 mg/kg) had no effect on the reduction of bilirubin levels in neonates (18). Most studies expressed the effectiveness of fenofibrate in reducing the duration of phototherapy (15, 17).

In the present study, the reduced duration of phototherapy and early discharge were observed, which is consistent with other studies but contrasted with Gowda's study (18). The reason for the difference could be related to the dose of fenofibrate, which was 5 mg/kg in their study, but was 10 mg/kg in the present and other studies. On the other hand, an increase in dose of the drug requires follow-up exam. The patients in the present study were examined 24 to 48 hours after discharge, but not for longer period, and this could be one of the limitations in this study in comparison with the other studies. During the hospital stay and at out-patient clinic exam after discharge no adverse drug reactions were observed, but it should be kept in mind that the prolonged side effects of fenofibrate are rare. In the intervention group of the current study, no drug complications were found before discharge and severe hyperbilirubinemia, leading to exchange transfusion was not observed. In the study of Kumar et al. (15), all neonates were followed up for a month. No side effects were observed after the use of a single dose of fenofibrate. It also demonstrated that fenofibrate could be used as an effective and potentially safe drug for uncomplicated hyperbilirubinemia. In a study of Chaudhary et al. (8), no drug complications were seen in fenofibrate group and it was concluded that fenofibrate was an effective and safe drug for the treatment of neonatal hyperbilirubinemia, which are agreement with those of this study, indicating the usefulness of the drug in the examined neonates at least in a short term, and a follow-up is needed for long-term examination. Further, the follow-up period has been considered one month in most studies, which require a long-term follow-up, as well as the study of the need of re-admission in the neonates with jaundice received fenofibrate.

**4-1. Limitations of the study**

Failure to record the serum bilirubin level in both groups after the fourth day until discharge can be one of the limitations of the study. In other words, a significant number of neonates were discharged on the fourth day in the intervention group. The newborns of the control group remained in the hospital for not reaching the serum bilirubin levels below 10 mg/dl (discharge level), and serum bilirubin level was rechecked after receiving phototherapy again, while the serum bilirubin level of the fourth day was not measured in the discharged newborns of the intervention group. This led to a decrease in the number of newborns of the intervention group on the fourth day. In other words, if we could measure the serum bilirubin level in the days after discharge in the control group, we would obtain the serum bilirubin level in them; therefore, we could have a better comparison of the bilirubin level on the...
fourth day onwards. Moreover, there was no significant difference in serum bilirubin levels in the two groups at discharge, which could be due to the decreased number of samples in the intervention group because of the early discharge.

4-2. Suggestions
We recommend doing the same study in the G6PD deficient and preterm babies.

5- CONCLUSION
In general, the results of this study indicated that the administration of fenofibrate with phototherapy leads to a decrease in bilirubin level, a shorter hospitalization and a faster discharge in intervention group compared to control group, so this method is economically based on the cost-effectiveness of the drug and can be used as an auxiliary treatment for jaundice. However, in order to investigate the complications and side effects of the drug, further pharmacological experiments with prolonged follow-up are required.

6- CONFLICT OF INTEREST: None.

7- ACKNOWLEDGEMENT
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8- REFERENCES


