# Effect of Clofibrate in non-hemolytic indirect hyperbilirubinemia in full term neonates

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**Citation**

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**Abstract**

Background and Objective: Jaundice is most common clinical problem in neonatal period which may result in brain damage even in healthy full term newborns. The aim of this study was to characterize the therapeutic effect of clofibrate in full term neonates who present with non-hemolytic jaundice.

Patients and Methods: A clinical controlled study was performed on 60 full term neonates who presented with non- hemolytic jaundice. 30 neonates were treated with a single oral dose of clofibrate (100mg/kg) plus phototherapy (case group), while 30 neonates received only phototherapy (control group). Both groups were compared regarding to post therapeutic mean total and indirect plasma bilirubin levels, admission duration and the rate of exchange transfusion.

Results: The reduction rate of total and indirect plasma bilirubin levels were significantly higher in the clofibrate- treated group as compared with the control group (P<0.05). The mean admission duration reduced from 2.9 +/- 0.9 days in the control group 2.2 +/- 0.6 days in clofibrate- treated group (P=0.002). The mean plasma total bilirubin level was lower in the clofibrate- treated group. No cases required phototherapy after 48 hour in clofibrate- treated group, while 9 neonates (30%) and 2 neonates (6.7%) required phototherapy after 72 hour and 96 hour respectively in the control group. There was no difference between both groups for sex, the time of developing jaundice and the rate of exchange transfusion.

Conclusions: A single dose of clofibrate reduces total and indirect plasma bilirubin levels in neonates; in addition it reduces admission duration and phototherapy requirement without any side effects.

## INTRODUCTION

Hyperbilirubinemia is a common problem of neonatal period ant it is usually benign, but it may result in life long neurologic sequelae in infants who were not treated (Kernicterous)[1]. Thus treating indirect hyperbilirubinemia at the appropriate time is of high importance in neonates. Increased bilirubin production, hepatic uptake reduction, impaired bilirubin conjugation and increased enterohepatic bilirubin circulation are the pathologic ethiologies of hyperbilirubinemia in newborns[2]. Despite recognition enzymatic pathways of bilirubin production and elimination, phototherapy serves as the primary treatment in neonates with unconjugated hyperbilirubinemia[3]. Exchange transfusion is the first successful therapeutic modality for sever neonatal jaundice, where other therapeutic modalities, such as phototherapy, have failed[4]. Although, some pharmacologic agents, such as D-penicillamin, Phenobarbital, agar, metalloporphyrins, and recently clofibrate are suggested for treating neonatal jaundice, further investigations are needed to confirm the efficacy and safety of these agents, prior to their routine clinical usage[5]. Clofibrate is a proxisome proliferator- activated receptors (PPARS) activator, which decreases serum cholesterol and triglycerides levels[6]. It is also a glucoronyl transferase inducer which may increase bilirubin conjugation and excretion[7]. This agent has been suggested for prevention and treatment of neonatal hyperbilirubinemia[8]. The aim of the present study is to prove the effectiveness of oral clofibrate in the treatment of non-hemolytic hyperbilirubinemia in the healthy full term neonates.

## PATIENTS AND METHODS

During a 6 months period (June 2005-December 2005), 60 neonates with jaundice, admitted at Ekbatan neonatal department, were selected. All cases were healthy, breast

fed, full term neonates with birth weights more than 2500gr, and total serum bilirubin level of 15-25mg/dl. Infants with any congenital anomalies, hemolytic diseases (Rh or ABO incompatibility), sepsis signs or dehydration, and infants who required exchange transfusion where excluded. Infants were randomly divided into two groups: clofibrate- treated group and control group. All neonates received phototherapy in both groups. Each phototherapy unit (Tosan Co Ltd) contained 8 blue lamps (with a wave length of approximately 420-450nm) which adjusted at a 25cm distance above the infants cots. Phototherapeutic lamps were changed regularly after 1500 hours of usage. A single 100mg/kg dose of clofibrate was administered orally in the clofibrate- treated group. Total and direct serum bilirubin levels were determined at admission, 12 hours later, and then every 24 hours. Phototherapy and bilirubin measurement were continued until the total serum bilirubin concentration declined to less than 12mg/dl. Exchange transfusion was indicated at serum total bilirubin concentration of >30 mg/dl or 25 mg/dl and above, and also when phototherapy had failed. Laboratory investigations included: complete blood count, maternal and neonatal blood groups, direct comb's test, reticulocyte count, total and direct serum bilirubin levels, glucose 6 phosphate dehydrogenase level, and a peripheral blood smear. All infants were examined at the second day after discharge for evaluation of icter and any probable pharmacologic side effects. Bilirubin was measured using Techinca RA1000 instrument. Data where analysed using SPSS 13. Chi-square was used to compare sex and the time of developing icter. Total and indirect bilirubin level changes were analysed by ANOVA test. P.value<0.05 was considered to be significant.

## RESULTS

From sixty neonates studied, 36 (60%) were boys and 24 (40%) were girls. The mean admission duration was 2.6 +/- 0.8 days (1-5 days). There were no differences between both groups for sex and the time of developing icterus (P>0.05)(Table 1).

Our results showed that total and indirect serum bilirubin levels at admission, 12, and 24 hours post therapeutically was significantly lower in clofibrate- treated group as compared with control group.

No cases in treatment group required phototherapy after 48h; while 9 (30%) neonates required phototherapy after 72h and 2 (6.7%) required phototherapy after 96h in the control group. None of the cases in our study required exchange transfusion.

The reduction rate of plasma total and indirect bilirubin levels, were higher in clofibrate- treated group as compared with phototherapy group (P<0.05)(Table 2, 3) (Figure 1, 2).

The mean hospitalization duration reduced from 2.2 +/- 0.9 days in control group to 2.2 +/- 0.6 days in the treatment group (P=0.002).

**Figure 1**

Table 1: Comparison of the sex and the time of developing jaundice in clofibrate- treated and control groups

| | Treatment Groups | | P.Value |
|---|---|---|---|
| | Phototherapy (N=30) | Phototherapy + Clofibrate (N=30) | |
| *Sex* | | | |
| Boy | 21(70%) | 15(50%) | P=0.11 df=1 Chi2=2.5 |
| Girl | 9(30%) | 15(50%) | |
| *time of developing jaundice* | | | |
| days 2 & 3 | 23(76.7%) | 24(80%) | P=0.60 df=2 Chi2=1.02 |
| days 4-7 | 6(20%) | 6(20%) | |
| after1st week | 1(3.3%) | - | |

**Figure 2**

Figure 1: Total bilirubin changes in clofibrate- treated and control groups

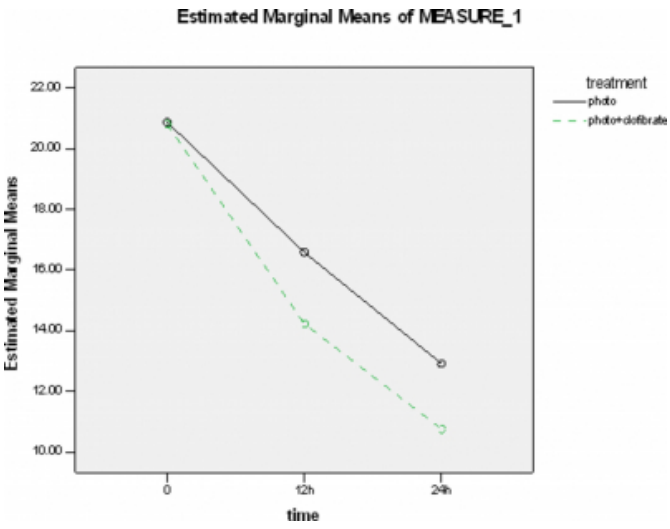

**Figure 3**

Figure 2: Indirect bilirubin changes in clofibrate- treated and control groups

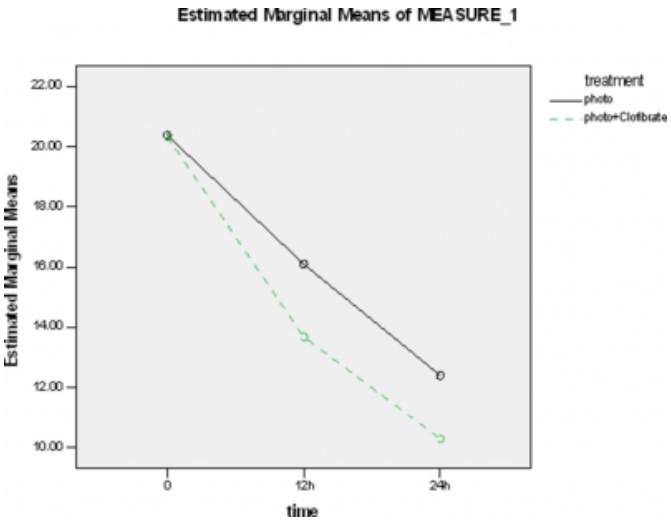


**Figure 4**

Table 2: Total bilirubin changes in clofibrate- treated and control groups

| *Treatment groups* | *Total bilirubin at admission* | *Total bilirubin at 12h post therapeutic* | *Total bilirubin at 24h post therapeutic* | ** P.Value* |
|---|---|---|---|---|
| *Phototherapy (N=30)* | *20.9 +/- 4.3* | *16.6 +/- 3.8* | *12.9 +/- 2.8* | *P=0.002* |
| *Clofibrate + Phototherapy (N=30)* | *20.8 +/- 2.9* | *14.2 +/- 2.8* | *10.8 +/- 2.5* | *df=2 F=6.7* |

* Repeated measurement ANOVA

**Figure 5**

Table 3: Indirect bilirubin changes in clofibrate- treated and control groups

| *Treatment groups* | *Indirect bilirubin at admission* | *Indirect bilirubin at 12h post therapeutic* | *Indirect bilirubin at 24h post therapeutic* | ** P.Value* |
|---|---|---|---|---|
| *Phototherapy (N=30)* | *20.4 +/- 4.2* | *16.1 +/- 3.7* | *12.4 +/- 2.7* | *P=0.002* |
| *Clofibrate + Phototherapy (N=30)* | *20.3 +/- 2.8* | *13.7 +/- 3* | *10.3 +/- 2.5* | *df=2 F=6.7* |

* Repeated measurement ANOVA

## DISCUSSION

The present study showed that administration a single oral dose of clofibrate (100mg/kg) in a healthy full term neonate, with non-hemolytic hyperbilirubinemia, will significantly reduce plasma total and indirect bilirubin levels after 12h; and therefore admission duration. These findings are consistent with the results of other studies, which have shown the efficacy of clofibrate in treating neonatal hyperbilirubinemia. The therapeutic effect of clofibrate in non-hemolytic neonatal hyperbilirubinemia was studied in a double blind controlled trial in France, where 47 neonates were treated with a single oral dose of clofibrate (50mg/kg) plus phototherapy and 46 neonates received corn oil plus phototherapy; and they showed that serum total bilirubin level was significantly lower in the former group (clofibrate plus phototherapy) [9]. In another study in Iran, it was showed that clofibrate reduces total plasma bilirubin level, admission duration, and the need for phototherapy in neonatal non-hemolytic hyperbilirubinemia[10]. Clofibrate increases bilirubin conjugation and excretion and may cause a 100% increase in hepatic bilirubin clearance with in 6h; so it may significantly reduce plasma bilirubin levels[11]. It is simply absorbable in the gasterointestinal (GI) system. Although it has side effects in long term consumption such as: diarrhea, vomiting, drowsiness, hepatomegaly, increasing the cholestasis rate, increasing gal-stone prevalence, pancreatitis, renal failure, and peripheral neuropathy; but there are no reports of side effects with a single oral dose[12]. Administration a single dose of clofibrate (100mg/kg) was simply tolerated in our study, without any side effects at hospitalization period and even at follow up visits (second and seventh days post discharge). Phenobarbital, like clofibrate, is a glucoronyl transferase inducer, but its efficacy in bilirubin reduction is lower than clofibrate. In addition, it has a long half-life and may causes drowsiness in infants; thus although Phenobarbital is a hepatic bilirubin metabolism inducer, it is not suggested for the treatment of neonatal hyperbilirubinemia[13, 14]. Recent clinical trials have shown that a single dose of mesoporphyrin has the best efficacy with minimal side effects, when is used prophylactically in premature infants and also curatively in full term neonates[14]. Actually, clofibrate is the only available pharmacologic agent that could be used effectively in non-hemolytic neonatal hyperbilirubinemia without any side effects.

## CONCLUSION

Many pharmacologic agents, such as Phenobarbital, agar, and metaloporphyrins have been suggested for the treatment of neonatal jaundice, but none of them is completely acceptable for the routine clinical usage. It seems that clofibrate is an appropriate pharmacologic agent for non-hemolytic neonatal jaundice due to, its availability, reduction in plasma bilirubin levels and admission duration, and simple oral consumption.

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