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COMPARING THE EFFECT OF CLOFIBRATE AND PHENOBARBITAL ON THE NEWBORNS WITH HYPERBILIRUBINEMIA

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ABSTRACT

The aim of treating hyperbilirubinemia is preventing the serum bilirubin to reach neurotoxic levels, which is done by phototherapy or blood transfusion. However, pharmacological treatments still remain vague. Therefore the effects of adding either clofibrate or phenobarbital on treatment outcomes was evaluated in icteric non-hemolitic newborns. Ninety neonates were divided in three groups. Two groups were prescribed 100 mg/kg clofibrate or 5 mg/kg phenobarbital orally as single dose on arrival, in addition to phototherapy. The control group only received phototherapy. Serum bilirubin was evaluated at the reception and 12, 24, 48 and 72 hours after beginning of drug therapy. Total bilirubin levels decreased in treated groups compared with the control group in all samples taken (12, 24, 48 and 72 hours). Clofibrate effect in decreasing bilirubin level was more prominent (14 % and 32 % after 12 and 72 h respectively). In addition duration of hospitalization and length of phototherapy decreased in clofibrate and phenobarbital groups compared with control group (1.5, 2 days respectively, vs. 2.6 days). Therefore using clofibrate and phenobarbital in icteric neonates are supportive not only by decreasing the serum bilirubin level, but also by lessening the duration of hospitalization and phototherapy. Thus in addition to cost benefits for the patient these drugs can reduce the risks of transfusion, and clofibrate seems more promising in this regard.

Keywords: hyperbilirubinemia, jaundice, non-hemolytic, phototherapy

INTRODUCTION

Hyperbilirubinemia is the most common morbidity in the neonatal period and 5-10 % of all newborns require intervention for pathological jaundice. It is also the most common clinical problem among the newborns, especially in south of Asia (Maisels and Watchko, 2012). Hyperbilirubinemia can be cau*sed by overproduction of bilirubin, decrease* in liver absorption, conjugation impairment and increase in bilirubin enterohepatic cycle (Stevenson et al., 2004). In babies whose bilirubin blood levels reach risky levels, bilirubin may cross the blood brain and cause reversible damage (called early acute bilirubin encephalopathy) or permanent damage (called kernicterus). Although phototherapy and in case of very high serum bilirubin levels, blood transfusion has been used, but these methods prove to have side effects (Maisels and Newman, 2005). Evidently clofibrate and phenobarbital are useful for treatment of

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hyperbilirubinemia in newborns (Dortmann et al., 1992; Dennery, 2002).

Thus the reduction of serum bilirubin level, is an important approach in jaundice newborns. Clofibrate and phenobarbital are not in routine therapeutic regimens of these patients; therefore it was aimed to compare their effectiveness in the treatment of icteric newborns that received phototherapy as the sole therapy regimen.

METHODS AND MATERIALS

In a randomized clinical trial (registration number: IRCT201202199073N1), 90 term newborns (48 male, 42 female) aged between 3-10 days, which were diagnosed with non-hemolytic jaundice at the hospital, were evaluated. The birth weight and delivery age of studied cases were 3185 gr ± 340 and 38.8 weeks ± 0.7 respectively. Including criteria were as follow: term neonates (37-42 weeks age), birth weight 2/5-4 kg, breast feeding, jaundice beginning at days 3-11 after birth, and indirect bilirubin level between 15-20 mg/dl. Laboratory tests including ABO and Rh, cell blood count (CBC), retic count, peripheral blood smear, G6PD enzyme assay and combs test were performed for all the cases. Infants with hemolytic hyperbilirubinemia, background disorders, sepsis, physical anomalies and impaired hematologic tests were excluded. Included infants were classified in three groups randomly. Group 1 was prescribed 100 mg/kg oral clofibrate, as a single dose in the first day and distilled water on the two following days. Group 2 was prescribed 5 mg/kg oral phenobarbital as a single dose on the first day and distilled water on days 2 and 3. Finally, control group was prescribed distilled water for 3 days. Phototherapy was performed for all the groups (wave length 420-460 nm). Total serum bilirubin, direct and indirect bilirubin were evaluated at the reception and 12, 24, 48 and 72 hours after therapy. Duration of hospitalization and length of photoherapy were also considered. The experiments were undertaken with the understanding and written permission from each child's parents.

The data were analyzed using GraphPad Prism software. The data were analyzed by one-way analysis of variance (ANOVA), followed by Duncan's multiple comparison tests. Results are expressed as the group mean ± SD, P values < 0.05 are considered significant.

RESULTS

The difference between age, weight and delivery age of studied newborns in 3 tested groups was not significant. In this study 70 % of the enfants were born with normal delivery and 30 % by cesarean section. There was no significant difference regarding the type of delivery between the groups. Serum bilirubin level of newborns in the study groups, on arrival was 17.5 ± 1.4 mg/dl, there was no important difference between the groups. However, decrease in the serum bilirubin level differed significantly between the 3 groups 12, 24, 48 and 72 h after the beginning of therapy (Figure 1). That is, 12 h after therapy serum bilirubin level in group 1 (clofibrate) and group 2 (phenobarbital) decreased by 21 % and 16 % respectively while it decreased only 8.5 % in control group. Furthermore, the rate of bilirubin decrease in group 1 was sharper than group 2 (Figure 1). After 24 h the corresponding figure decreased 37 %, 26.8 % and 18.5 % in group 1, 2 and control respectively.

The duration of hospitalization in the infants was 2 days ± 0.7. That is group 1, were hospitalized for 1.5 days ± 0.5, group 2 for 2 days ± 0.6 and control group for 2.6 days ± 0.6. Therefore duration of phototherapy was also significantly different among the groups.

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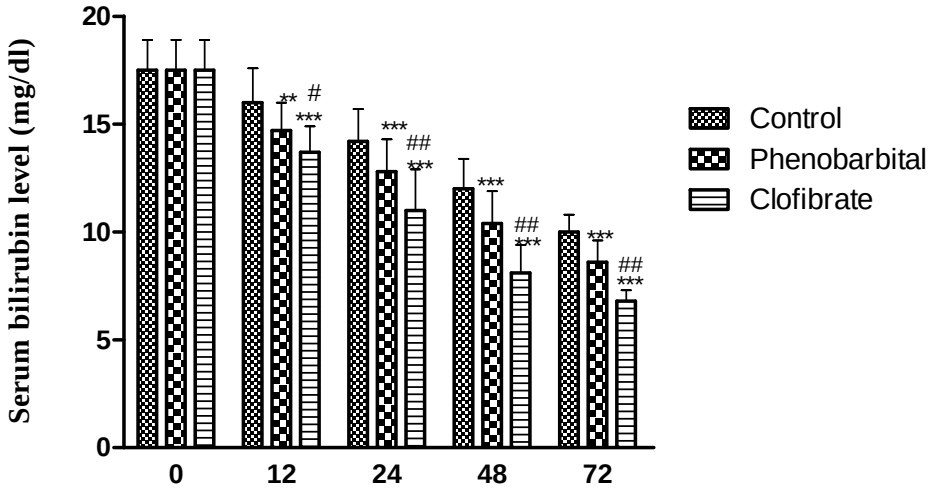

Figure 1: The effect of 100 mg/kg clofibrate or 5 mg/kg phenobarbital in addition to phototherapy, and phototherapy alone on the level of serum bilirubin 0, 12, 24, 48, and 72 h after reception. Results are expressed as group mean ± SD, n=30 in each group, ***P < 0.001 and **P < 0.01 compared to control values, # P < 0.05 and ## P < 0.01 compared to phenobarbital values

Group 1 underwent 1/5 days ± 0.5 of phototherapy, while group 2 and controls went through 2 days ± 0.6 and 2.6 days ± 0.6 of phototherapy, respectively. According to our results, no side effects were observed by clofibrate and phenobarbital single dose in this study.

DISCUSSION

Based on our findings, clofibrate effect on decreasing the serum bilirubin level was further than phenobarbital. Adding these drugs to phototherapy had a much higher effect in reducing the serum bilirubin level than using phototherapy alone 12, 24, 48, 72 h after reception. Besides, clofibrate reduced the duration of phototherapy and hospitalization that is of great importance. Prescribing a single dose of these two drugs had no side effects in newborns, which is in accordance with previous reports (Lindenbaum et al., 1981; Suh et al., 1996).

The management and detection of neonatal jaundice in healthy term and near term infants continue to remain a challenge partly because jaundice is common. Although kernikterus is rare but it is very important because of its consequences. Therefore finding approaches for better management of hyperbilirubinemia is critical. While phototherapy is an effective intervention that decreases bilirubin concentration (Sankaran, 2010). Due to its complications it would be vital trying to reduce the duration of phototherapy.

It has been reported that clofibrate decreases the bilirubin level of icteric newborns (Lindenbaum et al., 1981). Similarly, the duration of hospitalization and phototherapy was decreased. In study of Suh and co-workers (1996), phenobarbital was prescribed for jaundice newborns or to their pregnant mothers three days before delivery. Their results showed that serum bilirubin level in newborns taking phenobarbital was significantly lower than those whom the drug was prescribed for their mothers and also control group. Phenobarbital also proved efficacy on decreasing serum bilirubin level in our study. It should be mentioned that, in the previous study 3 mg/kg phenobarbital was used as intramuscular injection, in the present study 5 mg/kg phenobarbital was used orally. Further investigations may be necessary to evaluate the best route of drug prescription in icteric newborns.

In another study in Mexico (Bonifacio et al., 2001), similar evaluation on icteric

newborns was performed using two drugs phenobarbital and clofibrate together. Their results showed that there were no significant differences between the effects of these two drugs in decreasing the serum bilirubin level in infants. This is in contrast with our results that clofibrate was more effective than phenobarbital in treatment of newborns with hyperbilirubinemia.

Some studies have focused on the dose of drugs used in treatment of hyperbilirubinemia. Zahedpasha and co-workers (2007) showed that there is no significant difference between 25 and 50 mg/kg of clofibrate in decreasing the serum bilirubin level in icteric newborns.

In general, according to the results of our study, we concluded that, clofibrate and phenobarbital are effective for treatment of hyperbilirubinemia in icteric newborns and clofibrate is more suitable. Therefore clofibrate could be used as a safe drug in addition to phototherapy for treatment of newborns with non-hemolytic hyperbilirubinemia, due to its appropriate effectiveness and possibility of single dose prescription. It also reduces the length of hospitalization that would be of importance regarding financial matters as well.

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