Journal of
Babol University of Medical Sciences
JBUMS
e-ISSN: 2251-7170 p-ISSN: 1561-4107

Efficacy of Orlistat on Hyperbilirubinemia in Full Term Neonates

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Article Type

Research Paper

Received:
Jun 20th 2023
Revised:
Sep 2nd 2023
Accepted:
Oct 22nd 2023

ABSTRACT

Background and Objective: Jaundice is common in infants and occurs because of hyperbilirubinemia, which can lead to brain injury in neonates. Phototherapy, in addition to its serious side effects, does not seem to be enough in resolving jaundice. This clinical trial aims to compare the efficacy of orlistat and phototherapy combination therapy with that of phototherapy alone in the treatment of neonatal jaundice.

Methods: This clinical trial was performed on 120 term neonates with jaundice. Block randomization was used to allocate the infants to the intervention and control groups. The intervention group received orlistat (4 mg/kg body weight) for three consecutive oral doses at the first, second and third day of hospitalization, along with phototherapy. The control group received a placebo and phototherapy. Total and direct plasma bilirubin levels were measured at baseline (before intervention) as well as 24 and 72 h after treatment.

Findings: There were no statistically significant differences between the two groups in terms of infant sex, weight, or age. The mean total and direct bilirubin levels in the experimental group did not change compared to those in the control group at the end of the trial (10.44±1.35 vs. 10.6±2.8 and 0.4±0.1 vs. 0.5±0.1, respectively).

Conclusion: Orlistat appears to be ineffective in accelerating bilirubin reduction in neonates with jaundice, at least for the first three days of life.

Keywords: *Hyperbilirubinemia, Phototherapy, Neonates, Orlistat.*

Cite this article: Habibi M, Bahadoran E, SamieeRad F, Javadi A, Roozbehani G. Efficacy of Orlistat on Hyperbilirubinemia in Full Term Neonates. *Journal of Babol University of Medical Sciences*. 2024; 26: e30.

[DOI: 10.22088/jbums.26.1.30]

Introduction

Neonatal Hyperbilirubinemia, a condition that causes an increase in bilirubin levels, is the most common reason of hospitalization in infants. In the first week following birth, this phenomenon affects approximately 60% of full-term and 80% of preterm infants (1, 2). Hyperbilirubinemia can cause bilirubin encephalopathy or kernicterus if not detected and treated promptly (3).

One of the early lines of treatment for jaundice is phototherapy, whereby light is employed to convert bilirubin into photoisomers that can be eliminated through bile and urine (4). If phototherapy does not yield a response, or in cases of severe jaundice, blood exchange transfusion may be considered (5).

Phototherapy, once considered benign, may cause adverse effects. These include, but are not limited to, DNA damage, thermal and hydroelectrolytic imbalance, bronze baby syndrome, skin lesions, hematologic alterations, paralytic ileus, ocular effects, and neoplasms (6, 7). Therefore, in recent years, several studies have explored the application of methods and treatments using an array of substances to reduce associated complications. Among these studies, high-dose intravenous immunoglobulin, metalloporphyrins, ursodeoxycholic acid, and phenobarbital have been used (8-11).

Orlistat, a reversible inhibitor of gastric and pancreatic lipases, works locally within the lumen of the stomach and small intestine, preventing lipase from hydrolyzing dietary fat and inhibiting dietary fat absorption (12). Several studies have investigated the effects of orlistat on unconjugated hyperbilirubinemia (UCB). Orlistat increases fecal fat excretion and reduces UCB in Gun rats (13). Moreover, it has been shown that plasma UCB concentrations were negatively correlated with fecal fat excretion and dietary fat content. Orlistat was as effective as phototherapy for the treatment of UCB in Gunn rats (14). In another study, the administration of orlistat resulted in a decline in UCB levels in individuals with Crigler-Najjar syndrome. The decrease in plasma UCB concentration was intimately associated with the induction of fecal fat excretion by orlistat (15).

Considering the importance of neonatal jaundice, as well as the complications associated with phototherapy, it seems necessary to use complementary therapies along with phototherapy to accelerate bilirubin reduction as much as possible. To our knowledge, no study has investigated the effectiveness of orlistat as a complementary pharmaceutical treatment along with phototherapy for hyperbilirubinemia in infants. Therefore, we conducted a clinical trial to address this issue.

Methods

After being approved by the ethics committee of Qazvin University of Medical Sciences with the code IR.QUMS.REC.1397.278 and registered in the Iranian Clinical Trials Registration Center with the code IRCT20190105042241N1, this double-blind randomized clinical trial was conducted on 120 infants with indirect hyperbilirubinemia who were admitted to the Kowsar Hospital in Qazvin, Iran, in 2019. According to a study by Habibi et al. (16), 48 samples were calculated for each group. Considering a 20% drop, 60 samples were considered for each group.

Term infants with physiological jaundice, birth weight 2000-4000 g, age 1-7 days, serum bilirubin level 6.9-21 mg/dL less than 15% of direct bilirubin (direct serum bilirubin level in these infants was less than 2 mg/dL) were included in the study. Premature infants, congenital abnormalities, neonates with infection, meningitis, dehydration, any clinical or laboratory evidence of hemolysis, glucose 6-phosphate dehydrogenase deficiency (G6PD), ABO incompatibility, positive Coombs test, hypothyroidism, mechanical ventilation and infants who developed gastrointestinal problems after oral administration of orlistat were excluded.

[DOI: 10.22088/jbums.26.1.30]

Neonates were randomly divided into intervention and control groups using a random number table to give each participant the same chance to be located in either group. After explaining the study goals and the cons and pros of the intervention, informed consent was obtained from the parents who provided written consent. In case of gastrointestinal side effects, the drug was stopped, and phototherapy was continued. All infants were treated with intensive phototherapy according to the Clinical Practice Guideline Manual of the American Academy of Pediatrics (17). The Tosan apparatus, equipped with four Philips lamps, was utilized to administer phototherapy to both groups, with the device positioned 25 cm away from the infant's surface and a minimum radiation intensity of 10μW/cm2/nm. In addition to phototherapy, the experimental group received 4 mg/kg orlistat (containing 120 mg of drug per capsule; Sanofi Company, France) for three consecutive days. Infants who recovered after 24 and 48 h and were discharged, and received the second and third doses of the drug, respectively, in an outpatient setting to prevent recurrence. The control group received the same amount of distilled water as the placebo. Orlistat or placebo was administered by nurses based on the researcher's prescription. The blood samples were collected by nurses and sent to the laboratory. All who administered the medication and took blood samples, as well as the laboratory staff, were blinded to the type of medication used. A checklist for data collection, including the baby's demographic information including sex, age at admission, birth weight, and bilirubin level at the time of admission (before intervention) and 24 hours and 72 hours after the first drug dose, was prepared by one of the researchers, who was aware of the research process but did not know the type of prescribed drug. Total and direct serum bilirubin levels were measured in both groups at baseline (before intervention) and at 24 and 72 h after the start of treatment in the university's reference laboratory.

Data were entered into SPSS software version 22. After checking the normality of the data using the Kolmogorov-Smirnov test, the t-test for independent samples (total bilirubin) or the Mann-Whitney U test (direct bilirubin) was used for analysis, and $p<0.05$ was significant in considered.

Results

In this study, out of 120 babies with jaundice, 60 babies (34 boys and 26 girls) were included in the intervention group and received a combination of phototherapy and orlistat, while other 60 babies (27 boys and 33 girls) were placed in the control group and treated only with phototherapy. There was no statistically significant difference between the two groups in terms of sex, weight and age of the baby (Table 1).

Table 1. Comparison of Gender, Age, and Birth Weight Distribution of Neonates in Intervention and Control Groups

Demographic Information	Intervention Group Number(%)	Control Group Number(%)	p-value
Gender			
Male	34(56.7)	27(43.3)	0.273
Female	26(43.3)	33(56.7)	
Age			
<3	24(40)	25(41.7)	
3-7	33(55)	33(55)	1
>7	3(5)	2(3.3)	
Birth Weight			
2000-3000	27(45)	25(41.7)	0.854
>3000	33(55)	35(58.3)	

[DOI: 10.22088/jbums.26.1.30]

Moreover, at the beginning, 24 and 72 hours after the intervention, there was no statistically significant difference between the total and direct mean serum bilirubin levels between the two groups (Table 2).

Table 2. Comparison of Serum Total and Direct Bilirubin at the Baseline, 24 and 72 hours After Treatment in Intervention and Control Groups

Bilirubin at different times	Intervention (orlistat+phototherapy) Mean±SD (mg/dL)	Control (phototherapy) Mean±SD (mg/dL)	p-value
At hospitalization			
Total	14.84±2.99	14.2±2.6	0.341
Direct	0.4±0.1	0.5±0.1	0.471
24h after intervention			
Total	11.65±2.56	10.75±2.39	0.114
Direct	0.5±0.1	0.4±0.1	0.166
72h after intervention			
Total	10.44±1.35	10.6±2.8	0.628
Direct	0.4±0.1	0.5±0.1	0.403

Discussion

According to the results of this study, there were no statistically significant differences between the two groups when comparing the mean total and direct serum bilirubin levels either at baseline or after 24 and 72 hours of intervention. In recent years, several studies evaluated the effectiveness of pharmacological agents, such as orlistat, in the treatment of hyperbilirubinemia. Compared to infants fed with the formula, effective fat absorption in breastfed infants may limit UCB excretion, worsening neonatal hyperbilirubinemia (18). The stimulation of fecal fat excretion in Gunn rats with indirect hyperbilirubinemia using orlistat increases fecal UCB excretion and decreased plasma UCB levels (13, 14).

Nonetheless, there is no clinical evidence of a relationship between neonatal jaundice and fecal fat excretion during the first few days after birth. De Carvalho et al. showed that compared to formula-fed infants, breast-fed infants had lower bowel movements and higher serum bilirubin during the first three days of life (19). Similarly, Gourley et al. reported a negative relationship between fecal production and serum bilirubin levels in healthy-term infants during the first three weeks of life (20). However, none of these studies quantified fecal fat content; therefore, it is unclear whether the differences observed were related to a reduction in fecal fat in breastfed infants. Buiter et al. (21) showed that infants fed with either breast milk or formula showed no differences in bilirubin concentration or fecal production content, negating the relationship between neonatal jaundice and breastfeeding in healthy infants during the first days after birth. Furthermore, owing to the improved absorbability of formula milk since 1985, fat excretion and fecal production are comparable between infants fed either breast or formula milk, resulting in similar capabilities in the luminal uptake of UCB and prevention of enterohepatic circulation (21).

Overall, studies on Gunn rats (13, 14) and Crigler-Najjar (15) have suggested a role for dietary fat absorption in determining the therapeutic response to orlistat. The lack of difference between the intervention and control groups in this study may be related to the effects of this parameter. Therefore, future studies should investigate the effect of fecal fat content on serum UCB levels and response to orlistat therapy. On the other hand, to exert its therapeutic efficacy in humans, orlistat has been proposed to be consumed daily for 4-6 weeks, which can be another reason for the lack of significant difference between

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the study groups in the present clinical trial, in which only three doses of the drug were administered. The therapeutic response to orlistat can also be affected by other factors, such as gastrointestinal lipase levels and intestinal bacterial flora (18). The lipase enzymes present in the infant's intestine can originate from the pre-duodenum, pancreas, or breast milk. Pancreatic lipase is secreted from approximately the 30th week of pregnancy, but it has a very low concentration in the first year of life due to insufficient development of the pancreas in term and preterm infants (22). Although pancreatic lipase alone is not capable of effectively hydrolyzing milk triglycerides in vitro, the combination of preduodenal and pancreatic lipases is 20-fold more potent in releasing milk-free fatty acids (22). Considering that orlistat is an inhibitor of pancreatic lipase, the failure of the drug to improve hyperbilirubinemia in this study may be partly related to the low concentration of pancreatic lipase in the intestine of infants during the first year after birth (23).

Orlistat appears to be ineffective in accelerating bilirubin reduction in neonates with jaundice, at least for a short time and the first three days of life. Nevertheless, it is recommended to investigate the potential role of other factors such as fecal fat excretion, treatment duration and dose, intestinal lipase content and composition, and intestinal microbial flora in determining the therapeutic response to this drug among infants with neonatal hyperbilirubinemia.

Conflict of interest: The authors declare that they have no conflicts of interest.

Acknowledgment

We hereby acknowledge the Research and Technology Vice-Chancellor of Qazvin University of Medical Sciences and the Clinical Research Development Unit of Kowsar Hospital, Qazvin.

[DOI: 10.22088/jbums.26.1.30]

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[DOI: 10.22088/jbums.26.1.30]