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Effect of Probiotics on Serum Bilirubin Level in Term Neonates with Jaundice: A Randomized Clinical Trial

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Abstract

Background

In recent years, the tendency to use drugs has been increasing in the treatment of neonatal jaundice. Several drugs have been used since then, but the effect of probiotics on serum bilirubin level (SBL) is not so clear. This study was conducted to evaluate the effect of probiotics on SBL and the duration of phototherapy in term neonates with hyperbilirubinemia.

Materials and Methods: In this randomized clinical trial, we studied 150 term neonate with jaundice hospitalized for phototherapy in Amirkola Children's Hospital, Babol- Iran, during October 5, 2016 till May 19, 2017. Eligible neonates were randomly divided into two; intervention (n=75), and control (n=75) groups. Both groups received standard conventional phototherapy, but the intervention group received 10 drops/day of probiotics (Pedilact Zisttakhmir. Co. Iran), until hospital discharge. The outcome variables were SBL and the duration of phototherapy. The data were analyzed by SPSS 22.0 and the P (0.05 was considered significant.

Results: The mean SBL before intervention in the intervention and control groups was 16 ±1.9 and 16.9±1.9 mg/dl, respectively (P>0.05). After 24, 48 and 72hours it decreased to 13.73±1.72, 10.92±1.87 and 10.25±1.32 in the intervention and 13.66±1.91, 11.01±1.69 and10. 09±1.38 in the control groups, respectively, but a comparison of the amount of SBL reduction between the two groups was not significant (P>0.05). The duration of phototherapy in the intervention group and the control group was 3.61±1.17 days and 3.72±1.18 days respectively (P>0.05).

Conclusion

Oral probiotics in neonates with jaundice have no significant effect on SBL and the duration of phototherapy. Further studies are needed with longer time follow-up.

Key Words: Bilirubin, Jaundice, Newborn, Phototherapy, Probiotic.

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1- INTRODUCTION

Approximately 60% of term neonates and 80% of preterm infants in their first week of life develop into neonatal jaundice. The most common cause of hyperbilirubinemia is the physiologic jaundice, which is diagnosed by rejecting other causes jaundice like hemolysis, infection and metabolic disorders (1-3). In 2% of term neonates, bilirubin levels can reach to 20 mg/dl requiring therapeutic intervention, and if left untreated, it can lead to bilirubin induced neurologic dysfunction and chronic neurological damage (4). The goal of the treatment of hyperbilirubinemia is to prevent neurological damage. The most common treatment for neonatal jaundice is phototherapy. The safety of phototherapy has been proven for decades (5).

However, higher bilirubin levels may require exchange transfusion. Previous studies have suggested some agents such as metalloporphyrins, phenobarbital, clofibrate and Intravenous immunoglobulin (IVIG) for the treatment of jaundice (6, 7). Also, activated charcoal, agar and cholestyramine have been used as a supplement to reduce bilirubin levels, but these agents are not so safe to use routinely. Some studies have evaluated the effect of probiotics on the serum bilirubin levels, and reported that the time required for phototherapy had been reduced (8, 9).

But there are some studies done elsewhere showed no effect of probiotics on SBL reduction (10, 11). Also, there is not enough evidence to recommend it for serum bilirubin level reduction in neonatal jaundice. So the purpose of this study was to evaluate the effect of probiotics on reducing the SBL, the duration of phototherapy and hospital stay in term infants who were hospitalized due to jaundice.

2- MATERIALS AND METHODS

2-1. Study design and population

This is a double-blind randomized clinical trial was done on neonates with hyperbilirubinemia otherwise normal visited at Amirkola Children's Hospital (ACH) of Babol city, Mazandaran province, North of Iran, hospitalized only because of indirect hyperbilirubinemia. They were admitted and underwent phototherapy based on the guideline of the American Academy of Pediatrics (AAP) (12) for the treatment of neonatal hyperbilirubinemia, during October 5, 2016 till May 19, 2017. A sample of 75 subjects was selected in each group. The allocated sample size can detect the effect size of 0.5 mg/dl in differentiating the levels of bilirubin between groups with 95% confidence interval and 80% power.

2-2. Inclusion and exclusion criteria

The inclusion criteria were neonates (older than 72 hours) with hyperbilirubinemia otherwise normal, who visited at Amirkola Children's Hospital only because of indirect hyperbilirubinemia. Exclusion criteria were as the following: ABO incompatibility, Rh incompatibility, Glucose-6-phosphate dehydrogenase (G6PD) deficiency, birth weight <2,500 grams, previous sibling blood transfusion, gestational age < 37week $\pm$7 days and taking any medication like phenobarbital and all kinds of folk remedies for jaundice.

2-3. Methods

All the neonates who met the inclusion criteria were selected, informed consent was taken from parents; afterward they were assigned in two groups by simple randomization using computerized random-number table. Both groups were matched for confounding factors including age, gender and weight at birth. Routine tests to work-up neonatal indirect hyperbilirubinemia including total and direct bilirubin measurement, maternal and neonatal blood group, direct Coombs test, glucose-6-phosphate dehydrogenase

deficiency test, thyroxine (T4), thyroid-stimulating hormone (TSH), peripheral blood smear, and reticulocyte count were performed for all participants.

2-4. Intervention

Both groups were hospitalized and underwent conventional phototherapy by phototherapy devices (David Co, China) with the same quality, based on the guideline of the American Academy of Pediatrics (AAP) monogram for the treatment of neonatal hyperbilirubinemia (12). In the intervention group, probiotics (Pedilact, Zisttakhmir Co, Iran) 10 drop/day was prescribed until the discharge from hospital. The primary outcome was SBL, and the secondary outcomes were the time needed for phototherapy and length of stay.

2-5. Laboratory measurements and measuring tools

The SBL was measured in both groups during the hospitalization and discharge, SBL at the time of admission, 24, 48, 72hours and at the time of discharge used for comparison between the two groups. SBL was measured using spectrophotometry with biochemistry kits made in Iran at the Amirkola Children's Hospital laboratory. This technique measure the serum bilirubin levels (SBL) with the accuracy of ± 0.5 mg/dl.

2-6. Ethical consideration

Informed consents were taken from the parents and the protocol of the trial was submitted in the Ethics Committee of Babol University of Medical Sciences (MUBABOL, HRI.REC. 1395. 80) and it was registered at www.irct.ir under the number IRCT.2017032333129N1.

2-7. Statistical analyses

The data were analyzed using SPSS version 22.0 software. The paired t-test, ANOVA and repeated measure were performed to show the changes of bilirubin levels before and after intervention and the independent t-test was applied for comparison of bilirubin levels and duration of phototherapy between experimental and control groups. The P-values less than 0.05 were considered significant.

3-RESULTS

The study was performed on 150 neonates in two groups of 75 neonates. Comparison of the baseline demographic data of the two groups is presented in **Table.1**. There was not any significant difference between two groups. Mean SBL in both groups at admission, 24, 48 and 72hours thereafter are shown in **Table.2**. With phototherapy serum bilirubin level in all patients in both groups were reduced (P< 0.001), but no significant difference was seen between the intervention and control groups, after 24 hours (P=0.80), 48 hours (P=0.76) and 72 hours (P=0.74). The duration of hospitalization and phototherapy was 3.61 ± 1.17 days in the intervention group and 3.72 ± 1.18 days in the control group and there was no significant difference between the two groups (P= 0.58) (**Figure.1**).

Table-1: Baseline demographic data in experimental and control group

Variables		Groups		P-value
		Experiment (n=75) Number (%)	Control (n=75), Number (%)	
Gender	Boy	36(48)	37(49.34)	0.86
	Girl	39(52)	38(50.66)	
Weight (gr)		3356±15	3214±23	0.75
Type of delivery	NVD	39(52)	38(50.66)	0.88
	C/S	36(48)	37(49.34)	

NVD: normal vaginal delivery; C/S: cesarean section.

Table-2: The mean SBL at admission, 24, 48 and 72 hr after phototherapy in both groups

Groups	Time				P-value*
	At admission	After 24 hr	After 48 hr	After 72 hr	
Experimental	16.00±1.90	13.73±1.72	10.92±1.87	10.25±1.32	<0.001
Control	16.29±1.90	13.66±1.91	11.01±1.69	10.09±1.38	<0.001
P-value**	0.35	0.80	0.76	0.74	

*: Repeated Measures ANOVA; **: Independent Samples Test.

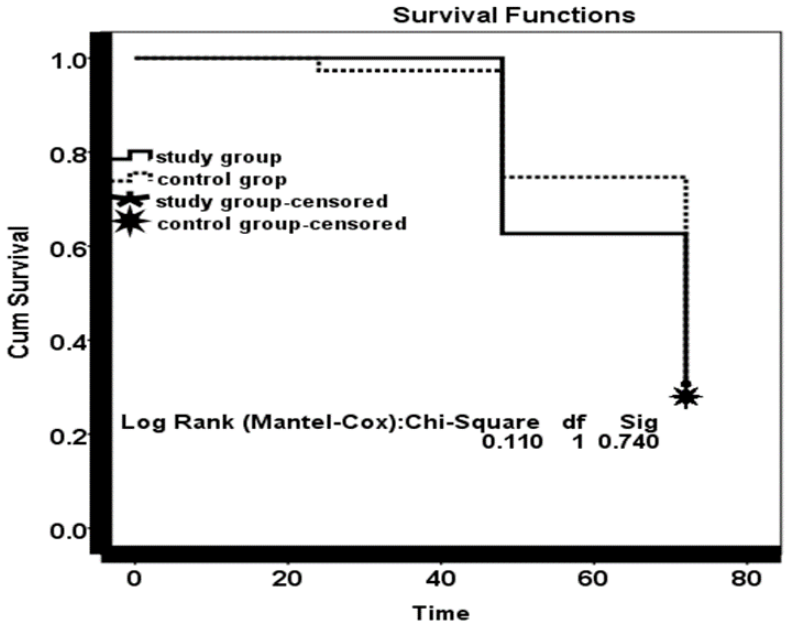

Fig.1: Comparison of time required to reach the serum bilirubin levels below 10 mg/dl in two experimental and control groups by Kaplan Meyer.

4- DISCUSSION

The result of our study revealed that Probiotics with phototherapy does not affect serum bilirubin levels and the duration of hospitalization for phototherapy. Overall the total numbers of the clinical trials regarding the impact of probiotics on hyperbilirubinemi (HB) are scant. The results of our study confirmed the findings or other researches like Serce et al. In a prospective, double-blind, placebo controlled trial on 119 neonates they investigated the efficacy of Saccharomyces boulardii supplementation on SBL and hyperbilirubinemia. They concluded that Saccharomyces boulardii did not influence the clinical course of hyperbilirubinemia significantly. The explanation of Serce et al. regarding the lack of beneficial effect of probiotics on SBL is also applicable to our study, too (10). It may be related to the doses of probiotic bacteria strains, their ability to survive and proliferating in the intestinal environment. Pedilact is a probiotic contains Lactobacillus rhamnosus, Lactobacillus reuteri and Bifidobacterium infantis with a colony forming units (CFU) 10^9 per ml of the culture. It also has Fructooligosaccharides (FOS) as a prebiotic (13). In fact, it is a symbiotic. The ingredient and the serotype of the bacteria in the Pedilact are not as the same as the other type of the available

commercial probiotic drops. So its effect on SBL may differ to the other probiotics or symbiotic drops. Most of the clinical trial reported beneficial effect of probiotics on SBL and hyperbilirubinemia Demirel et al. assessed the probiotic effect of Saccharomyces boulardii in jaundice and treatment of 179 very low birth weight infants. They reported that the duration of phototherapy in infants receiving probiotics was shorter than that of the control group. There was no difference in SBL between the two groups in the present study (14). The difference between this study and the present study may be due to the fact that probiotics strains are different. Yuan et al. investigated the efficacy of oral probiotics and its effect on immunity in treating hyperbilirubinemia of neonates. They concluded that additional oral probiotics may improve the effect of phototherapy on hyperbilirubinemia and promote immune function (8).

Mu et al. in a clinical trial studied the effect of Saccharomyces boulardii on the serum bilirubin level. At the end of the study, they found Saccharomyces boulardii is effective in reducing SBL (9). Armanian et al. conducted a study on 50 preterm infants to evaluate the role of prebiotics on jaundice. In this study, oligosaccharides were used as prebiotics group. In this study, the frequency of bowel movements in the intervention group increased and the level of bilirubin decreased (15).

In our study, the frequency of bowel movements was not measured, which is one of the limitations of our study. Also, the reason for the difference in the result between our study and the above study could be related to the different supplement probiotics. Lingling et al. observed that the use of probiotics Mami Ai reduces breast milk jaundice by constructing intestinal microflora in newborns (16). Also Yu et al. (2003) examined the role of probiotics in the prevention of jaundice in 74 neonates. They reported that the incidence of jaundice was significantly lower in the intervention group than in the control group (33.3% vs. 57.14%) (17). Bisceglia et al. performed a study on 76 neonates. The rate of bilirubin in the group receiving probiotics 72 hours after birth was significantly lower than the control group. In this study, the method of measuring bilirubin with the help of skin bilirubinometer was probably the reason for the difference in the findings (18).

4-1. Limitations of the study

This is the first study done in Iran to evaluate the effect of Pedilact on neonatal jaundice. We could not evaluate neonates for colonization of probiotic bacteria. Not a significant difference in SBL in the two groups may be associated with this fact that our selected probiotics may not colonize the neonate's intestine. So, more evidences are required to recommend for clinical use in neonatal hyperbilirubinemia.

5- CONCLUSION

Oral administration of probiotics was not effective in reducing SBL and the duration of phototherapy and hospital stay. More clinical trials with larger sample size and check the colonization of neonate's intestinal flora seem to be needed.

6- CONFLICT OF INTEREST

The authors have nothing to declare.

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