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~~Effect of Probiotic on the treatment of jaundice in full term neonates: A Randomized Clinical Trial~~

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Abstract

Purpose: Jaundice is the most causes of admissions in neonatal period. Nowadays, in addition to usual phototherapy, other auxiliary methods are used to reduce jaundice and Hospitalized Duration. This study aimed to investigate the effect of probiotic on treatment of hyper-bilirubinemia in full term neonates.

Methods: In this randomized clinical trial, 83 full term neonates who admitted to Hospital for receiving phototherapy in the first 6 months of 2015 were divided randomly into two groups; synbiotic (SG, n= 40), and the control group (CG, n = 43). Both groups received usual phototherapy but SG received extra 5 drop/day of synbiotic. Serum bilirubin, urine, stool, feeding frequency and weight were measured daily until hospital discharge. The P-Value < 0.05 was considered statistically significant.

Results: The mean total serum bilirubin in synbiotic group was lower than control group (9.38±2.37 and 11.17±2.6 mg/dl respectively). The urine and stool frequency in the synbiotic group was significantly more ($p<0.05$). The duration of hospitalization in synbiotic group was shorter than control group.

Conclusion: Use of Synbiotic as an adjuvant therapy in our study had a significant treatment effect on jaundice in full term neonates. Further studies including larger samples with long follow up are essential to confirm the routine use of synbiotic in neonatal jaundice.

Key words: Hyper-bilirubinemia; Probiotic; Synbiotic; Phototherapy; Jaundice; Neonate.

Introduction

Jaundice is the most common medical condition within few days after birth in newborns. Physiologic jaundice during the first week of life is seen in about 60-80% of neonates. [1] [2] [3].Two factors may lead to high levels of unconjugated bilirubin, these include sterile intestines of neonates at birth; in this case, conjugated bilirubin cannot be converted to stercobilin or urobilirubin to be passed out of the body without involving the intestinal flora. Secondly, many neonates intestinal beta-glucuronidase enzyme converts bilirubin back to the unconjugated form. Neonate's feeding assists in the establishment of a normal intestinal flora and enhances meconium passage. Meconium have contains abundant bilirubin. In cases of delayed feeding or inability to pass out meconium, the exposure of beta-glucuronidase enzyme is prolonged in the intestine and therefore elevating the possibility of converting the unconjugated form of bilirubin to the conjugated form(2) (3). Inadequate intake of fluids , significant weight loss and decreased bowel movements puts neonates at high risk of hyperbilirubinemia (2).

Phototherapy is the most common intervention in the treatment of neonatal hyperbilirubinemia. Phototherapy reduces the level of total bilirubin or slow down the increases in almost all patients, regardless of the cause (4). Phototherapy seems safe, but possible side effects include transient erythematous rash, loose stools, hyperthermia, dehydration (5), and gray baby syndrome (6). The mother and baby can suffer psychologically and emotionally, due to the phototherapy when they are physically separated (7) (8). Although blood transfusion is expensive and time consuming, but it's the most effective method for the rapid removal of excess bilirubin from the blood circulation (4). The mortality and morbidity associated with blood transfusions, because it's rarely done, is not fully known (8).

Elevated serum total bilirubin can result in bilirubin encephalopathy, resulting in kernicterus with risk of permanent severe neurodevelopmental disabilities or death.

Herbs from shatru, jujubes, manna and clay, are also used for the treatment of hyperbilirubinemia in Iran (9). Another treatment for elevated bilirubin level is the intake of probiotics. Probiotics are live microorganisms which when consumed by certain humans or animals, has a beneficial effect on the microbial flora. Most probiotics belong to a large group of bacteria that live in human gut flora in a commensalism relationship (10)(11). The main effect of probiotics is to stabilize the intestinal micro flora, it is observed that constant consumption of probiotics reduces the incidence of various diseases, hospitalized children, and those who do not consume milk or are living in deprived conditions are vulnerable to diseases. Probiotic products are available for sale in the commercial market in the form of tablets, capsules, powders, fortified yogurt, milk and cheese (12). Apart from the effect of probiotics in the treatment of hyperbilirubinemia, they are also used for the treatment of children with acute diarrhea, necrotizing enterocolitis and allergies (13–15). This study aimed to investigate the effect of synbiotic on hyper-bilirubinemia treatment in term neonates.

Materials and Methods

This study is a clinical trial carried out on 83 full term and exclusively breast-fed neonates without pathologic jaundice who admitted to Shahid Madani Hospital, Khorramabad, Iran in the first 6 months of 2015 with serum bilirubin level between 15 to 20 mg/dl. They should not be suffering from sepsis, fauvism, congenital anomalies, asphyxia, heart disease and IUGR before inclusion. The neonates were randomly placed into two groups. Randomization was carried out using sequential numbers obtained from the computer center of the neonatal ward. The control group underwent only routine treatment of hyperbilirubinemia, i.e. phototherapy. For phototherapy, fluorescent lamps were used in the neonatal ward. The distance between fluorescent lamps and babies was 30 to 50 cm. newborn's eyes and genital parts were covered. For every two hours of phototherapy, half an hour break from phototherapy devices, and neonates were breastfed with open eyes.

The neonates in the synbiotic group, received 5 drop/day of synbiotic (Pedilact drop, manufactured by Zist-Takhmir Company, Iran) in addition to routine phototherapy as stated above. To sanitize every baby, each has its own drop in the refrigerator which was maintained at 2 to 8ºC. It was often placed in room temperature for 10 minutes prior to use, and 5 drops was administered daily in the synbiotic group.

The serum bilirubin level feeding, urine and stool frequency in both groups were measured daily. The weight (gram) of neonates was measured daily also. Those with bilirubin level <11 mg/dl were discharged. This study was approved by the Research Ethics Board of Lorestan University of Medical Sciences. **IRCT Code: IRCT2015112925287N1**

Data analysis

Descriptive statistics was evaluated as (mean, standard deviation and frequency), to compare statistics, repeated measure analysis and t test was used with a significance level of <0.05. Data are expressed as Mean ± SEM (standard error of the mean). To evaluate the hypothesis of equal variance in outcomes, random effects with matrix of covariance was used.

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Results

In this study, 83 full term neonates with hyper-bilirubinemia in two groups; synbiotic (n= 40), and the control group (n = 43) were studied (figure 1). The final bilirubin level was 9.38±2.37 and 11.17±2.6 mg/dl in the synbiotic intervention and control group respectively. The average number of days of hospitalization in the intervention and control group was 2.5±0.58 and 2.9±0.89 days respectively. Mean and SEM of the both groups were shown in Figure 2. The effect of the synbiotic intervention on the variables such as bilirubin, urine frequency and defecation was statistically significant compared to the control group

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(p<0.05). The mean total bilirubin level was lower in the intervention group. In synbiotic group compared to the control group urine frequency (6.86 vs. 5.500) and stool frequency (5.528 vs. 3.903) were more significantly (Figure 3).

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According to table 1, it was observed that there is a significant difference between the average number of days of hospitalization between the groups (p<0.05). The average number of days of hospitalization in the probiotic group was lower than the control group. There was a significant difference in the bilirubin levels, frequency of stools, feeding and urine frequency in both groups during hospital stay (Figure 3) (p <0.05). The mean frequency of defecation and total levels of bilirubin were significantly different between-groups (p <0.05). The frequency of feeding was higher in the synbiotic group as compared to control group. For all the above-mentioned parameters at three different times, the bilirubin level, defecation, urine frequency and feeding, there was a significant difference (p<0.05) observed. There was no significant difference within the groups studied.

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Discussion

The present study investigated the effect of synbiotic compared with phototherapy alone during hyperbilirubinemia treatment in term neonates. Hyperbilirubinemia is one of the most frequent problems in newborns and 60% of term neonates encounter jaundice in the first week of life. Elevated amount of unconjugated bilirubin in serum and across the blood-brain barrier subsequently leads to bilirubin encephalopathy, kernicterus and the risk of permanent severe neurological impairments (16,17).

A meta-analysis conducted by Chen et al., aimed at systematically evaluating the safety and efficacy of probiotics supplement therapy for pathological neonatal jaundice, showed that probiotics supplementation therapy is a safe and efficient treatment for pathological neonatal jaundice (19). In another systematic review by Deshmukh et al., (20) to evaluate the safety and efficacy of probiotics in reducing the need for phototherapy and its duration for the treatment of neonatal hyperbilirubinemia, a limited low-quality evidence shows that the supplementation of probiotic may decrease phototherapy duration in neonatal jaundice. A routine use of probiotics as preventive measures or for the treatment of neonatal jaundice cannot be recommended.

In a study using probiotics in combination with phototherapy, there was a decreased in the days of hospitalization for neonates with hyperbilirubinemia and no adverse effect was detected (21). In another study, probiotic yeast, was administered once a day in premature neonates with birth weight under 1500 grams, short term intake of probiotic decreased the length of phototherapy, justified by improving intestinal transit time and inhibiting reabsorption of bilirubin (4). L. acidophilus consumption in experimental animal models reduces enzyme fecal activities including nitroreductase, glucuronidase, and azoreductase (22,23).

Newborns that were breastfed may be vulnerable to early-onset exaggerated physiologic jaundice due to the deprivation of relative caloric during the first few days of life (24). A reduced amount and feeding frequency may result in a mild dehydration and a delayed meconium passage. As compared to formula-fed newborns, breastfed infants are 3-6 times vulnerable to jaundice (< 12 mg per dL) or severe jaundice (< 15 mg per dL [257 µmol per L])(25,26).

In the present study, there was no difference initially in the variables (weight, bilirubin, defecation, feeding, sleep, and urination) before the commencement of the study. However, following the administration of the treatment and observation at day 1, 3, and 7, the baby gained weight but this difference was not significant ($P<0.05$). There was a sharp decrease in the level of bilirubin in the treatment group on the 7^{th} day as compared with the control, showing the intervention was effective ($P<0.05$). However, the level of defecation, feeding, sleep and urination was significantly increased ($P<0.05$) (Figure 2).

Conclusions

In conclusion, this study shows a reduction in hyperbilirubinemia and hospitalization day using synbiotic, as an adjuvant therapy. Further studies including larger samples with long follow up are essential to confirm the routine use of synbiotic in neonatal jaundice.

List of abbreviations

Fructooligosaccharides (FOS)

Ethical approval and consent to participate

All procedures performed in this study involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. Consent to participate: from the under 16 years old was given by a parent or legal guardian

Consent for publication: Not applicable

Availability of data and material: Data sharing not applicable to this article as no datasets were generated or analyzed during the current study.

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Competing Interests: The other authors have no conflicts of interest to disclose.

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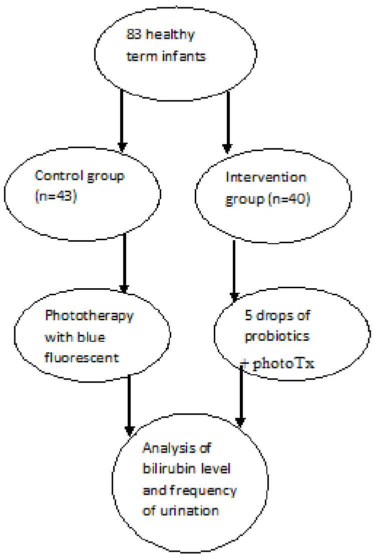
Figure 1. Flow chart of the study



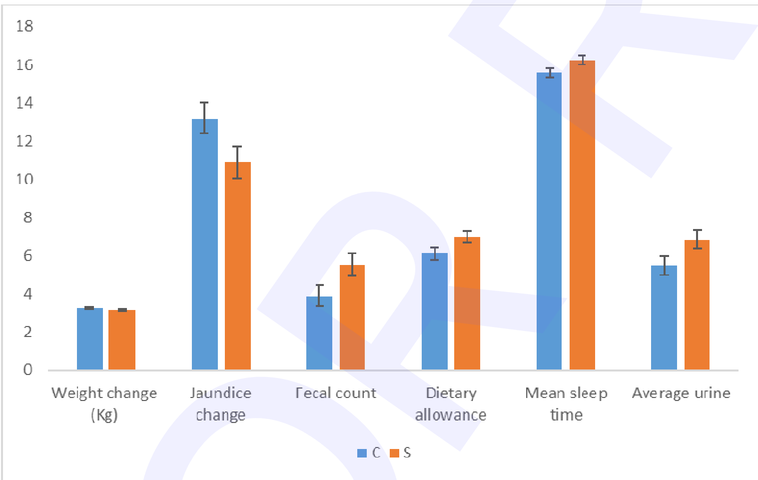


Figure 2. Mean and SEM variables examined in the intervention (symbiotic S) and control (C) groups

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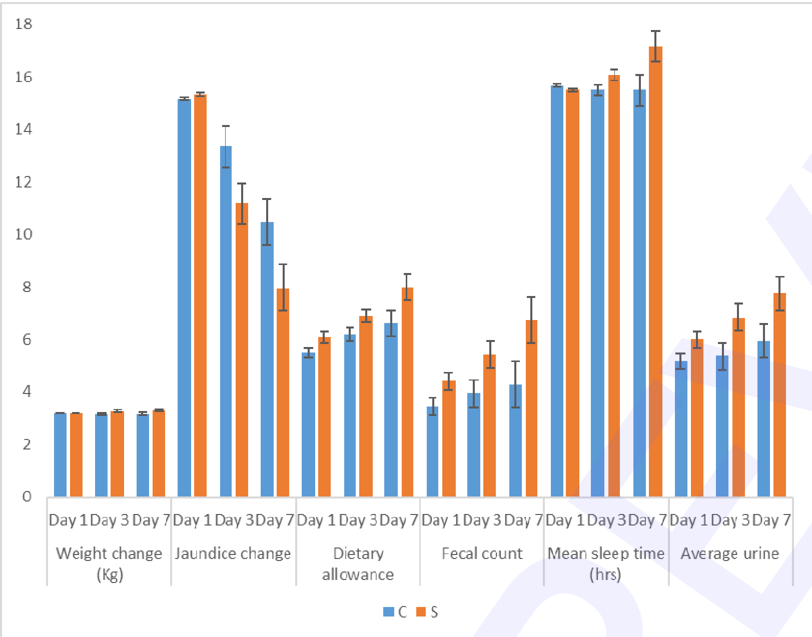

Figure 3. Mean SEM of variables studied in the both groups (symbiotic S, control C) during hospital stay

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Table 1: Comparison of demographic data of the newborn and mother in both groups

Variable	Experimental group	Control group	Statistics
Gestational age (hour)	39.2 ± 3.9	39.0 ± 4.1	0.90
Infant height (cm)	43.4 ± 3.8	43.9 ± 3.5	0.77
Mean Hospital Stay (days)	2.5±0.58	2.9±0.89	0.001