



The Effect of Lactoacidophilus Probiotic on Duration of Physiologic Jaundice in Neonates with 37-42 Weeks Gestational Age: A Randomized Clinical Trial

Badri Farhand¹, Elahe Dehghan Nayeri², Tamara Shirzad kebria³, Mahsa Ghaffarzadeh Khoei⁴, Alireza Jashni Motlagh^{5*}

¹MSc, Neonatal Intensive Care Nursing, Clinical Research and Development of Kamali Hospital center, Alborz University of medical sciences, Karaj, Tehran, Iran.

²MSc, Health Care Management, Clinical Research and Development of Kamali Hospital Center, Alborz University of Medical Sciences, Karaj, Tehran, Iran.

³MSc Midwifery, Alborz University Of Medical Sciences, Karaj, Iran.

⁴MSc Midwifery, Clinical Research and Development of Kamali Hospital center, Alborz University of Medical Sciences, Karaj, Tehran, Iran.

⁵Pediatrician and Neonatologist Assistant Professor of Pediatrics & Amp; Neonatology, Alborz University of Medical Sciences, Karaj, Tehran, Iran, Email: aj_motlagh@yahoo.com

ABSTRACT

Introduction & Background: According to socioeconomic burden of neonatal jaundice, it is important to provide interventions that reduce the severity and duration of treatment. Given the ease of probiotics usage; the aim of this study was to determine the effect of probiotics on the level of bilirubin and during hospitalization due to physiological jaundice in term neonates.

Methods: The present study was a randomized clinical trial study performed in Kamali Hospital, Alborz Province, Iran, which has the most equipped neonatal intensive care unit. The study samples were all neonates with 37-42 weeks gestational age hospitalized in neonatal intensive care unit and neonates with physiologic jaundice referred to the hospital up to 5 days after birth. Sampling was based on availability and randomized using a randomized number table. the intervention group received lactosacidophilus probiotic with milk two time per day in addition to phototherapy; And the control group was treated only with phototherapy. the bilirubin of both groups was checked daily and written in a table ; Finally, bilirubin level at admission and discharge time and also duration of hospital stay in both groups were compared using SPSS software.

Results: There was no statistically significant difference between demographic characteristics in the control and Intervention groups. The results showed that there was no statistically significant difference between two group bilirubin level mean at discharge and hospitalization time ($p=0.68$). The Mann-Whitney test showed that the length of stay in the hospital was 0.7day shorter in the Intervention group and this difference was statistically significant ($p=0.002$).

Conclusion: use of Lactobacillus bifidus Probiotic reduces hospital stay duration in neonates with physiological jaundice but has no effect on bilirubin level.

ARTICLE HISTORY

Received October 06, 2020
Accepted November 14, 2020
Published December 18, 2020

KEYWORDS

Lactobacillus bifidus,
Probiotics, Physiological
jaundice, Term newborn.

* **Contact:** Alireza Jashni Motlagh, Pediatrician and Neonatologist Assistant Professor of Pediatrics & Amp; Neonatology, Alborz University of Medical Sciences, Karaj, Tehran, Iran, aj_motlagh@yahoo.com

2020 The Authors. This is an open access article under the terms of the Creative Commons Attribution Non-Commercial Share Alike 4.0 (<https://creativecommons.org/licenses/by-nc-sa/4.0/>).

INTRODUCTION

Infantile hyperbilirubinemia is one of the most common neonatal matters, with approximately 60% of term infants and 80% of preterm infants developing jaundice in the first week of life, and approximately 10% of breastfeeding infants in the first month of birth still Jaundice [1]. Infantile jaundice is one of the most common causes of hospital readmission in the first week after birth [2].

Neonatal jaundice is a type of increased unconjugated bilirubin in serum because of increased bilirubin production, increased erythrocyte mass, short life of red blood cells, ligandin and glucuronyltransferase deficiency and increased enterohepatic circulation. It is very common, usually harmless, and not associated with any other disease [3]. Increased unconjugated hyperbilirubinemia is toxic and also harmful to the brain and may lead to kernicterus. It is related to the lack of full development of the neonatal blood-brain barrier, causing severe and lasting damage to the neonatal nervous system. Management of Indirect hyperbilirubinemia may require phototherapy or exchange transfusion [4].

Phototherapy is usually used in order to prevent and treat severe hyperbilirubinemia; it cause Total Bilirubin reduction and Prevention of Neonatal Blood Exchange. So this method has been introduced and used as a low-risk and beneficial therapy method for decades [5]. Phototherapy in most cases requires hospitalization, which can lead to baby-mother separation, impeding breastfeeding, breastfeeding failure, increased parental anxiety and increased hospital costs [6]. It also can cause complications such as hyperthermia, erythematous rashes, increase intangible fluids excretion and diarrhea [7]. Given the socio-economic burden associated with neonatal jaundice, it is important to provide newer interventions that reduce the incidence, severity, and duration of phototherapy [8]. Studies related to management of neonatal jaundice have suggested strategies to increase conjugated bilirubin, decrease the enterohepatic cycle [9] and inhibit bilirubin production and hemolysis [10]. Probiotics are a product consists of living microorganisms that alter microbial flora through colonization in a part of the host body and thus have beneficial effects on host health [11]. Probiotic microorganisms generally include Lactobacillus bifidobacterium and streptococcus, in order to their ability to improve intestinal motility, decrease intestinal-hepatic circulation and suppress beta-glucuronidase activity and balancing intestinal pH, they can potentially decrease the severity and duration of neonatal jaundice [12]. Given the low cost and ease of use and access to probiotics, the researcher decided to

conduct a study to determine the effect of probiotics on the duration of physiological jaundice treatment in term neonates.

METHODOLOGY

The present study was a randomized clinical trial study performed in Kamali Hospital which has the most equipped neonatal intensive care units in Alborz Province. The study samples included all breastfeeding neonates with 37-42 weeks gestational age in neonatal intensive care unit and neonates with physiological jaundice referred to Kamali hospital up to 5 days after birth.

Neonates undergoing phototherapy with The 4 lamp tubes of Mehravaran Medical Engineering (MTT)

Exclusion criteria included, parents reluctance to participate in research at any time of study, infection, sepsis, fever, hypothyroidism and any other factors causing pathologic neonatal jaundice, receiving any blood products and blood transfusions, indicate any kinds of neonatal anomalies.

The sample consisted of 71 neonates, however 7 cases were excluded due to discharge with personal consent, indicate pathologic bilirubin following metabolic disorders, and start serum therapy and medication to reduce bilirubin (Figure 1).

After receiving the approval of the Ethics Committee in Medical Research, the researcher received a conscious consent from the parents of the newborns after mentioning the objectives of the study and attracting cooperation.

Sampling was according to availability, gestational age and chronological age, inclusion and exclusion criteria of neonates; then demographic characteristics of neonates were recorded in a researcher-made questionnaire. At first, the neonates's bilirubin was checked using a serum sample in the laboratory. After that, infants were divided into two groups of intervention (pair) and control (individual) randomly.

In the intervention group, 1 cc of probiotic Lactoacidophilus (powered by Fanadaru Fanavar Mehr Company) were added to Maternal expressed milk two times a day and the baby was fed with a lactation cup. In the control group, the neonates was fed with pure Maternal expressed milk and the bilirubin of all infants was checked daily and written in a table. Finally, the level of bilirubin at admission and discharge and also duration of hospitalization in both groups were compared. It is worth mentioning that the person who added probiotic to the infant's daily milk and monitored the level of bilirubin was not aware of the study and its goals. Data were analyzed by SPSS software version 19, using Kolmogorov-Smirnov test, T-test, Mann-Whitney and mean

comparisons were used to compare the level of bilirubin and duration of hospitalization in neonates.

Ethical Considerations

The present study was conducted under the supervision of the Research department of Alborz University of Medical Sciences and approved by the Ethics Committee with code (Abzums.Rec.1395.48). Before starting the study, the goals of the study and the confidentiality of all information for the parents of the infants were explained and Informed consent was obtained from all parents.

RESULTS

The birth weight mean was 3.403 kg in the intervention group and 3.180 kg in the control group. Neonates in the intervention group were born at 38.22 weeks (GA) on average and controls at 38.33 weeks (GA) old. Bilirubin level at baseline was not significantly different between the two groups. Demographic characteristics of neonates in study were listed in (Table 1).

In order to investigate the effect of probiotics on reducing neonatal bilirubin level, independent t-test was used to compare neonatal bilirubin mean between admission and discharge period. Although in the intervention group the mean reduction of bilirubin was 0.31 mg / dl and showed no significant difference ($p = 0.67$) (Table 2).

Other results showed that the average length of stay in hospital was 0.7 day shorter in the intervention group and this difference was statistically significant ($p = 0.02$) (Table 3).

DISCUSSION

The present study showed that the bilirubin level in neonates with physiological jaundice was 0.3 mg / dl lower in the Lactobacillus bifidus group but was not statistically significant. Although several other randomized trials have evaluated probiotics in neonates' pathological jaundice; such as Liang et al. trial about the effect of Lactobacillus bifidus in neonates' jaundice during 7 to 10 days showed that the level of bilirubin in the intervention group was 5.96 lower than the control group and was statistically significant [13]. Liu et al. study (2015) showed that the neonates' bilirubin level at 4 and 7 days after treatment with Lacto Bacillus bifidus lower in the intervention group than the control group. The results of these studies were not in line with the results of the present study, which may be due to the difference in the type of jaundice.

In a 2015 Serce et al. study showed that Saccharomyces blurdy probiotic had no effect on neonatal jaundice at 24,48,72 and 96 hours after use [14]. Also Zahed Pasha et al. study showed that paddy lactate (a mixture of Lactobacillus

rhamnosus, Lactobacillus reuteri and Bifidus) had no effect on bilirubin levels at 24, 48, 72 and 96 hours after use and there was no significant difference between the two groups and it's aligned with Tafti et al. study in [15]. In a systematic review study in 2017, Deshmukh et al. Showed that bilirubin levels did not differ significantly between the two groups at 24,48,72 hours after probiotic use, but at 96 and 7 days after use the difference would be significant. It was also shown that prophylaxis use of probiotic had no effect on of neonatal jaundice prevention. The use of probiotics makes phototherapy duration shorter but it's not recommended to reduce neonatal jaundice incidence and decreased bilirubin levels.

The results of the present study showed a hospital stay decrease in the intervention group compared to the control group ($p = 0.002$), Liang and et al.'s study also showed that probiotic had a significant effect on bilirubin level and length of hospital stay. A systematic review also showed that use of probiotic was effective on infants' hospital stay and phototherapy duration [16]. No adverse events were reported in this study; several studies like Chandrasikhar et al. [17]. and Deshmukh et al. state that there is no adverse effects of Lactobacillus on the duration of neonatal phototherapy were observed. In a systematic review of 13 clinical trials, Zhi Chen found that six studies reported no adverse events, but in five studies 20 case clinical signs, including fever, diarrhea, rash, and fatigue were reported. Although there was no significant difference in control and intervention groups.

Despite systematic review studies, the number of studies on specific probiotic species and infants physiological jaundice is very limited, so it is recommended to conduct more specific studies.

One of the limitations of this study is the inability to study the gastric flora and the effect of probiotics, so it is recommended to conduct more clinical studies in this field. Another limitation of the study was the sample size, which due to the lack of access to this species of probiotics due to sanctions in the country. Following this problem, we were forced to adjust the sample size, and also recommended to do future study with a larger sample size.

CONCLUSION

Use of Lactobacillus bifidus Probiotic reduces hospital stay duration in neonates with physiological jaundice but has no effect on their bilirubin level.

ACKNOWLEDGMENT

The authors wish thanks the kind support of the Center for Clinical Research and Development of

Kamali Hospital for conducting this study and publishing the results. We would also like to thank Dr. Mohammad Mohammadi and Dr. Zohreh Khodaei for their sincere cooperation in providing probiotics.

REFERENCES

1. Excellence NifC. Jaundice in newborn babies under 28 days. NICE London; 2016.
2. Rennie J, Burman-Roy S, Murphy MS. Neonatal jaundice: summary of NICE guidance. *Bmj*. 2010; 340: c2409.
3. Olusanya BO, Kaplan M, Hansen TW. Neonatal hyperbilirubinaemia: a global perspective. *The Lancet Child & Adolescent Health*. 2018; 2(8):610-20.
4. Armanian AM, Jahanfar S, Feizi A, Salehimehr N, Molaiezhad M, Sadeghi E. Probiotics for the prevention of hyperbilirubinaemia in neonates. *Cochrane Database of Systematic Reviews*. 2019 (8).
5. Golshan Tafti M, Eftekhari F, Shajari A. The Effects of Probiotics on Indirect Bilirubin Level in the Infants with Neonatal Jaundice. *Alborz University Medical Journal*. 2019; 8(1):61-8.
6. Burke BL, Robbins JM, Mac Bird T, Hobbs CA, Nesmith C, Tilford JM. Trends in hospitalizations for neonatal jaundice and kernicterus in the United States, 1988–2005. *Pediatrics*. 2009; 123(2): 524-32.
7. Liu W, Liu H, Wang T, Tang X. Therapeutic effects of probiotics on neonatal jaundice. *Pakistan journal of medical sciences*. 2015; 31(5): 1172.
8. Deshmukh J, Deshmukh M, Patole S. Probiotics for the management of neonatal hyperbilirubinemia: a systematic review of randomized controlled trials. *The Journal of Maternal-Fetal & Neonatal Medicine*. 2019; 32(1):154.63-
9. Sato H, Uchida T, Toyota K, Kanno M, Hashimoto T, Watanabe M, et al. Association of breast-fed neonatal hyperbilirubinemia with UGT1A1 polymorphisms: 211G> A (G71R) mutation becomes a risk factor under inadequate feeding. *Journal of human genetics*.7:(1)58;2013 .
10. Blackburn MG, Orzalesi MM, Pigram P. The combined effect of phototherapy and phenobarbital on serum bilirubin levels of premature infants. *Pediatrics*. 1972; 49(1):110-2.
11. Schrezenmeir J, de Vrese M. Probiotics, prebiotics, and synbiotics—approaching a definition. *The American journal of clinical nutrition*. 2001; 73(2):361s-4s.
12. Yiji C, Zuo-yi S-xW, Shi-Xiao W. Characteristics of enterohepatic circulation in neonates and mechanism of using microbiological preparation to treat neonatal jaundice. *Journal of Pediatric Pharmacy* {Internet}. 2003; 9(2).
13. Liang F. Clinical efficacy of Gold Bifid on neonatal hyperbilirubinemia. *Chine J Microeco*. 2012; 10(2): 909-12.
14. Serce O, Gursoy T, Ovali F, Karatekin G. Effects of *Saccharomyces boulardii* on neonatal hyperbilirubinemia: a randomized controlled trial. *American journal of perinatology*. 2015; 32(2): 137-42.
15. Zahed Pasha Y, Ahmadpour-Kacho M, Ahmadi Jazi A, Gholinia H. Effect of Probiotics on Serum Bilirubin Level in Term Neonates with Jaundice; A Randomized Clinical Trial. *International Journal of Pediatrics*. 2017; 5(10): 5953-5958.
16. Chen Z, Zhang L, Zeng L, Yang X, Jiang L, Gui G, et al. Probiotics supplementation therapy for pathological neonatal jaundice: a systematic review and meta-analysis. *Frontiers in pharmacology*. 2017; 8(4): 432-440.
17. Chandrasekhar J, Varghese TP, Gopi A, Raj M, Sudevan R, Jayakumar H. Treatment effect of probiotic *Bacillus clausii* on neonatal jaundice in late preterm and term newborn babies: An experimental study. *Pediatr Ther*. 2017; 7(326): 2161-0665.

The Effect of Lactoacidophilus Probiotic on Duration of Physiologic Jaundice in Neonates with 37-42 Weeks Gestational Age: A Randomized Clinical Trial

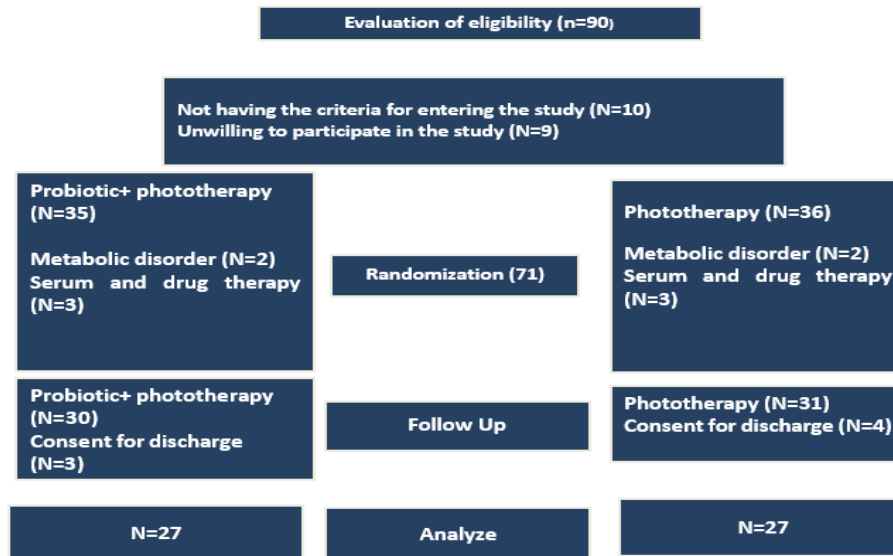


Figure 1. Consort Diagram

Table 1. Characteristics of infants participating in the intervention and control groups

Demographic characteristics						
Group		N	Minimum	Maximum	Mean	Std. Deviation
Birth Weight	Intervention	27	2610	5100	3403.33	561.022
	Control	27	2600	3900	3180.74	319.506
Gestational age	Intervention	27	37	40	38.22	0.974
	Control	27	37	41	38.33	1.209
Bilirubin	Intervention	27	-	-	12.8704	3.08381
	Control	27	-	-	13.7119	3.29563

Table 2. Mean comparison of bilirubin in the control and intervention groups

Group	Mean± Std. Deviation	N	Maximum	Minimum	t	p-value
Control	-4.18±2.76	27	11.20	0.21	0.431	0.668
intervention	-4.49±2.62	27	10.10	0.70		

Table 3. Mean comparison of length of stay in hospital

Group	Mean± Std. Deviation	N	Minimum	Maximum	Mann-Whitney U	P
Control	2.63±.79	27	1	4	197.5	0.002
intervention	1.93±.73	27	1	3		