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Original Article

The effectiveness of *Lactobacillus reuteri* on serum bilirubin levels in neonatal hyperbilirubinemia with phototherapy

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Abstract

Background Hyperbilirubinemia occurs in 60% of full term and 80% of premature infants. Phototherapy is the main treatment, but it has side effects, sometimes requires hospitalization, and causes the baby to be separated from the mother. Underdeveloped gut microflora and increased enterohepatic circulation in newborns contribute to increased serum bilirubin levels in early life.

Objective To assess the efficacy of adding probiotic *L. reuteri* on phototherapy in full-term neonates with hyperbilirubinemia.

Methods In this double-blind, randomized clinical trial, full term infants with hyperbilirubinemia at Dr. Zainoel Abidin Hospital, Banda Aceh, Aceh, Indonesia, were randomly assigned to either an intervention or control group. All subjects received phototherapy. The intervention group was also given five drops of *L. reuteri* once a day orally before phototherapy started, while the control group received a placebo. Bilirubin levels after 24-hour phototherapy were evaluated in both groups.

Results A total of 42 term neonates met the inclusion criteria. The intervention group had a significantly greater decrease in total serum bilirubin (TSB) level (6,517 mg/dL) than did the control group (4,434 mg/dL) (P<0.001), as well in indirect bilirubin levels in the intervention group had decrease 6.40 mg/dL while in the control group 4.43 mg/dL after 24 hours of phototherapy (P<0.001).

Conclusion In full-term neonates with hyperbilirubinemia who underwent 24-hour phototherapy, adding probiotic *L. reuteri* leads to a significantly greater reduction in total and indirect bilirubin levels compared to the control group. **[Paediatr Indones. 2023;63:219-25; DOI: https://doi.org/10.14238/pi63.4.2023.219-25]**.

Keywords: *: probiotics; L. reuteri; hyperbilirubinemia; full-term neonates; phototherapy*

Hyperbilirubinemia is the most common clinical symptom in newborns and occurs in 1 out of every 2,500 infants.[1,2] Elevated indirect bilirubin is found in 60% of term infants and 80% of premature infants.[3-5] Risk factors such as nutrition, ethnicity, and genetic, are associated with the incidence of hyperbilirubinemia in neonates.[1,5,6] Hyperbilirubinemia is a normal transitional symptom, because the liver is not fully functional in newborns, leading to elevated indirect bilirubin levels in the blood.[7,8] Indirect hyperbilirubinemia that is not managed properly can potentially be toxic, and even fatal, if bilirubin crosses the brain barrier (kernicterus). Neurological sequelae are a long-term consequence of indirect hyperbilirubinemia, if the baby survives.[2,9]

The risk of severe hyperbilirubinemia in neonates globally has currently decreased with more screening, as well as faster diagnosis and treatment, but low- and middle-income countries reportedly have an incidence 100 times higher than that of developed

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countries.[10] Phototherapy is the mainstay of treatment in full term neonates with hyperbilirubinemia, but its use can prolong hospital stay, result in separation of the infant from the mother, and become a barrier to breastfeeding with potential for lactation failure. Phototherapy also has associated side effects such as temperature instability and dehydration, which can cause parental anxiety and increase hospitalization costs. Considering the overall socioeconomic burden associated with neonatal hyperbilirubinemia, the search for novel interventions that will reduce the incidence, severity, and duration of treatment in phototherapy is underway.[10,11] Previous studies used several adjunct therapies to reduce bilirubin levels such as metalloporphyrins, clofibrate, intravenous immunoglobulin (IVIG), activated charcoal, and cholestyramine, but these have side effects and are not recommended for routine use.[2,7,10]

Probiotics are microorganisms that can reduce material transit time from the intestine and increase stool frequency in neonates. Disruption of microflora has an important role in neonatal jaundice and enterohepatic circulation, but the benefit of intervention with probiotics to reduce bilirubin levels is still controversial.[10,12,13] Study assessing the effectiveness of probiotics, especially *L. reuteri*, in reducing bilirubin levels in infants has been limited. But several studies have had promising results, possibly leading to its use as an adjuvant therapy in the treatment of hyperbilirubinemia, with reduced side effects compared to light therapy and reduced hospital costs.[14-16] As such, we aimed to assess the efficacy of adding probiotic *L. reuteri* on phototherapy in full-term neonates with hyperbilirubinemia.

Methods

This study was a double-blind, randomized controlled trial. Neonates admitted to the Perinatology and Neonatal Intensive Care Unit (NICU) at Dr. Zainoel Abidin Hospital, Banda Aceh, Aceh, Indonesia, from July to December 2021 because of indirect hyperbilirubinemia and who underwent phototherapy were enrolled in our study. The inclusion criteria were full term neonates with gestational age of 37 to 42 weeks, who required phototherapy based on the *American Academy of Pediatrics* (AAP) guidelines for the treatment of neonatal hyperbilirubinemia,[17] had chronological age 2-28 days, birth weight of 2,500-4,000 grams, were exclusively breastfed and were delivered vaginally. Neonates with other underlying disease, congenital anomalies, or requiring exchange transfusion, were excluded. Subjects were included by consecutive sampling. All subjects underwent data collection for gestational age, chronological age, sex, birth weight, and serum bilirubin levels before the start of phototherapy. They were assigned to either the control or intervention group by simple random sampling (a sealed envelope containing an odd-even number). Healthcare staff and parents were blinded to the group assignment, except for one nurse. Both groups received phototherapy by the same protocol and device. The intervention was carried out by giving *L. reuteri DSM 17938* probiotic before starting phototherapy, with one dose of 5 drops from a 1 mL syringe mixed with breast milk, without touching the oral mucosa. One minimum dose consisted of 100 million *L. reuteri DSM 17938* (*Interlac Oil Drops*, *Interbat*). The control group received a placebo preparation in the form of breast milk without a probiotic from a similar type of 1 mL syringe used by the intervention group. Only one nurse knew the subjects' group assignments. A physician (researcher) observed the outcomes of the decrease in bilirubin levels in each group.

Subjects underwent serum bilirubin level reexamination after 24 hours of phototherapy using the same equipment as in the initial examination. If the TSB level fell 1-2 mg/dL below the level at phototherapy onset, then phototherapy would be discontinued. Changes in TSB, as well as direct and indirect bilirubin levels after 24 hours phototherapy were analyzed.

The minimum required sample size was calculated using the formula for numerical comparative analytical study of two independent groups. The standard deviation was based on the study by Torkaman *et al.*,[18] in which there was a difference in bilirubin levels of 2 mg/dL between patients receiving phototherapy alone compared to those receiving phototherapy and probiotics. In our study, the estimated sample size was 19 patients per group plus to account for a 10% drop-out rate. Hence, there were 21 subjects in each group, for a total sample of 42 subjects.

Subject characteristics were analyzed as categorical data (gender, gestational age, chronological age, birth weight, history of delivery, exclusive breastfeeding) and numerical data (serum bilirubin level) expressed as proportion. The level of significance was P< 0.05. Data normality was tested by Shapiro-Wilk test. Normally-distributed numerical data were reported as mean and standard deviation (SD) and analyzed by unpaired (independent) T-test. Non-normally distributed data were analyzed by non-parametric test (Mann Whitney) and expressed as median (range). Data were processed using *Statistical Package for the Social Science (SPSS) version 23* software. Written informed consent form was obtained from all subjects' parents. This study was reviewed and approved by the Ethics Committee of Universitas Syiah Kuala Medical Faculty.

Results

A total of 46 neonates were assessed for eligibility, but 2 subjects were excluded due to family members declined consent for the study. After randomization, subjects were allocated to either the intervention (n=22) and control (n=22) group. In the intervention group, 1 subject received a diet other than breast milk during phototherapy; in the control group, 1 subject's parents refused to do a repeat blood test after 24 hours of light therapy, so they were excluded from the study. Thus, total of 42 subjects were analyzed, with 21 subjects in each group. The subject recruitment scheme can be seen in **Figure 1**.

The baseline characteristics of subjects are shown in **Table 1**. The intervention group was predominantly males (61.9%), while the control group was predominantly female (52.4%). The mean gestational age of neonates was similar in the intervention and control groups (38.29 *vs.* 38.38 weeks, respectively). However, the control group had a slightly higher mean birth weight (3,052.38 grams) than the intervention group (3,033.81 grams). The mean chronological ages of neonates in the intervention and control groups were also similar [5.14 (SD 1.80) *vs.* 5.19 (SD 2.18) days, respectively)]. However, the chronological age of the control group was slightly more diverse than that of the intervention group, as indicated by the larger standard deviation of the control group.

Subjects' mean total serum bilirubin (TSB) level before receiving phototherapy was 17.56 mg/dL, mean direct bilirubin level was 0.45 mg/dL, and mean indirect bilirubin level was 17.11 mg/dL. Among the three bilirubin levels, TSB and indirect bilirubin were increased above normal values. The description of mean bilirubin levels in subjects before treatment is shown in **Table 2**.

Independent T-test was used to compare TSB, direct and indirect bilirubin between the intervention and the control groups after 24 hours of phototherapy. **Table 3** shows that mean TSB was significantly lower in the intervention group (11.09 mg/dL) than in the control group (13.08 mg/dL) (P<0.001) after 24 hours of phototherapy. Also, the mean indirect bilirubin level was significantly lower in the intervention group (10.75 ng/dL) than in the control group (12.71 ng/dL (P<0.001). However, mean direct bilirubin was not significantly different between groups (0.34 vs. 0.36 ng/dL, respectively) (P=0.093).

We also analyzed the magnitude of changes in TSB, direct bilirubin, and indirect bilirubin levels from before and after subjects underwent 24-hour phototherapy for both groups. **Table 4** shows that the reduction of mean TSB and indirect bilirubin levels were significantly greater in the intervention compared to the control group (P<0.001). But mean direct bilirubin reduction was not significantly different between groups.

Discussion

Neonatal hyperbilirubinemia is one of the most common disorders in newborns, characterized by a physiological increase in indirect bilirubin in serum and resulting in permanent neurological deficits if not treated properly.[1,5,17] Neonatal hyperbilirubinemia is caused by a range of factors, notably reduced liver function, a larger number of erythrocytes with a shorter half life in peripheral blood, and an accelerated enterohepatic circuit.[1,2,19] In the process of bilirubin metabolism, the intestine has an important role in mediating the transformation of direct bilirubin into indirect bilirubin, which is further converted into bilinogen to be excreted from the body.[6,10]

Phototherapy is the treatment of choice for neonatal hyperbilirubinemia, but it has side effects

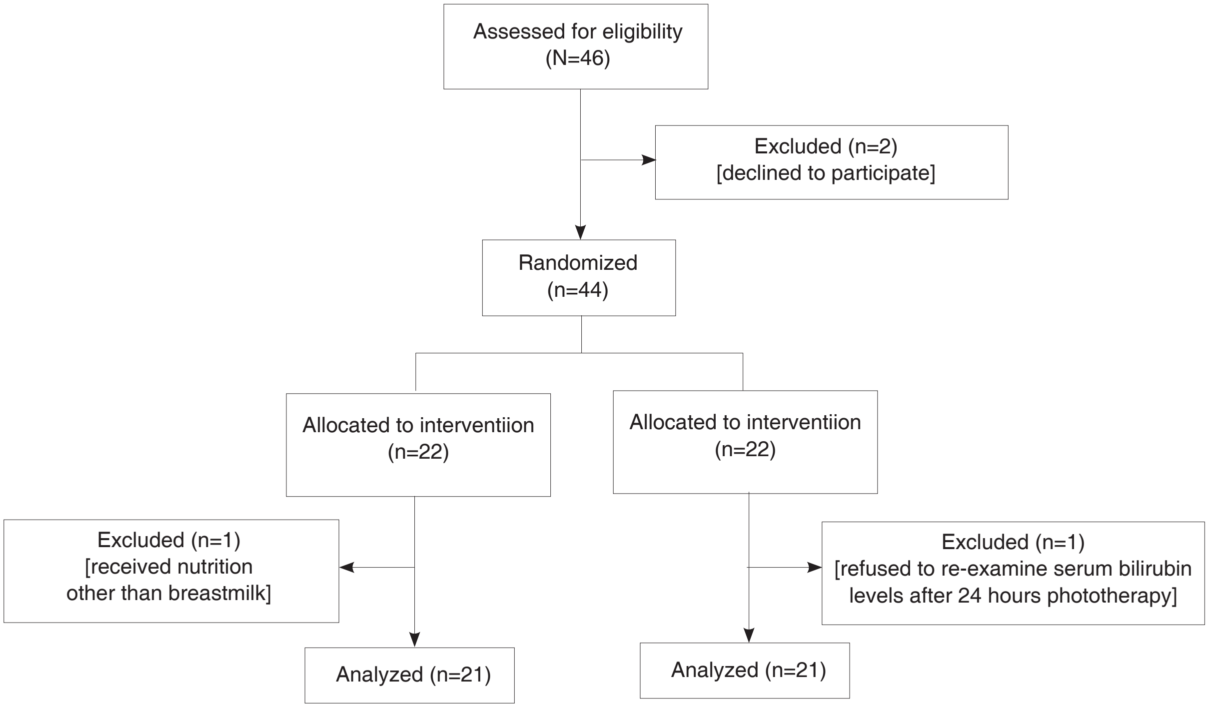

Figure 1. Flowchart of the study

Table 1. Baseline characteristics of subjects

Characteristics	Intervention (n=21)	Control (n=21)
Mean gestational age (SD), week	38.29 (1,23)	38.38 (1.32)
Mean birth weight (SD), gram	3,033.81 (366.48)	3,052.38 (368.26)
Mean chronological age (SD), day	5.14 (1.80)	5.19 (2.18)
Sex, n (%)		
Male	13	10
Female	8	11

Table 2. Characteristics of mean serum bilirubin levels of neonates before treatment

Parameter	Intervention (n=21)	Control (n=21)	P value
Mean TSB (SD), mg/dL	17.61 (1.57)	17.51 (1.48)	0.835
Mean direct bilirubin (SD), mg/dL	0.46 (0.13)	0.44 (0.09)	0.554
Mean indirect bilirubin (SD), mg/dL	17.15 (1.56)	17.07 (1.43)	0.866

Table 3. Comparison of bilirubin levels after 24 hours of phototherapy

Bilirubin serum levels	Intervention (n=21)	Control (n=21)	95%CI*	P value
Mean TSB (SD), mg/dL	11.09 (1.18)	13.08 (1.24)	-2.74 to -1.23	<0.001
Mean direct bilirubin (SD), mg/dL	0.34 (0.12)	0.36 (0.10)	-0.09 to 0.05	0.572
Mean indirect bilirubin (SD), mg/dL	10.75 (1.19)	12.71 (1.20)	-2.71 to -1.22	<0.001

Independent T-test, *of differences between the 2 groups

Table 4. Changes in bilirubin serum levels after 24-hour phototherapy

Changes in bilirubin levels	Intervention (n=21)	Control (n=21)	95%CI	P value
Mean TSB (SD), mg/dL	-6.52 (0.20)	-4.43 (0.11)	-2.55 to -1.61	<0.001
Mean direct bilirubin (SD), mg/dL	-0.11 (0.02)	-0.08 (0.01)	-0.09 to 0.01	0.093
Mean indirect bilirubin (SD), mg/dL	-6.40 (0.21)	-4.36 (0.12)	-2.53 to -1.56	<0.001

and causes separation of mother and baby.[2,17,20,21] Phototherapy also produces photoisomerization of hydrophobic indirect bilirubin to polar isomers that can expel into bile without conjugation. After phototherapy, some isomers of bilirubin such as E and Z are found in the intestinal lumen as water-soluble products, although lumirubin, the principal product of phototherapy, is rarely converted into native bilirubin. Phototherapy effectiveness can be increased by bilirubin sequestration from enterohepatic circulation.[22,23]

Administration of probiotics is intended to increase the number of beneficial bacteria in the intestine so that it can reduce enterohepatic circulation and accelerate the transit time of material in the intestinal lumen.[10] Lactobacillus reuteri is one type of microbiota in the human gastrointestinal tract. It has been shown to be effective in treating digestive disorders such as constipation and diarrhea, infant colic, as well as reducing necrotizing enterocolitis (NEC) in very low birth weight infants. Lactobacillus reuteri is a major triggering factor for the immune system after birth.[24-27]

The basic characteristics of our subjects were similar between two groups. Mean TSB and indirect bilirubin levels were increased compared to normal in all subjects before treatment. Light therapy is recommended for neonates with hyperbilirubinemia, with regards to TSB levels that exceed the line shown for each category on the AAP curve.[17] After 24 hours of light therapy, mean TSB and indirect bilirubin values were significantly lower in the intervention compared to the control group ($P<0.001$). The mean decrease was also significantly greater in the intervention group, with regards to TSB levels and indirect bilirubin, compared to the control group.

Our results were in agreement with those of Torkaman *et al.*[18] who assessed the effectiveness of probiotics (*B. lactis, L. acidophilus, B. bifidum,* and *L. rhamnosus*) in 92 neonates treated with light therapy and found that probiotics were beneficial in significantly reducing the duration of hospitalization ($P<0.05$). Another study also reported that the probiotic Saccharomyces boulardii could reduce the duration of light therapy and hospital stay in 179 very low birth weight (LBW) infants with hyperbilirubinemia. An increase in feeding tolerance was also found after *S. boulardii* supplementation in LBW.[28]

A similar study found that supplementation with the probiotic *L. rhamnosus* immediately after birth had a beneficial effect on bilirubin metabolism and could reduce the risk of hyperbilirubinemia.[29] Moreover, *L. bulgaricus*, Bifidobacterium, and *Streptococcus thermophilus* reduced bilirubin levels quickly and safely.[30] A meta-analysis of 13 clinical trials involving 1,067 infants, found that probiotic supplementation was effective in the treatment of neonatal hyperbilirubinemia with light therapy without any side effects (RR 1.19; 95%CI 1.12 to 1.26; $P<0.00001$).[31] Deshmukh *et al.*[13] reviewed nine articles involving 2,040 infants and found that probiotic supplementation could reduce the duration of light therapy in infants with hyperbilirubinemia (n=415; mean difference -11.80; 95%CI -17.47 to -6.13; $P<0.0001$). Most studies reported beneficial effects of probiotics as demonstrated by a reduction in TSB levels in neonates with indirect hyperbilirubinemia with light therapy.

In contrast, a previous study evaluated the effectiveness of probiotics (*L. rhamonus, L. reuteri*, and *B. infantis*) on TSB levels and duration of light therapy in 150 term neonates with hyperbilirubinemia. The TSB levels before and after light therapy in the control and the intervention groups were not significantly different ($P>0.05$).[8] A study used the probiotic *S. boulardii* in 119 neonates with hyperbilirubinemia and reported no significant difference between the intervention and the control groups.[12] In addition, another study also reported that probiotics were not effective in reducing the duration of light therapy in 126 full term neonates with hyperbilirubinemia.[32]

The results of our study were consistent with some previously reported studies,[18,28-32] but contradicted others.[8,12,32] The differences may have been due to different probiotic strains and doses used. Our study showed no side effects in the entire intervention group receiving *L. reuteri*.

This study had several limitations. The sample size was small, the study was carried out in one place, and the intervention with *L. reuteri* was only given once, so the effective dose of remains unknown. Further studies regarding the effective dose, which probiotic strain is more appropriate to reduce bilirubin levels, and long-term side effects that can arise are also needed. In addition, the frequency of defecation in both groups was not assessed and should be considered in a future study.

To the best of our knowledge, this study is the first to use probiotics, especially *L. reuteri*, to treat indirect hyperbilirubinemia in infants who received phototherapy in Indonesia. Our results can be used as a reference for further studies. Probiotic *L. reuteri* may eventually be recommended as an adjuvant therapy in neonates with indirect hyperbilirubinemia. In conclusion, oral administration of probiotics especially *L. reuteri*, can reduce TSB and indirect bilirubin levels more rapidly after 24 hours of phototherapy in neonates with hyperbilirubinemia, while the decrease in direct bilirubin levels is not significantly different.

Conflict of interest

None declared.

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References

1. Gomella TL, Cunningham MD, Eyal FG. Hyperbilirubinemia. Neonatology: Management, procedures, on-call problems, diseases, and drugs. 5th ed. New York: Lange Medical Book/ McGraw-Hill; 2013. p. 293-301.
2. Sukadi A. Hiperbilirubinemia. In: Kosim MS, Yunanto A, Dewi R, Sarosa GI, Usman A, editors. Buku ajar neonatologi. 1st ed. Jakarta: Badan Penerbit Ikatan Dokter Anak Indonesia; 2008. p. 147-69.
3. Young Infants Clinical Signs Study Group. Clinical signs that predict severe illness in children under age 2 months: a multicentre study. Lancet. 2008;371:135-42. DOI: https://doi.org/10.1016/S0140-6736(08)60106-3.
4. Burke BL, Robbins JM, Bird TM, Hobbs CA, Nesmith C, Tilford JM. Trends in hospitalizations for neonatal jaundice and kernicterus in the United States, 1988-2005. Pediatrics. 2009;123:524-32. DOI: https://doi.org/10.1542/peds.2007-2915.
5. Marcdante KJ, Kliegman R. Hyperbilirubinemia. In: Clarence W, Gowen J, editors. Nelson essentials of pediatrics. 8th ed. Philadelphia: Saunders; 2019. p. 672-9.
6. Hansen TW, Wong RJ, Stevenson DK. Molecular physiology and pathophysiology of bilirubin handling by the blood, liver, intestine, and brain in the newborn. Physiol Rev. 2020;100:1291-346. DOI: https://doi.org/10.1152/physrev.00004.2019.
7. Wrong RJGH, Sibley DG. Therapy of unconjugated hyperbilirubinemia. 8th ed. Philadelphia: Mosby; 2006. p. 1440-5.
8. 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. Int J Pediatr. 2017;5:5925-30. DOI: https://doi.org/10.22038/ijp.2017.24996.2117.
9. Tomashek KM, Crouse CJ, Iyasu S, Johnson CH, Flowers LM. A comparison of morbidity rates attributable to conditions originating in the perinatal period among newborns discharged from United States hospitals, 1989-90 and 1999–2000. Paediatr Perinat Epidemiol. 2006;20:24-34. DOI: https://doi.org/10.1111/j.1365-3016.2006.00690.x.
10. Chen K, Yuan T. The role of microbiota in neonatal hyperbilirubinemia. Am J Transl Res. 2020;12:7459-74. PMID: 33312382.
11. Dennery PA. Pharmacological interventions for the treatment of neonatal jaundice. In: Seminars in Neonatology. United States: WB Saunders. 2002;7:111-9. DOI: https://doi.org/10.1053/siny.2002.0098.
12. Serce O, Gursoy T, Ovali F, Karatekin G. Effects of *Saccharomyces boulardii* on neonatal hyperbilirubinemia: a randomized controlled trial. Am J Perinatol. 2015;30:137-42. DOI: https://doi.org/10.1055/s-0034-1376390.
13. Deshmukh J, Deshmukh M, Patole S. Probiotics for the

management of neonatal hyperbilirubinemia: a systematic review of randomized controlled trials. J Matern Fetal Neonatal Med. 2019;32:154-63. DOI: https://doi.org/10.1080/14767058.2017.1369520.

14. Armanian AM, Barekatain B, Hoseinzadeh M, Salehimehr N. Prebiotics for the management of hyperbilirubinemia in preterm neonates. J Matern Fetal Neonatal Med. 2016;29:3009-13. DOI: https://doi.org/10.3109/14767058.2015.1113520
15. Yang N, Yang RX, Wang AH, Zhang YQ. The effect of intestinal flora on the neural development of severe hyperbilirubinemia neonates. Eur Rev Med Pharmacol Sci. 2019;23:1291-5. DOI: https://doi.org/10.26355/eurrev_201902_17024.
16. Vanderhoof JA, Young RJ. Pediatric applications of probiotics. Gastroenteral Clin North Am. 2005;34:451-63. DOI: https://doi.org/10.1016/j.gtc.2005.05.001.
17. American Academy of Pediatrics Subcommittee on Hyperbilirubinemia. Management of hyperbilirubinemia in the newborn infant 35 or more weeks of gestation. Pediatrics. 2004;114:297-316. DOI: https://doi.org/10.1542/peds.114.1.297.
18. Torkaman M, Mottaghizadeh F, Khosravi MH, Najafian B, Amirsalari S, Afsharpaiman S. The effect of probiotics on reducing hospitalization duration in infants with hyperbilirubinemia. Iran J Pediatr. 2017;27:5096. DOI: https://doi.org/10.5812/ijp.5096.
19. Ambalavanan N, Carlo WA. Jaundice and hyperbilirubinemia in the newborn. In: Kliegman RM, Stanton BF, St Geme JW, Schor NF, editors. Nelson textbook of pediatrics. 20th ed. Philadelphia: Saunders;2016. p. 871-80.
20. Drew JH, Marriage K, Bayle VV, Bajraszewski E, McNammara JM. Phototherapy. Short and long-term complications. Arch Dis Child. 1976;51:454-8. DOI: https://doi.org/10.1136/adc.51.6.454.
21. LaRusso J, Wilson J, Ceilley R. Phototherapy-induced purpuric eruption in a neonate. J Clin Aesthet Dermatol. 2015;8:46-8. PMID: 25852815
22. Tan KL. Phototherapy for neonatal jaundice. Clin Perinatol. 1991;18:423-39. DOI: https://doi.org/10.1016/S0095-5108(18)30506-2.
23. Hansen TWR, Maisels MJ, Ebbesen F, Vreman HJ, Stevenson DK, Wong RJ, *et al.* Sixty years of phototherapy for neonatal jaundice–from serendipitous observation to standardized treatment and rescue for millions. J Perinatol. 2020;40:180-93. DOI: https://doi.org/10.1038/s41372-019-0439-1.
24. Britton RA. Lactobacillus reuteri. The microbiota in gastrointestinal pathophysiology. Academic Press. 2017;1:89-97. DOI: https://doi.org/10.1016/B978-0-12-804024-9.00008-2.
25. Srinivasan R, Kesavelu D, Veligandla KC, Muni SK, Mehta SC. *Lactobacillus reuteri DSM 17938*: review of evidence in functional gastrointestinal disorders. Pediatr Ther. 2018;8:2161-5. DOI: https://doi.org/10.4172/2161-0665.1000350.
26. Coccorullo P, Strisciuglio C, Martinelli M, Miele E, Greco L, Staiano A. *Lactobacillus reuteri (DSM 17938)* in infants with functional chronic constipation: a double-blind, randomized, placebo-controlled study. J Pediatr. 2010;157:598-602. DOI: https://doi.org/10.1016/j.jpeds.2010.04.066.
27. Halloran K, Underwood MA. Probiotic mechanisms of action. Early Hum Dev. 2019;135:58-65. DOI: https://doi.org/10.1016/j.earlhumdev.2019.05.010.
28. Demirel G, Celik I, Erdeve O, Dilmen U. Impact of probiotics on the course of indirect hyperbilirubinemia and phototherapy duration in very low birth weight infants. J Matern Fetal Neonatal Med. 2013;26:215-8. DOI: https://doi.org/10.3109/14767058.2012.725115.
29. Mutlu M, Irmak E, Aslan Y, Kader S. Effects of Lactobacillus rhamnosus GG as a probiotic on neonatal hyperbilirubinemia. Turk J Pediatr. 2018;60:482-7. DOI: 10.24953/turkjped.2018.05.003.
30. Liu W, Liu H, Tang X. Therapeutic effects of probiotics on neonatal jaundice. Pak J Med Sci. 2015;31:1172-8. DOI: https://doi.org/10.12669/pjms.315.7921.
31. 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. Front Pharmacol. 2017;8:432-6. DOI: https://doi.org/10.3389/fphar.2017.00432.
32. Goodarzi, Saadat S, Arshadzadeh M, Hengami NK, Darban B, Haghshenaz H. Efficacy and safety of probiotics in neonatal hyperbilirubinemia: randomized controlled trial. J Neonatal Nurs. 2021;6:432-8. DOI: https://doi.org/10.1016/j.jnn.2021.10.003.