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RESEARCH ARTICLE

The effect of *Lactobacillus acidophilus, Streptococcus thermophilus, and Bifidobacterium longum* probiotics on bilirubin levels of neonates with hyperbilirubinemia

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ABSTRACT

Hyperbilirubinemia, a common illness in newborns that can lead to hospital readmission, has been treated with blue light phototherapy. This treatment, either on its own or in combination with probiotics, has shown fast and significant decreases in bilirubin levels in the blood, helping to speed up the fading of jaundice. This study aims to examine the effects of combining phototherapy with probiotics containing *Lactobacillus acidophilus, Streptococcus thermophilus,* and *Bifidobacterium longum* on newborns with hyperbilirubinemia. The study was conducted at Sultan Agung Islamic Hospital (RSI Sultan Agung), Semarang, using a randomized controlled trial design. It included newborns who were hospitalized between August and November 2022. The control group was administered phototherapy, whereas the treatment group received both phototherapy and probiotics for 7 days. SPSS software analysis demonstrated a statistically significant reduction in average levels of total and indirect bilirubin in the intervention group (6.50 mg/dl and 7.20 mg/dl) compared to the control group (6.70 mg/dl and 7.48 mg/dl). These findings highlight the potential effectiveness of the combined approach in controlling hyperbilirubinemia. The study proposes using probiotics as a safe additional treatment for neonatal hyperbilirubinemia, showing that it is well-tolerated and safe for the participants. Although the combination of probiotics and phototherapy did not show a significant difference compared to phototherapy alone, it did result in a faster average decrease in hyperbilirubinemia. This could reduce the necessity for hospital readmissions to manage this condition. The findings underscore the potential of probiotics as a helpful supplement to established treatment methods for newborn hyperbilirubinemia.

1. Introduction

Bilirubin is a byproduct of the breakdown of red blood cells. Unconjugated bilirubin is a type of bilirubin soluble in fat and can penetrate the barrier of the central nervous system (Yanagi *et al.*, 2017). In certain neonates, there is an excessive production of bilirubin, specifically unconjugated bilirubin, which exceeds the normal levels. Neonatal hyperbilirubinemia, characterized by high levels of total serum bilirubin (TSB) over 5 mg/dL in infants less than one month, is a common prevalent cause of newborn readmission post-hospitalization. This situation may be physiological and spontaneously revert to its normal state. Physiological hyperbilirubinemia often arises within the initial week of an infant's life, characterized by an elevation in unconjugated bilirubin exceeding 2 mg/dL. In the case of term newborns who are nursed, the highest levels of bilirubin will range from 7 to 14 mg/dL, followed by a progressive decline throughout 2 to 4 weeks. Newborns

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produce 2-3 times more bilirubin than adults.

Hyperbilirubinemia is a common and important issue in clinical practice, especially in newborns. It affects around 8% to 11% of infants, and there is a greater risk when the level of bilirubin in the blood exceeds the 95th percentile for age within the first week of life. Neonatal jaundice, which affects 60%-80% of healthy infants, is characterized by a yellowish tint of the skin and sclera caused by high bilirubin levels. This condition often causes concern among parents and leads to seeking medical help. According to the National Neonatal-Perinatal Database, there is a 3.3% occurrence of neonatal hyperbilirubinemia among babies born in hospitals. The review article examines a disease that poses a serious risk to life, which includes both physiological and pathological jaundice. Physiological jaundice is the main type, but pathological jaundice occurs as a result of causes such as blood group incompatibility, causing hemolytic jaundice (Ullah et.al., 2016). A study conducted in Indonesia revealed that the occurrence of hyperbilirubinemia at Cipto Mangunkusumo Hospital (RSCM) was 58% among babies with bilirubin levels over 5 mg/dL, and 29.3% among those with bilirubin levels surpassing 12 mg/dL (Sampurna *et al.*, 2018). The relevance of hyperbilirubinemia in the possibility of serious repercussions, including the development of bilirubin-induced neurologic dysfunction (BIND) and bilirubin encephalopathy. These issues occur when unconjugated bilirubin passes across the blood-brain barrier, causing neurological harm. Therefore, to successfully reduce these consequences, it is essential to comprehensively comprehend newborn hyperbilirubinemia, including dysbiosis management (Ansong *et al.*, 2022).

The complex development of newborn hyperbilirubinemia is strongly linked to an imbalance in the gut microbiota, known as dysbiosis. Dysbiosis, marked by a decrease in the production of short-chain fatty acids (SCFAs), causes a disturbance in the integrity of the blood-brain barrier. This disturbance enables free bilirubin to penetrate the central nervous system, leading to neuronal harm. The involvement of microbes is crucial, as indicated by their connection to a higher likelihood of readmission for phototherapy. This emphasizes the complex relationship between the composition of gut microbiota and difficulties associated with hyperbilirubinemia (Akagawa *et al.*, 2021). Additionally, a study has provided evidence that colonies of Bifidobacterium were dominant in the neonatal jaundice (NJ) group, which is recognized for its immunomodulatory effects. Lactobacillus, a type of bacteria commonly used in medical treatments, has been found to have beneficial effects on bilirubin metabolism. The NJ group demonstrated elevated *Escherichia coli* concentrations, which were positively associated with bilirubin levels. This indicates that bilirubin could serve as a potential biomarker for diagnosing NJ. The study highlighted the significant importance of neonatal enterohepatic circulation in the process of bilirubin metabolism. It observed changes in the levels of beneficial bacteria in the intestines and identified *Staphylococcus* spp. and *E. coli* as potential indicators of neonatal hyperbilirubinemia (Zhang *et al.*, 2022).

Now, gut dysbiosis is widely regarded as a possible biomarker for newborn hyperbilirubinemia. Several studies have observed neonatal hyperbilirubinemia and its impact on gut microbiota throughout the first year of life, indicating a transient disruption. Neonates who recovered from neonatal hyperbilirubinemia showed a reestablishment of microbial equilibrium, similar to infants who did not have hyperbilirubinemia. Additionally, there were no notable disparities in the growth of infants at 12 months. This suggests that early intervention transiently influences the gut microbiome, with little enduring consequences on baby well-being. Importantly, the imbalance of microbial communities discovered in this study has the potential to be used as a diagnostic indicator for neonatal hyperbilirubinemia. The study highlights the potential benefits of integrating early gut microbiota treatments with conventional treatment to improve outcomes for newborn hyperbilirubinemia (Ding *et al.*, 2021). Some studies have also demonstrated that the gut microbiota in neonates with both normal and abnormal jaundice exhibit no significant differences in overall diversity but do show notable variations at the phylum and genus levels. Bacteroidetes have been identified as a crucial biomarker for differentiating pathological jaundice. The Firmicutes and Proteobacteria had significant impacts on the primary component differences. The correlation study established a connection between certain microbial taxa and clinical indicators, indicating potential consequences for intestinal inflammation and bilirubin metabolism. The study conducted by You *et al*. (2023) revealed *Bacteroidetes, Actinobacteria, Bifidobacterium, Rothia, Planctomycetes,* and *Bradyrhizobium* as essential indicators for differentiating between forms of jaundice.

Current therapeutic strategies generally focus on phototherapy (PT), a procedure that has been shown to effectively reduce levels of total serum bilirubin (TSB) to safe levels. While PT has shown effectiveness, it is not free from constraints, including possible enduring adverse effects such as retinal harm, hemolysis, and an elevated susceptibility to malignancies. Acknowledging these constraints emphasizes the necessity of investigating alternate therapeutic routes (Ansong *et al.*, 2022). Several in vitro research studies investigating the potential

carcinogenic dangers associated with traditional light sources in phototherapy have demonstrated little adverse effects, potentially because of the protective effect of hemoglobin. Recent epidemiological studies have shown a higher incidence of cancer in children who have been exposed to phototherapy. This highlights the importance of interpreting these findings carefully, particularly in extremely low birth weight (ELBW) infants. The introduction of a novel phototherapy light source necessitates a reassessment of possible negative responses. Furthermore, evidence suggests that the uncertain cause of the bronze baby syndrome, associated with phototherapy, necessitates further research to discover photoproducts and improve our understanding of the condition (Itoh *et al.*, 2017). Blue light phototherapy is widely acknowledged as a direct, effective, and safe approach for treating neonatal hyperbilirubinemia. However, concerns about possible negative consequences such as the destruction of red blood cells, allergic responses, harm to DNA, and the development of cancer highlight the need for consistent and logical clinical guidelines to be put in place. To ensure the safety and welfare of infants, it is imperative to promptly create standardized and normalized protocols for phototherapy. A thorough investigation is crucial for revealing the underlying processes behind negative responses to phototherapy in newborns and for improving treatment approaches to achieve the best possible results (Wang *et al.*, 2021). In this context, probiotics are seen as a viable and creative option as an additional therapy, using their significant influence on the gut flora to reduce the burden of hyperbilirubinemia.

With its diverse and holistic nature, the probiotic method offers a comprehensive and integrative strategy for effectively treating newborn jaundice, a difficult illness. This technique presents a promising path for future therapeutic breakthroughs in this field (Akagawa *et al.*, 2021).The positive impacts of probiotics in the management of newborn hyperbilirubinemia span multiple aspects. Probiotics enhance the establishment of advantageous microorganisms, leading to a more favorable gastrointestinal environment. Their capacity to inhibit the proliferation of harmful microorganisms additionally reinforces the intricate equilibrium within the gut. In addition, probiotics promote more frequent bowel movements, reducing the process of enterohepatic circulation and inhibiting the enzyme β-glucuronidase activity. Furthermore, these microorganisms promote the synthesis of tight junction proteins, strengthening the integrity of the intestinal barrier. Finally, the probiotics cause an elevation in polyamines, promoting enhanced intestine development. This offers a comprehensive method to tackle hyperbilirubinemia in newborns (Akagawa *et al.*, 2021). Another study discovered that the effectiveness of incorporating *Lactobacillus reuteri* probiotics into phototherapy was successful in lowering bilirubin levels in full-term infants with hyperbilirubinemia. A randomized controlled experiment involving 42 newborns discovered that the group receiving *Lactobacillus reuteri* as an intervention experienced a more substantial reduction in total and indirect bilirubin levels after 24 hours of phototherapy in comparison to the control group (Rezki *et al.*, 2023). A further study discovered that newborns who were administered *Lactobacillus reuteri* had modestly reduced average bilirubin levels. In contrast, those who received *S. boulardii* had greater levels than the control group. The group administered with Lactobacillus reuteri exhibited a reduced requirement for light therapy, as substantiated by risk zone evaluation (Teran *et al.*, 2021). Probiotic therapy has been found to effectively reduce gut dysbiosis, increase stool SCFA levels, and enhance head circumference growth in infants with congenital gastrointestinal surgery disorders unrelated to neonatal hyperbilirubinemia. This supplementation entails the utilization of a three-strain bifidobacterial product, including B. breve M-16V and *B. longum subsp. infantis M-63,* and *B. longum subsp. longum* BB536 (Rao *et al.*, 2023).

The complex characteristics of newborn hyperbilirubinemia require a comprehensive comprehension and strategy for its care. The presence of an imbalance in the gut microbiota, known as dysbiosis, and its consequences and the drawbacks of conventional phototherapy highlight the importance of investigating alternative treatments. Due to their many mechanisms and beneficial effects on gut health, probiotics are becoming a promising addition to conventional treatments. They provide a complete approach to improving care outcomes and decreasing the length of hospital stays for affected newborns. This study examines the effects of combining phototherapy with probiotics containing Lactobacillus acidophilus, Streptococcus thermophilus, and Bifidobacterium longum on newborns with hyperbilirubinemia.

2. Materials and Methods

This study utilized a randomized control trial (RCT) design, which involved examining variables such as hyperbilirubinemia, regular blood tests, and the average decrease in bilirubin levels. The study received ethical approval from the ethics committee of Sultan Agung Islamic Hospital Semarang, guaranteeing compliance with ethical norms.

The study patients consisted of neonates with hyperbilirubinemia who were admitted at RSI Sultan Agung Semarang from August to November 2022. The sample size 20 for both the control and treatment groups

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was obtained using the "Sample Size Formula" of

$$N = \frac{Z^2 \times P \times (1-P)}{E^2}$$

The inclusion criteria included infants born at full term (37 to 42 weeks gestational age) exclusively breastfed. The treatment of neonatal hyperbilirubinemia, as recommended by the American Academy of Pediatrics (AAP), involves phototherapy. This treatment requires exposing the baby to a specific light intensity (8 and 30 μW/cm²/nm) and a specific wavelength of blue light (ranging from 420 to 470 nanometers). The duration of the treatment depends on the levels of bilirubin in the baby's body, but it usually lasts up to 7 days. Precise temperature management is necessary to maintain the ambient environment between 36.5°C and 37.5°C. Moreover, it encompasses the execution of steps to safeguard the eyes. Frequent monitoring is a crucial component of this therapeutic approach, with the frequency being varied according to the clinical circumstances and risk factors, often taking place every 8 to 12 hours (American Academy of Pediatrics, 2022). The exclusion criteria encompassed infants with preexisting medical conditions, congenital abnormalities, or those need exchange transfusion. Subject selection was done using consecutive sampling.

The intervention in this trial consisted of administering the L-Bio supplement, which contains probiotics such as *Lactobacillus acidophilus, Streptococcus thermophilus, and Bifidobacterium longum,* before starting phototherapy. Each participant in the intervention group received a dose of 5 drops dispensed from a 1 mL syringe and mixed with breast milk. The dose was administered twice daily, with each drop containing $1x10^9$ cfu. Care was taken to avoid contact with the oral mucosa. Conversely, individuals in the control group received a placebo solution containing breast milk devoid of any probiotic substance. The placebo was administered before the initiation of phototherapy using a 1 mL syringe, which was the same type as the one used for the intervention group. In addition, clinical parameters, including total bilirubin, direct bilirubin, and indirect bilirubin, were assessed before (Pre-treatment) and following (post-treatment) the intervention.

Data were analyzed using SPSS software. The significance level was established at $p < 0.05$ to ensure reliable statistical results. Wilcoxon test was used to analyze the differences in bilirubin levels before and after treatment in both the control and treatment groups. Mann-Whitney test was used to compare the bilirubin levels in the control and treatment groups before and after the probiotic intervention.

3. Result

Table 1 shows that 80% of respondents in the control group are male, whereas 75% of respondents in the treatment group are male. Although there are variations, the gender distribution does not exhibit statistical significance ($p>0.05$). The statistical analyses reveal no significant differences in total bilirubin, direct bilirubin, and indirect bilirubin between the control and treatment groups for these parameters ($p>0.05$). The levels of hemoglobin, hematocrit, leucocytes, and platelets were not significantly different ($p>0.05$) between the control and treatment groups.

The Shapiro-Wilk test showed that most of the

Table 1. Characteristics of the research subjects

	Controls (n=20)	Treatment (n=20)	p value
Gender			
• Male, n (%)	16 (80)	15 (75)	0.31
• Female, n (%)	4 (20)	5 (25)	0.31
Total bilirubin (mg/dL)			
• Pre-treatment	14.16 ± 4.22	14.25 ± 3.99	0.95
• Post-treatment	7.48 ± 2.11	7.20 ± 2.80	0.38
Direct bilirubin (mg/dL)			
• Pre-treatment	0.52 ± 0.20	0.68 ± 0.42	0.85
• Post treatment	0.80 ± 0.18	0.70 ± 0.17	0.26
Bilirubin indirect (mg/dL)			
• Pre-treatment	13.64 ± 3.24	13.59 ± 3.69	0.81
• Post treatment	6.70 ± 2.37	6.50 ± 2.79	0.51
Hemoglobin (g/dL)	16,23	15.34	0.07
Hematocrit (%)	47,99	46.03	0.15
Leukocytes (/μl)	15,97 10^3	13.07 10^3	0.11
Platelets (/μl)	284.50 10^3	257.95 10^3	0.26

Table 2. Result of Wilcoxon test for the level of total bilirubin, direct and indirect bilirubin

Variables	Pre-Treatment	Post Treatment	p value
Total Bilirubin (mg/dL)			
• Control Group	14.16	7.48	0.00
• Treatment Group	14.25	7.20	0.00
Direct Bilirubin (mg/dL)			
• Control Group	0.52	0.80	0.32
• Treatment Group	0.68	0.70	0.37
Indirect Bilirubin (mg/dL)			
• Control Group	13.64	6.70	0.00
• Treatment Group	13.59	6.50	0.00

Table 3. Result of Mann Whitney test for the level of total bilirubin, direct and indirect bilirubin

Variables	Control Group	Treatment Group	p-value
Total Bilirubin (mg/dL)			
• Pre-Treatment	14.16	14.25	0.95
• Post Treatment	7.48	7.20	0.38
Direct Bilirubin (mg/dL)			
• Pre-Treatment	0.52	0.68	0.85
• Post Treatment	0.80	0.70	0.26
Indirect Bilirubin (mg/dL)			
• Pre-Treatment	13.64	13.59	0.81
• Post Treatment	6.70	6.50	0.51

total bilirubin, direct bilirubin, and indirect bilirubin data in the control and treatment groups were not normally distributed ($p<0.05$). Only data on bilirubin in the control group before treatment, total bilirubin in the treatment group before and after treatment, and indirect bilirubin data in the treatment group after treatment showed normal data distribution ($p>0.05$). Wilcoxon test showed that the total bilirubin levels and indirect bilirubin levels in the control and treatment groups before probiotic intervention were significantly different ($p<0.05$) from the level after the intervention. Meanwhile, direct bilirubin in both groups before and after treatment was not significantly different ($p>0.05$). Mann Whitney test showed that the total, direct, and indirect bilirubin levels before and after probiotic treatment in both control and treatment groups was not significantly different ($p>0.05$).

4. Discussion

This study evaluated the effects of combining phototherapy with probiotics containing *Lactobacillus acidophilus, Streptococcus thermophilus,* and *Bifidobacterium longum* in hyperbilirubinemia newborns. The hyperbilirubinemia patients in this study were dominated by males, 80% and 75% of the total respondents in the control and treatment groups, respectively. The prevalence of male neonates is consistent with previous research on jaundice, which found that male babies have a greater occurrence (Bening *et al.*, 2017). Regarding the impact of the intervention, the Wilcoxon signed-rank test demonstrated noteworthy decreases in the total and indirect bilirubin levels in both the control and treatment groups. The treatment group showed a significant and quick decline, highlighting the effectiveness of the intervention. This is consistent with Rezki *et al.* (2023), who reported the effectiveness of the intervention in reducing the length of hospital stays. Additionally, it aligns with a previous study that used probiotics, specifically *Lactobacillus bulgaricus,* live *Bifidobacterium,* and *Streptococcus thermophilus*, to treat neonatal jaundice. Orally administered probiotics expedited the bilirubin decrease, as Liu (2015) reported.

The observed elevation in direct bilirubin levels in both groups, as demonstrated by the Wilcoxon test, is an anticipated consequence of phototherapy. The increased levels caused by phototherapy have been extensively recorded in the literature (Sydney Children's Hospital, 2022). The research we conducted enhances our comprehension of the intricate impacts of phototherapy on various bilirubin constituents. It highlights the need to consider both indirect and direct bilirubin levels when evaluating the treatment results. Nevertheless, the multivariate analysis of the Mann-Whitney test did not uncover significant differences between the control and treatment groups. Potential factors that may have influenced this conclusion include inadequate research methodology, limited sample size, and variability in newborn responses caused

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by characteristics such as gestational age and birth weight. Limitations, such as the uneven application of interventions and unaddressed confounding variables, were recognized. It is crucial to address these constraints in future research to achieve a more comprehensive understanding of the consequences of interventions.

However, most prior studies have demonstrated that probiotics effectively reduce serum bilirubin levels. The results of a recent study conducted by Jenabi *et al*. (2022) demonstrated that using probiotics as a supplementary treatment with phototherapy for neonatal jaundice could significantly decrease the duration of hospital stays and phototherapy sessions. This approach reduces expenses and lessens the separation between neonates and their mothers. Although a minor elevation in bilirubin levels may not result in significant adverse effects, newborn jaundice can result in escalated medical expenses and heightened parental anxiety. The study emphasizes the significance of promptly diagnosing and treating hyperbilirubinemia. Phototherapy, a widely used treatment, elicits worries over the possibility of DNA harm and consequences. There is evidence supporting the use of probiotics alongside phototherapy in the treatment of neonatal hyperbilirubinemia. This combination has been found to decrease the side effects of phototherapy, reduce the length of hospital stay for neonates with hyperbilirubinemia, shorten the duration of phototherapy, and alleviate water loss caused by blue light phototherapy (Kamal *et al*., 2019). In addition to reducing water loss, several studies have demonstrated that using *B. animalis* CP-9 probiotics decreases the likelihood of hypocalcemia during phototherapy. Prior studies have emphasized the potential danger of hypocalcemia linked to extended phototherapy. Hence, using *B. animalis* CP-9 as a supplement, particularly within the first 24 hours of the therapeutic period, can help reduce the likelihood of hypocalcemia by reducing the total duration of phototherapy (Tsai *et al*., 2022).

Overall, the study showed that the combined intervention of *Lactobacillus acidophilus, Streptococcus thermophilus, Bifidobacterium longum* probiotics, and phototherapy effectively reduced bilirubin levels. Notably, there were significant reductions in both total and indirect bilirubin. While well-understood, the simultaneous increase in direct bilirubin levels after phototherapy contributes a subtle aspect to the overall evaluation of the intervention's effect. Although the multivariate analysis did not show any statistically significant results, the study nevertheless offers vital insights into the impacts of the intervention. This highlights the importance of conducting future research with improved design considerations and carefully evaluating confounding factors. Nevertheless, it is essential to recognize the constraints of the study, such as its inadequate research design marked by limited sample size, inefficient randomization, and the use of incorrect statistical methods, resulting in insignificant findings. The inherent variety in how newborns respond, influenced by factors such as how long they were in the womb, body weight at birth, and their genetics, makes it challenging to apply the findings to a larger population. The study's limitations are exacerbated by inconsistencies in the implementation of therapies, specifically with probiotics, and unexplained confounding factors such as maternal health and antibiotic use. Moreover, the limited duration of the observation period may not adequately capture the enduring effects of the intervention. At the same time, discrepancies in the definitions of variables and outcomes could undermine the validity of the results. To enhance our understanding of the impacts of interventions, future research should diligently tackle these limitations, aiming for a more thorough and detailed investigation of the combined use of probiotics and phototherapy in treating newborn hyperbilirubinemia.

5. Conclusions

Intervention of probiotics, specifically *Lactobacillus acidophilus, Streptococcus thermophilus,* and *Bifidobacterium longum*, to newborns with hyperbilirubinemia did not result in any notable distinctions compared to the control group. This lack of significant differences may have been influenced by unaccounted external factors. However, there is a promising possibility that combining probiotics and phototherapy can speed up the decrease in total and indirect bilirubin levels in studies. During 7 days, the treatment group had a more rapid decline compared to the control group, which alone received phototherapy. Potential future directions include investigating the impact of external variables, optimizing probiotic treatment procedures, conducting extended follow-up investigations, exploring supplementary combination therapies, delving into mechanistic analyses, considering research tailored to specific populations, prioritizing rigorously controlled randomized trials, and conducting thorough safety evaluations. These efforts strive to improve probiotic treatments' effectiveness, safety, and suitability for neonatal hyperbilirubinemia.

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Conflict of interest

All authors have no conflict of interest in this

article.

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