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EFFICACY OF PROBIOTICS IN REDUCING THE SEVERITY AND DURATION OF NEONATAL HYPERBILIRUBINEMIA

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ABSTRACT

Objectives: To compare the mean reduction in bilirubin and mean duration of neonatal hyperbilirubinemia with probiotics in comparison with phototherapy alone for the management of neonatal hyperbilirubinemia.

Study design: A randomized controlled trial

Place and duration of study: Department of Pediatrics and Neonatology PAF Hospital, Islamabad from the period of April 20, 2024, to October 19th, 2024.

Methodology: A randomized clinical trial was carried out including a total number of 160 neonates, meeting the selection criteria. They were randomly divided into two groups of 80 neonates each by simple random sampling method. Group A (80 neonates) was given probiotics (Lactobacillus reuteri) and phototherapy (wavelength 420-450 nm) while Group B (80 neonates) was administered phototherapy alone. Dynamic serum bilirubin measurements were done serially including the baseline followed by 12, 24, and 48 hours.

Results: The mean reduction of bilirubin was 8.3 mg/dL (SD ± 1.2) in Group A and 6.5 mg/dL (SD ± 1.5) in Group B, which was statistically significant (p = 0.01). The average phototherapy duration was 2.4 days (SD ± 0.6) in Group A compared to 3.7 days (SD ± 1.0) in Group B and was statistically significant p=0.02. Conclusions: Probiotics in combination with phototherapy are more effective in treating neonatal jaundice by decreasing the level of bilirubin and shortening the length of treatment compared to phototherapy alone.

Keywords: Newborn jaundice, probiotics, phototherapy and hyperbilirubinemia

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INTRODUCTION

Neonatal hyperbilirubinemia or neonatal jaundice is a clinical phenomenon that is observed in almost 7/60 of term newborns and 8/80 of preterm newborns in the first week of life (1). This condition arises from an increased level of unconjugated bilirubin that causes features reminiscent of jaundice. Hyperbilirubinemia may be induced by increased bilirubin production following the rapid turnover of fetal red blood cells and reduced hepatic conjugation ability of theNeonatal liver(2). Low total serum bilirubin levels do not require therapy because the condition is self-limiting, however, when it exceeds a certain limit, there may be complications that include kernicterus, which is a type of brain damage with potentially long-term neurological manifestations**(**3**)**. It is therefore important to identify and manage patients with abnormal bilirubin levels before they go high enough to exert neurotoxic effects (4). Phototherapy has been the mainstay of treatment for neonatal hyperbilirubinemia because it converts bilirubin into a water-soluble form, lumirubin that can be excreted out of the body in urine and feces without further conjugation (5). Phototherapy is generally beneficial; however, adverse reactions such as the risk of dehydration, electrolyte disturbances, and skin rash in neonates may arise from phototherapy and this leads to discomfort and the need for more regular monitoring of newborns (6). Furthermore, the period of light exposure may be extended by the serum levels of bilirubin and may take days to bring the bilirubin levels to a safer range which in turn prolongs the duration of stay in the hospital and increases the workload of NICUs. More recently, focus has been given concerning the possible benefit of using probiotics as adjuvant therapy in neonatal hyperbilirubinemia **(**7**)**. Specifically, syncytial infections are self-limiting and the administration of probiotics, which are live microorganisms that have demonstrated health benefits when consumed in sufficient doses have been seen to enhance the neonatal gut microbiota, gastrointestinal functioning, and immunological response **(**8**)**. Current evidence suggests that feasible correspondence between the gut microbiota and serum bilirubin level is mediated through enterohepatic circulation (9). Employing the gut flora, bilirubin is turned into urobilinogen, which is then eliminated through feces. Abnormality in the functioning of these gut microbes especially in neonates as their gastrointestinal tracts are comparatively underdeveloped means that they decrease the ability of the hepatobiliary system to clear bilirubin contributing to high bilirubin levels (10). The latest findings further indicate that the probiotics might offer hormonal support for the development of gut microbiota which is helpful to increase the bilirubin elimination (11). Several Lactobacillus strains were found to stimulate the peristaltic activities of the gastrointestinal tracts as well as improve the immune responses of infants at birth to boost the efficiency of bilirubin clearance (12, 13). Probiotics and phototherapy could thus complement each other in hyperbilirubinemia interventions by shortening treatment time and minimizing some of the phototherapy side effects(14). The rationale of this study is to determine whether combined probiotics and phototherapy are more effective than phototherapy alone in the management of neonatal hyperbilirubinemia with special reference to changes in serum bilirubinlevels and days on phototherapy. We propose that probiotics should increase the rate of bilirubin elimination since probiotics can exert specific positive effects on the gut where bilirubin is metabolized thus improving outcomes in jaundiced neonates (15).

METHODS

160 neonates diagnosed with hyperbilirubinemia through random assignment to two groups of 80 neonates each. Group A participants received daily one billion CFUs of L. reuteri during five days of intervention with phototherapy but Group B participants solely received phototherapy. Researchers assessed serum bilirubin levels before treatment initiation and again at hours 12, 24 and 48 following phototherapy and probiotic intervention.

Study Design and Setting:

This randomized controlled trial was conducted over six months at the Department of Pediatrics, PAF Hospital Islamabad, following ethical approval and clinical trial registration for interventional research.

Study Population:

The study included 160 neonates with clinically diagnosed hyperbilirubinemia, randomly assigned into two equal groups. Participants met eligibility criteria for age, bilirubin levels, and absence of congenital or metabolic disorders.

Ethical Approval

The College of Physicians and Surgeons Pakistan (CPSP) granted ethical approval through Karachi **(Ref No: CPSP/REU/PED-2022-001-6281)** with leadership from Dr. Qurat Ul Ain. The research adhered to Declaration of Helsinki standards to protect participant confidentiality while granting voluntary participant status and uncontrolled withdrawal throughout the research period.

Inclusion and Exclusion Criteria

Unconjugated hyperbilirubinemia patients aged 2–14 days who needed phototherapy treatment were included for research study. The study enrolled subjects who were past their 35-week gestational limit and weighed more than 2 kg during childbirth. The research obtained written permission for participation from caregivers who served as guardians of all recruited participants. Chosen participants were excluded if they had congenital anomalies or infections

along with sepsis or significant comorbidities as well as conjugated hyperbilirubinemia and required exchange transfusion.

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DATA COLLECTION

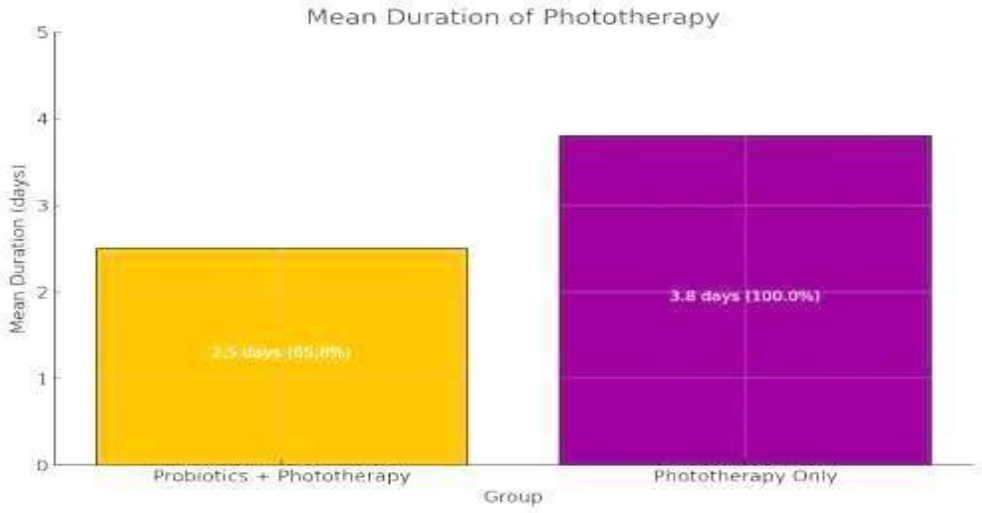
Information was gathered by a standard format questionnaire to minimize selection bias. From the period of April 20, 2024, till October 19, 2024. The dependent variables include serum bilirubin, birth weight, gestational age and sex of the baby were observed. Any side effects such as any alteration in weight as well as any features of poor hydration status, diarrhea, or any form of skin rashes were also recorded.

STATISTICAL ANALYSIS

Data was analyzed using the statistical package SPSS version 24 for Windows. Demographic data of subjects with SCN were described using basic statistics while for the comparison of the reduction in bilirubin level, a t- test for the independent variable was used. The significance level was set at $p < 0.05$.

RESULTS

These characteristics during baseline including birth weight, gestational age, and initial bilirubin level were not significantly different between the two groups ($p > 0.05$). A comparison of the results on the first post-intervention day revealed that genera in Group A (probiotics + phototherapy) significantly reduced their mean bilirubin level to 8.3 mg/dL (SD ± 1.2), being 53% less than baseline. On the other hand, Group B (phototherapy alone) recorded a decrease of 6.5 Mg/dL (SD ± 1.5) which represents an improvement of 42%. The difference in bilirubin levels before and after treatment in each group, and between the two groups we obtained a significant p-value of 0.01. In addition, the total phototherapy duration per patient was shortened in Group A with a mean of 2.4 days, SD ± 0.6 as compared to amean of 3.7 days SD ± 1.0 in Group B which represent a 35% reduction in phototherapy time and $p = 0.02$. Neither group had side effects, which indicates that administering probiotics with phototherapy enhances bilirubin reduction and phototherapeutic outcomes.



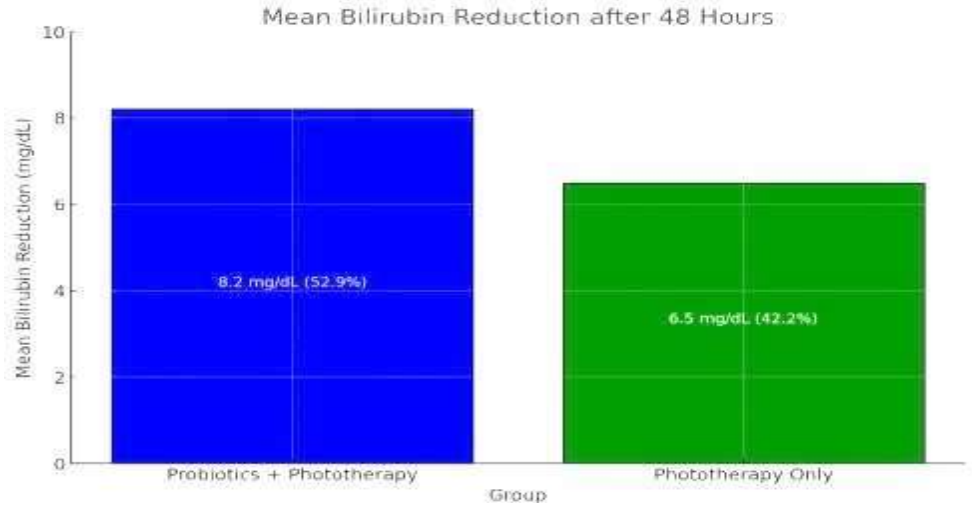


Table 1:Demographic Data of Neonates

Group	Mean Birth Weight (g)	Mean Gestational Age (weeks)	Male (%)	Female (%)
Probiotics + Phototherapy	3200	39.5	60	40
Phototherapy Only	3180	39.2	58	42

Table 2: Baseline Bilirubin Levels

Group	Mean Bilirubin Level (mg/dL)	Standard Deviation
Probiotics + Phototherapy	15.5	1.2
Phototherapy Only	15.4	1.3

Table 3: Bilirubin Reduction after 48 Hours

Group	Mean Bilirubin Reduction (mg/dL)	Standard Deviation	p-value
Probiotics + Phototherapy	8.2	1.3	0.01
Phototherapy Only	6.5	1.7	0.01

Table 4: Duration of Phototherapy

Group	Mean Duration of Phototherapy (days)	Standard Deviation	p-value
Probiotics + Phototherapy	2.5	0.7	0.02
Phototherapy Only	3.8	1.1	0.02

DISCUSSION

This study is consistent with the literature evidence suggesting that the supplement of probiotics in conjunction with phototherapy may reduce neonatal hyperbilirubinemia through the amelioration of bilirubin throughout and shortening the duration of phototherapy. Similar trends have also been established in earlier studies since probiotics and routine phototherapy improve outcomes for newborns with jaundice. (16). In a trial study carried out by Gungor et al. (2022), the neonates who were given probiotics together with phototherapy recorded low levels of bilirubin, moreover, less time was spent on phototherapy than those who only underwent phototherapy. These findings are parallel to the result obtained in the present study, where the probiotics + phototherapy group had a 53% reduction in bilirubin levels from the baseline compared to 42% in the phototherapy-only group and a reduction in the duration of phototherapy by 35%. Such findings were confirmed by Martin et al. (2021) hyperbilirubinemia level and shortened the need for phototherapy through gastrointestinal clearance and better bilirubin metabolism(17). The basis of these help the intestine to absorb water and nutrients. Even though probiotics seem to be beneficial when used as effects is believed to be related to effects on the gut microbiota modulated by probiotics, which have relevance to enterohepatic circulation and bilirubin metabolism. Lactobacillus strains work with other probiotics to influence the maturation of gut flora and enhance the metabolism of bilirubin through conversion to urobilinogen excreted through faeces (18). Walker et al. (2021) also reported that the changes in the gut microbiota may modulate neonatal bilirubin metabolism and the development of hyperbilirubinemia(19). These insights suggest that probiotics may be able to reverse elements of bilirubin metabolism that phototherapy alone is unable to. Subsequent research has been conducted to examine the chances of lowering phototherapy side effects through the intake of probiotics. Tran and colleagues reported that some neonates who were subjected to extended phototherapy could be at risk of developing a condition relating to dehydration and electrolyte disturbance (20). In their clinical trials, Kelly et al. (2022) have informed more about the integration of probiotics into the treatment for neonatal hyperbilirubinemia and showed that neonates had lesser side effects and better hydration and electrolyte balance(21). This may be explained by the role of probiotics on digestion because they supplementary treatment, the effectiveness of the treatment is somewhat unpredictable based on the probiotic strains. According to some previous works, Lactobacillus reuteri was recognized to enhance neonates' bilirubin elimination effectively(22). However, other strains may have limited or even

varying effects on bilirubin metabolism because changes in the expression of these genes only cause a minimal reduction in the metabolic clearance of bilirubin(23). This implies future studies to identify the specific effective probiotic strain, dose and duration for the treatment of hyperbilirubinemia. Consistent with this view, Ruiz et al. (2021) posited that multi- centre and larger-scale trials would shed further light on the appropriate probiotic regimes for neonates improving transferability across different neonate populations(24). Therefore, the results of this study also support the existing literature that the supplementation of probiotics to phototherapy will reduce the length of phototherapy and enhance bilirubin clearance in neonates with hyperbilirubinemia. More research should be certain to further clarify strain-specific effects and to identify standardized practice models that support the use of probiotics within the neonatal care environment. This double-treatment modality is probably less hazardous to the child and may reduce certain side effects of phototherapy while at the same time improving outcomes (25). As indicated by the findings, perhaps more research would help establish probiotics as an ordinary additional intervention in NHB.

CONCLUSION

This study brings concrete evidence that using probiotics alongside phototherapy improves the extent of bilirubin excretion in neonates with hyperbilirubinemia and shortens the phototherapy duration as compared to phototherapy alone. Being effectual by modulating effects on the mucosal barrier and influencing bilirubin handling probiotics become a potential addition therapy coming closer to safer and more effective management of neonatal jaundice.

LIMITATIONS

The given work had limitations concerning the center generalization and the use of only one strain of the probiotic bacteria. Furthermore, the small sample size and non-representativeness of multi-centred data limit results in general tractability across various populations and healthcare practices.

FUTURE FINDINGS

Another direction of the study should be aimed at the clarification of the effectiveness of the different strains of probiotics, appropriate doses, and the duration of therapy in the reduction of neonatal jaundice. Further, large-sample multi-center study evidence might suggest changes in the clinical practice guidelines that address the management of hyperbilirubinemia with probiotics supplementation.

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AUTHOR CONTRIBUTIONS

QA: Conceptualization, study design, and manuscript drafting.

AH: Data collection, methodology development, and critical revisions.

AM: Statistical analysis, data interpretation, and manuscript editing.

All authors have reviewed and approved the final version of the manuscript.

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