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Original Article

Therapeutic Effects of Probiotics In The Reduction of Neonatal Hyperbilirubinemia

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ABSTRACT

Objective: To evaluate probiotics' effects in reducing hyperbilirubinemia in late preterm and term neonates.
Study Design: Quasi-experimental study
Place and Duration of Study: Department of Neonatology, Pakistan Institute of Medical Sciences (PIMS), Islamabad Pakistan, from Oct 2018 to Mar 2019.
Methodology: The quasi-experimental study was conducted on 60 neonates with hyperbilirubinemia. They were randomly divided into two Groups. Group-A (n=30) received phototherapy. Group-B (n=30) received probiotics containing Lactobacillus reuteri at a dose of 5 drops daily for three days, in addition to phototherapy. Total serum bilirubin was calculated at 0, 24 and 72 hours for both Groups.
Results: In Group-A, the mean total bilirubin in mg/dl at 0, 24 and 72 hours were 18.14±2.35, 15.28±2.93 and 12.31±2.29, respectively. Similarly, in Group-B, it was 19.86±5.85, 16.23±4.01 and 10.75±2.23 at 0, 24 and 72 hours, respectively. There was an insignificant statistical difference in mean total bilirubin between Groups A and B at 0 and 24 hours (p<0.001). However, when comparison was made at 72 hours, a significant statistical difference was observed in Group-B (Intervention Group) (p=0.005)
Conclusion: Probiotics significantly lowered total serum bilirubin in neonates with hyperbilirubinemia. Further studies are required to evaluate its role in physiological and pathological jaundice.

Keywords: Hyperbilirubinemia, Hyperbilirubinemia, Neonatal jaundice, Limosilactobacillus reuteri, Infant.

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INTRODUCTION

In clinical practice, neonatal jaundice is very common, which is the yellowish pigmentation of skin, mucous membranes and sclera due to hyperbilirubinemia of >5mg/dl.[1,2] Approximately 60% of term and 80% of premature infants are hospitalized for hyperbilirubinemia in the first week of life. Hyperbilirubinemia is one of the most common causes of hospitalization in neonates.[3]

Jaundice may be physiological or pathological, but physiological icterus is a common cause of infantile hyperbilirubinemia, which is diagnosed by ruling out other important etiologies.[4,5] The most prevalent therapeutic method for managing infantile icterus and preventing its complications is phototherapy, which has been applied for decades as a safe method. Exchange transfusions are required for the higher levels of bilirubin. Most of the time, neonates are discharged within 48 hours of life unless there are some complications.6 5% to 10% were admitted to the neonatology unit for hyperbilirubinemia and treated with phototherapy for a longer duration. Recently, an increase in early hospital discharges has led to a rise in the rate of hyperbilirubinemia and kernicterus and, hence, an increase in hospital costs due to hospital readmissions.[7,8]

One of the causes of hyperbilirubinemia in a newborn is the failure to convert conjugated bilirubin to stercobilin due to the relative lack of bacteria in the gut during the first week of life. Hyperbilirubinemia is also attributed to the activity of the beta-glucuronidase enzyme in the sterile gut and the mild alkaline PH of the proximal intestine.[9] Probiotics reduce the degradation of bound bilirubin and hence decrease enterohepatic circulation. They stimulate intestinal peristalsis and help the excretion of bilirubin. The rationale of this study was to see the effects of reducing hyperbilirubinemia by using probiotics and to decrease the hospital stay and the financial burden on the family.

METHODOLOGY

The quasi-experimental study was conducted at the Department of Neonatology, Pakistan Institute of Medical Sciences (PIMS), Islamabad, Pakistan from October 2018 to March 2019, after approval from the Shaheed Zulfiqar Ali Bhutto Medical University

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Ethical Review Board (letter no F.1-1/2015/ERB/SZABMU/ dated 13-6-2017). The sample size was calculated using an Openepi calculator keeping Group-A mean(SD) at 12.12(2.16), Group B mean(SD) at 13.71(2.13).[10]

Inclusion Criteria: Neonates of either gender, born at term or late preterm with clinically visible jaundice in the phototherapy range were included.

Exclusion Criteria: Neonates who were preterm or syndromic, had sepsis or any other infection, hyperbilirubinemia in the exchange transfusion range or developing within the first 24 hours of birth, and conjugated hyperbilirubinemia were excluded.

A total of 60 noenates were included and randomly divided into two groups. Group-A (Control Group) was given phototherapy and a placebo. In contrast, Group-B (Intervention Group) was given the Probiotic containing Lactobacillus reuteri at five drops daily for three days (Figure).

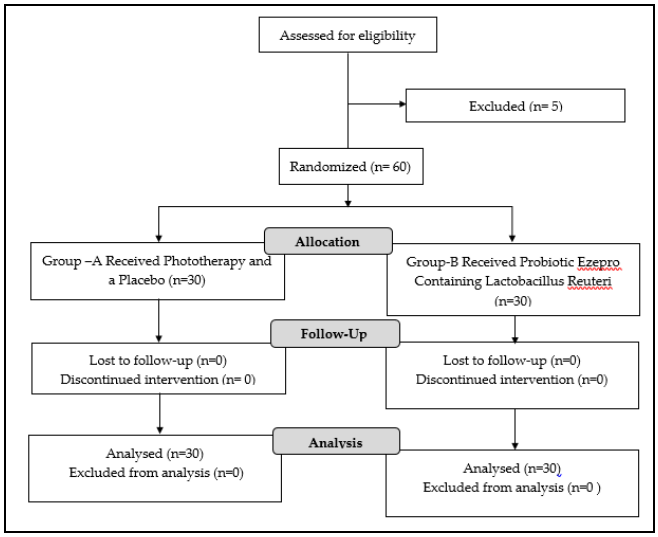

Figure: Patient Flow Diagram (n=60)

The total serum bilirubin was recorded at 0, 24 and 72 hours for both Groups.

Statistical Package for Social Sciences (SPSS) version 25.0 was used for the data analysis. Quantitative variables were expressed as Mean±SD and qualitative variables were expressed as frequency and percentages. Independent sample t-test was applied to explore the inferential statistics. The *p*-value of ≤0.05 was set as the cut-off value for significance.

RESULTS

In our study, Group-A 17(56.6%) and Group-B 16(53.3%) neonates had normal vaginal delivery. The other demographic details of the mother and newborn are given in Table-I.

Table-I: Comparison of Characteristics of Newborns and Mothers before Intervention (n=60)

Characteristics	Group-A (n=30)	Group-B (n=30)
Gender		
Male	22(73.3%)	16(53.3%)
Female	8(26.7%)	(46.7%)
Mode of Delivery		
Normal Vaginal Delivery	17(56.6 %)	16(53.3 %)
C-Section	13(43.4%)	14(46.7%)
Mother's Blood Group		
A Positive	7(23.4%)	3(10.0 %)
B Positive	5(16.7 %)	6(20%)
AB Positive	2(6.7%)	6(20%)
O Positive	12(40%)	11(36.6%)
A Negative	1(3.3%)	1(3.4%)
B Negative	1(3.3%)	2(6.6%)
AB Negative	1(3.3%)	-
O Negative	1(3.3%)	1(3.4%)
Baby's Blood Group		
A Positive	4(13.3 %)	7(23.3%)
B Positive	11(36.7 %)	10(33.4%)
AB Positive	1(3.3 %)	1(3.3%)
O Positive	10(33.4 %)	10(33.4%)
A Negative	-	0(3.3%)
B Negative	1(3.3 %)	-
AB Negative	3(10 %)	-
O Negative	-	2(6.6%)

Table-II: Comparison of Mean total Bilirubin in both Groups at different Time Intervals (n=60)

Parameters	Group-A	Group-B	*p*-value
Mean Age (Day of life)	6.66 ±2.78	6.1±3.60	0.25
Gestational Age (weeks)	37.93±1.39	37.43±1.38	0.08
Mean Total Bilirubin at 0 hour	18.14±2.35	19.86±5.85	0.07
Mean Total Bilirubin at 24hour	15.28±2.93	16.23±4.01	0.15
Mean Total Bilirubin at 72 hour	12.31±2.29	10.75±2.23	0.005

The mean gestational age was 37.93±1.39 weeks in Group-A and 37.43±1.38 weeks in Group-B (p=0.08). In Group -A, the mean age in days was 6.66±2.78, and in Group-B was 6.1±3.60 (p=0.25). The mean total bilirubin in mg/dl at 0, 24 and 72 hours in Group-A was 18.14±2.35, 15.28±2.93 and 12.31±2.29, respectively. Similarly, in Group-B, it was 19.86±5.85, 16.23±4.01 and 10.75±2.23 at 0, 24 and 72 hours, respectively. There was an insignificant statistical difference in mean total bilirubin between Groups A and B at 0 and 24 hours (p<0.001). However, when a

comparison was made at 72 hours, a significant statistical difference was observed in Group-B (Intervention Group) p=0.005, as shown in Table-II.

Regarding the efficacy of treatments, total bilirubin showed a significant differencde in both Groups A and B, as tabulated in Table-III.

Table-III: Comparison of Effectiveness of Treatment in both Groups (n=60)

	Mean Total Bilirubin at 0 hour	Mean Total Bilirubin at 72 hour	*p*-value
Group-A	18.14±2.35	12.31±2.29	<0.001
Group-B	19.86±5.85	10.75± 2.23	<0.001

DISCUSSION

Our study showed a significant reduction in Mean Total Bilirubin at 72 hours compared to the Control Group. The results were, however, non-significant at 24 hours of therapy, suggesting a longer treatment regimen of probiotics for the treatment of hyperbilirubinemia. Lactobacillus, a facultative anaerobe, is known to colonize regions with high beta-glucuronidase activity, such as the stomach, jejunum and duodenum.[10]

A study was conducted on a large scale in India by Chandrasekhar *et al*. in which 1043 babies born after 35 weeks of gestation were enrolled. Of these, 510 were given Bacillus Clausii prophylactically at a dose of 2ml twice daily for three days. The remaining 533 were included in the control Group. The primary outcome was to see both Groups' needs and duration of phototherapy. It was found that the need for phototherapy, as well as the duration of phototherapy, was significantly reduced in the Intervention Group: 18 hours in the Intervention Group and 24 hours in the control Group (p=0.027). It was concluded that prophylactic treatment of probiotics for three days significantly reduces the need and duration of phototherapy in neonatal jaundice.[11] In two other studies by Yuan C *et al*.and Suganthi *et al*. the incidence of hyperbilirubinemia was significantly lower with probiotics.[12,13]

The role of Saccharomyces boulardii was highlighted in a study by Demirel *et al*.on preterm, low-birth-weight neonates. The intervention Group comprised 81 neonates who were given 250 mg of S. boulardii once daily in addition to phototherapy, while the control Group (n=98) received phototherapy alone. It was found that the duration of phototherapy and feeding intolerance was significantly lower in the intervention Group.[14] In a study by Serce *et al*., however, S. boulardii did not significantly influence the clinical course of hyperbilirubinemia. Fifty-eight-term neonates were given S.boulardii at a dose of 125mg twice daily in addition to phototherapy. Total serum bilirubin was calculated for both Groups at 0, 24, 48, 72 and 96 hours of phototherapy. No significant difference was found in total serum bilirubin, nor was the duration of phototherapy affected significantly.[15] In another randomized controlled trial by Pasha *et al*., 150 neonates admitted for hyperbilirubinemia in the phototherapy range were included. Seventy-five of them were given Pedilact, which includes L. rhamnosus, L. reuteri and Bifidobacterium infantis at a dose of 10 drops daily until discharge from the hospital. Although a decreasing trend was seen in the total serum bilirubin and duration of phototherapy, they were not statistically significant.[16]

Torkaman *et al.* showed that probiotics did not change the total serum bilirubin. However, there was a significant reduction in the length of hospital stay in the intervention Group (p=0.004). A combination of Bifidobacterium lactis, Lactobacillus acidophilus, Bifidobacterium bifidum and Lactobacillus rhamnosus was given to 45 full-term neonates. The control Group (n=47) received a placebo and phototherapy alone. Probiotics may have a role as an adjunct treatment in neonatal hyperbilirubinemia.[17] Armenian *et al*. did a study and concluded that Prebiotic oligosaccharides increase stool frequency, improve feeding tolerance and reduce bilirubin levels in preterm neonates and, therefore, can be efficacious for the management of neonatal hyperbilirubinemia.[18]

LIMITATIONS OF STUDY

The parameters, such as defecation frequency and phototherapy duration, which had shown significant associations in other studies, were not measured.

CONCLUSION

Probiotics had a significant effect in lowering total serum bilirubin in neonates with hyperbilirubinemia. Further studies are required to evaluate its role in physiological and pathological jaundice. The prophylactic role of probiotics also needs to be considered.

Conflict of Interest: None.

Authors Contribution

Following authors have made substantial contributions to the manuscript as under:

AW & HS: Data acquisition, data analysis, data interpretation, critical review, approval of the final version to be published.

AM & YW: Study design, data interpretation, drafting the manuscript, critical review, approval of the final version to be published.

Authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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