Original Article

The Role of Probiotics in Enhancing Immune Function in Preterm Low Birth Weight Infants

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Abstract

Background: *The establishment of complete enteral nutrition is a significant difficulty in the management of preterm low birth weight (LBW) infants. Probiotics are live microbial supplements that populate the gut with favorable flora, increase feeding tolerance, and encourage the expansion of these premises. The aim of the study is to observe probiotics' activity in improving immunity in preterm, low birth weight neonates.* ***Materials and Methods:*** *This randomized controlled clinical trial was carried out in the Department of Paediatrics, Abdul Malek Ukil Medical College & Jononeta Nurul Hoque Adhunik Hospital, Noakhali during January to December 2023. A total of 130 LBW infants were included in this study. Selected infants were randomly allocated to either probiotic groups (n=65) or control groups (n=65). Collected data were classified, edited, coded and entered into the computer for statistical analysis by using SPSS-23.* ***Results:*** *The average initiation of feeding was 4.3±1.0 days in the probiotics group and 4.5±0.9 days in the control group. Probiotics significantly decreased the time to full enteral feed and hospital stay compared to the control group. In the probiotics group, the mean duration of postnatal antibiotics was 9.89±2.6 days, while in the control group, it was 10.87±2.8 days. Ninety-six (96.72%) patients in the control group and 100% patients in the probiotics group had necrotizing enterocolitis stage II or lower. Five (5) patients (10%) in the control group and 3 (6%) in the probiotics group were found to be infected more than 3 days after birth.* ***Conclusion:*** *Probiotic supplementation in preterm low birth weight infants improves feed tolerance, decreases hospital stay, reduces the risk of infection and improves weight gain in comparison to non-supplement group.*

Keywords: Probiotics, Immune Function, Preterm Low Birth Weight Infants.
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Introduction

Probiotics, defined as live organisms that provide health benefits to the host when consumed in adequate quantities, are often used in the premature infant population as a prophylactic measure against Necrotizing Enterocolitis (NEC), Late-Onset Neonatal Sepsis (LOS), feeding intolerance and all-cause mortality[1]. This practice remains a matter of ongoing debate due to concerns regarding the safety and efficacy of using live microbes as therapeutics for infants born prematurely, who are immunocompromised[1]. Preterm birth, defined as birth before 37 weeks of gestation, affects nearly 10% of pregnancies and is the leading cause of perinatal morbidity and mortality. Preterm infants are at increased risk of sepsis, death, and lifelong neurodevelopmental and cognitive impairment[2].

Probiotic feeding in preterm reduces the bowel reservoir of more pathogenic species, improves enteral nutrition, and reduces dependence on intravenous nutrition, improves gut mucosal barrier to bacteria and bacterial products, and upregulates protective immunity. The prevalence of Low Birth Weight in Bangladesh is 36%[3]. Therefore, feeding management is an emerging challenge for those involved in neonatal care. The colonization of the sterile gastrointestinal tract begins right after birth and quickly establishes a presence of dominant strains such as Bifidobacterium and Lactobacillus within the first few days of life in healthy infants who are breastfed[4].

Very low birth weight (less than 1.5 kg) is at risk of developing a severe bowel disorder, where a portion of the bowel becomes inflamed, infected, and dies, called necrotizing enterocolitis[5]. The main probiotic organisms used worldwide belong to the genera Lactobacillus and Bifidobacteria and are found in

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the gastrointestinal micro flora[6,7]. Prebiotics are found in fruit and vegetable components, they are nondigestible food ingredients that benefit the host by selectively stimulating the growth and/or activity of one or a limited number of bacteria in the colon and improving the host's health[8,9].

Consumption of prebiotics by preterm formula fed infants results in an increase of beneficial microorganisms in the colon and reduces harmful bacteria to levels similar to those seen in breastfed infants. This enhances the gastrointestinal mucosal barrier, reduces intestinal permeability, helps prevent infections, and ultimately supports better growth[10,11]. The primary goal of incorporating probiotics and prebiotics into formula for preterm infants is to enhance growth and development while reducing infections by fostering an intestinal microbiota similar to that found in breastfed infants[12,13]. In Bangladesh, with improved obstetric and neonatal care increasing number of preterm babies are surviving. Therefore, feeding care and promoting growth are emerging concerns for neonatologists. In Bangladesh, there are few studies on the use of probiotics in the treatment of preterm newborns.

Materials and Methods

This randomized controlled trial was carried out at the department of Paediatrics, Abdul Malek Ukil Medical College (AMUMC) and Jononeta Nurul Hoque Adhunik Hospital, Noakhali during January to December 2023 study period. The study protocol was approved by the institutional ethical committee (ref: BCPS/712/2021) and written informed consent was obtained from parents of all participating children. A total of 130 infants with LBW were selected and admitted in SCANU, Jononeta Nurul Hoque Adhunik Hospital during the study period. Inclusion criteria was gestational age <34 weeks and birth weight 1000- 1800 gram, able to take enteral feed by 3 days after birth and those for whom informed parental consent was obtained. Babies with major chromosomal syndrome, gastrointestinal anomalies, and newborns with severe perinatal asphyxia, newborns with severe IUGR and those with evidence or clinical suspicion of sepsis before randomization were excluded from the study. Selected infants were randomly allocated to either probiotic groups (n=65) or control groups (n=65). Control group means that did not get probiotics but fulfilled all inclusion criteria. A comprehensive history was collected from the mother or caregiver and from the obstetric records, and this information was entered into a structured questionnaire. The gestational age was assessed using the most accurate obstetric estimates and the modified Ballard score.

Probiotic product which was used in this study was probio powder in sachet, manufactured by Square Pharmaceuticals Limited, Bangladesh. One probiotic sachet contained 3 viable probiotic strains belonging to the genera Lactobacillus and Bifidobacterium (4 billion). This product was tested in microbiology lab for viability of the microorganism prior to its use. Trophic enteral feeding was started when vitals were stable, bowel sound audible, no abdominal distension observed, and no blood or bile return by nasogastric suction. A nasogastric tube of size 5 Fr or 6 Fr was introduced following the standard procedure and its position was verified.

Probiotic suspension was reconstituted just before administering to the neonates by dissolving the content of a sachet in 4ml of sterile water taken in a capped clean test tube. The probiotic fortified group was receiving a probiotic mixture (lactobacillus & bifidus) along with expressed breast milk through nasogastric tube or dropper once daily from the first feed. The volume of probiotic suspension was 1 ml at the start and then increased to 3 ml when feed volume reaches 5 ml/feed. One ml of the reconstituted supplement contained $1x10^9$ CFU. In neonates receiving antibiotics, probiotic was administered 2 hours after antibiotics during subsequent feed. Supplementation continued till the attainment of full enteral feed. The neonates in control group were fed breast milk only as per existing protocol. The amount of feeding in either group was advanced slowly if tolerated with no more than a 20 ml/kg increment per day. All other existing clinical management protocols and clinical practices were uninterrupted.

The neonates in both the groups were followed up clinically; daily weight was taken for all newborns and recorded in the weight chart. All newborns were monitored for clinical signs of sepsis. Gastrointestinal symptoms such as vomiting, abdominal distension, character of nasogastric aspirate, characteristics of feces and its colour were monitored twice daily and recorded in the case recording sheet. Probiotic supplementation was withheld when feed was withheld for any reason as decided by the consultants and supplementation resumed when enteral feeding was restarted. Relevant investigations were sent in either group whenever necessary: blood culture and sensitivity, complete blood count (CBC), CRP, peripheral blood film (PBF), plain x-ray abdomen, stool for occult blood test (OBT), others as demanded by clinical condition. Weight gain pattern in the two groups was assessed by statistical difference of Mean ± SD of birth weight and weight at discharge in two groups. Time to reach full feeding was calculated by the difference between the ages in days at the start of feed and the age of adequate breast feeding or getting 150 ml/kg/day of requirement of feed by nasogastric tube or dropper. Outcome measures

were weight gain pattern, number of days required to reach full enteral feeding, length of hospital stay. All the data was collected with the above-mentioned methods and entered into SPSS V23. The patients were examined by the researcher for certain signs and those were recorded in the checklist.

Results

The mean age was 4.5±2.7 days in probiotics group and 4.6±2.9 days in control group and male infants were predominant. The majority of the gestational age women were between 28-33 weeks in both groups (Table-I). Regarding residential status, no significant difference was found in residential status between probiotics and controlled groups (Figure-1). Table-II showed mean start of feeds was found 4.3±1.0 days in probiotics group and 4.5±0.9 days in control group. Probiotics significantly reduced the time to full enteral feed and hospital stay compared to the control group.

The mean birth weight was found to be 1362.0±176.9 gm in the probiotics group and 1373.0±154.6 gm in control group. Mean birth length was found 42.37±2.51 cm in probiotics group and 43.1±2.37 cm in control group. Mean birth head circumference was found 29.6±1.7 cm in probiotics group and 28.9±1.6 cm in control group. Table-III demonstrates that the mean weight at discharge was found to be 1587.1±173.8 gm in probiotics group and 1514.2±143.7 gm in control group. This difference was statistically significant between the two groups. The mean APGAR score at 1st minute was found 6.57±0.9 in probiotics group and 6.39±1.0 in control group. The mean APGAR score at 5th minute was found 7.85±1.0 in probiotics group and 7.62±1.1 in control group. The difference was not statistically significant between the two groups. The mean duration of post-natal antibiotics was found 9.89±2.6 days in probiotics group and 10.87±2.8 days in control group (Table-III).

All (100%) patients were found necrotizing enterocolitis stage <II in probiotics group and 63 (96.92%) in control group. Three (6%) patients were found infected >3 days of life in the probiotics group and 5 (10%) in the control group. There was no significant relation between the two groups (Table-IV).

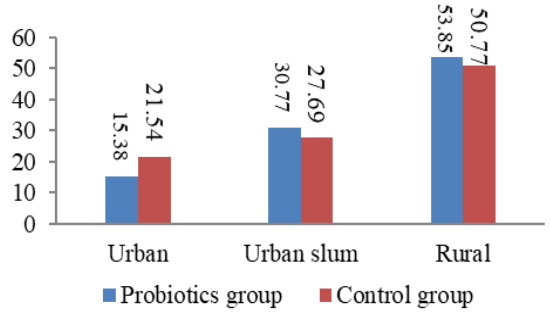

Figure-1: Residential status of the study population (n=130)

Table-I: Demographic characteristics of the study groups (n=130)

Variables	Probiotics group (n=65)		Control group (n=65)		p-value
	n	%	n	%	
Age (days)	4.5±2.7		4.6±2.9		0.49^{ns}
Gender					
Male	35	53.85	36	55.38	0.86^{ns}
Female	30	46.15	29	44.62	
Gestational age (week)					
<28	19	38.0	26	40.0	0.83^{ns}
28-33	31	62.0	39	60.0	
Mode of delivery					
Normal delivery	36	55.38	31	47.69	0.16^{ns}
Caesarean section	29	44.62	34	52.31	

*p-value obtained from $\chi 2$ test

Table-II: Comparison of start of feeds, time to reach full enteral feed and duration of hospital stay between the study groups by t-test significance (n=130)

Variables	Study group		p-value
	Probiotics n=65	Control n=65	
	Mean±SD	Mean±SD	
Start of feeds (days)	4.3±1.0	4.5±0.9	0.29^{ns}
Time to reach full enteral feed (days)	11.9±2.7	13.7±3.4	0.01^{s}
Duration of hospital stay (days)	14.57±2.8	15.9±3.6	0.04^{s}

Table-III: Comparison of birth weight, birth length, weight at discharge, birth head circumference, APGAR score and duration of post-natal antibiotics between the study groups by t-test significance (n=130)

Variables	Study group		p-value
	Probiotics n=65	Control n=65	
	Mean±SD	Mean±SD	
Birth weight (gm)	1362.0±17	1373.0±154.6	0.57^{ns}
Birth length (cm)	42.37±2.51	43.1±2.37	0.44^{ns}
Weight at discharge (gm)	1587.1±173.8	1514.2±143.7	0.03^{s}
Birth head circumference (cm)	29.6±1.7	28.9±1.6	0.72^{ns}
APGAR score			
At 1st minute	6.57±0.9	6.39±1.0	0.29^{ns}
At 5th minute	7.85±1.0	7.62±1.1	0.34^{ns}
Duration of post-natal antibiotics (days)	9.89±2.6	10.87±2.3	0.16^{ns}

*p-value obtained from 't' test

Table-IV: Relationship of necrotizing enterocolitis stage and infection >3 days of life between the study groups (n=130)

Variables	Probiotics group (n=65)		Control group (n=65)		p-value
	n	%	n	%	
Necrotizing enterocolitis stage					
<II	65	100.0	63	96.9	0.50^{ns}
≥II	0	0.00	02	3.08	
Infection >3 days of life					
Yes	4	6.15	6	9.2	0.71^{ns}
No	61	93.8	59	90.7	

*p-value obtained from $\chi 2$ test

Discussion

In this study the mean age was 4.5±2.7 days in probiotics group and 4.6±2.9 days in control group and male patients were predominant. Al-Hosni, et al.[14] reported mean age 4.2±2.1 days in probiotics-supplementation group and 4.1±2.3 days in non-supplement group. Hays, et al.[15] observed the mean age was 6.4±1.5 days in their study. Al-Hosni, et al.[14] reported 22 (44%) male patients in the probiotic supplementation group and 28 (55%) in the non-supplement group. Shashidhar, et al.[16] found 27 male patients in the probiotic group and 2 in the non-probiotic group. Braga, et al.[17] also found that 58 (48.7%) of the patients in the probiotic group were male, while 55 (49.1%) were in the control group. Besides, the majority of gestational age were between 28-33 weeks in both groups. Al-Hosni, et al.[14] discovered that the average gestational age was 25.7±1.4 weeks in the probiotics-supplementation group and 25.7±1.4 weeks in the control group. Shashidhar, et al.[16] reported that the average gestational age was 31.2±2.1 weeks in the probiotic group and 31±2.1 weeks in the control group.

According to this study, 31 patients (47.69%) in the control group and 36 patients (55.38%) in the probiotics group experienced a normal vaginal birth. On the other hand, 29 (44.62%) and 34 (52.31%) patients had a history of birth by caesarean section. Al-Hosni, et al.[14] reported that 30 patients (59%) in the control group and 22 patients (44%) in the probiotic supplementation group underwent cesarean sections. According to Shashidhar, et al.[16], 27 patients (51.9%) in the probiotic group and 38 patients (73%) in the non-probiotic group underwent cesarean sections. According to Braga, et al.[17], 64 patients (53.8%) and 55 patients (49.1%) in the control group underwent cesarean sections. The current research revealed that the probiotics group's mean feed start date was 4.3±1.0 days, while the control groups it was 4.5±0.9 days. According to Moni, et al.[3], the probiotics group and control group's mean feed start times were 2.23±0.68 days and 2.54±0.82 days, respectively.

The probiotics group of this study took an average of 11.9±2.7 days to obtain full enteral feed, while the control group took an average of 13.7±3.4 days. Enteral feeding was started at a comparable postnatal age in the probiotic and control groups, according to Shashidhar, et al.[16] The main result of time to full enteral feeding was 12.7±8.9 days in the non-probiotic group compared to 11.2±8.3 days in the probiotic group which was not statistically different. Probiotic-supplemented newborns reached complete feed earlier, according to Moni, et al.[3] (13.71±3.4 vs. 16.53±6.13 days). Samanta, et

al.[18] reported the number of days required to reach full enteral feeding was significantly low in babies who received probiotics (13.76±2.28 vs. 19.2±2.02 days).

There was a significant difference of hospital stay between probiotics and control group in this study (14.57±2.8 vs 15.9±3.4 days in the control group. According to Shashidhar, et al.[16] the average hospital stay was 27.6±18.5 days in the probiotic group and 31.2±22.9 days in the non-probiotic control group which was not statistically significant. Moni, et al.[3] found a mean hospital stay of 19.3±5.6 days in the probiotic group and 23.5±8.3 days in the control group. This difference was statistically significant. Samanta, et al.[18] reported the duration of hospital stay was also significantly low in the probiotic-exposed group compared with the control (17.17±3.23 vs. 24.07±4 days). The study found that the average birth weight was 1362.0±176.9 gm in the probiotics group and 1373.0±154.6 gm in the control group that was statistically significant. Al-Hosni, et al.[14] found that the probiotics-supplementation group had a mean birth weight of 778±138 gm, while the control group had a mean of 779±126 gm. Samanta, et al.[18] also found no significant difference in mean birth weight between probiotics and control group (1172 ± 143 gm vs. 1210 ± 143 gm).

The current study found that the mean APGAR score during the first minute was 6.57±0.9 in the probiotics group and 6.39±1.0 in the control group. The average APGAR score at 5 minutes was 7.85±1.0 in the probiotics group and 7.62±1.1 in the control group. The difference was not statistically significant between the two groups. Al-Hosni, et al.[14] discovered that the median APGAR score during the first minute was 5 in the probiotics-supplementation and control groups, respectively. The median APGAR score at the fifth minute was 7 in the probiotic supplementation group and 8 in the control group. The mean APGAR score at one minute was 6.6±2.6 in the probiotic group and 6.7±1.5 in the no probiotic group, according to Shashidhar, et al[18]. In the probiotics group, the mean APGAR score at minute five was 8.0±0.8, while in the control group it was 8.0±1.0. The study demonstrated that the average length of post-natal antibiotics was 9.89±2.6 days for the probiotics group and 10.87±2.8 days for the control group. There was no statistically significant difference between the two groups. Al-Hosni, et al.[14] showed that the average duration of antimicrobial treatment was 12.6±8.5 days in the probiotics-supplementation group and 11.7±7.3 days in the control group. This difference was not statistically significant like our study.

This study showed that all (100%) patients had necrotizing enterocolitis stage <II in probiotics group and 63 (96.9%) in control group. Shashidhar, et al.[16] reported 2 (4.1%) patients had necrotizing enterocolitis stage ≥II in probiotic group and 6 (12.5%) in non-probiotic group. Samanta, et al.[18] compared two groups (Bell stage ≥II) of NEC, and showed no significant difference. Current study showed 3 (6.0%) patients was found infected >3 days of life in probiotics group and 5 (10.0%) in control group. Stringent quality control ascertaining the safety and efficacy of these products for use in preterm infants is necessary, particularly given their fragile physiological condition and higher likelihood of having indwelling medical supports that act as sites at risk of infection[19,20]. While infrequent, reports of infections linked to contaminated probiotics exist,[21] further emphasizing the need for the implementation of strict quality control measures to prevent these avoidable and potentially life-threatening clinical events.

Conclusion

Probiotic supplementation in preterm low birth weight newborns improves feed tolerance, shortens hospital stays, reduces infection risk, and increases weight gain when compared to non-supplement group.

Conflict of interest

The authors declared that they have no conflict of interests.

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