Caspian Journal of Pediatrics
Babol University of Medical Sciences
e-ISSN: 2383-3106

Role of Probiotics in Preterm and Low Birth Weight Infants: A Randomised Controlled Trial

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Article Info.

Article type:
Research Article

Received: 27 Jan. 2025
Revised: 14 Aug. 2025
Accepted: 13 Oct. 2025
Published: 8 Dec. 2025

Keywords:
Bifidobacterium Breve,
Probiotics,
Sepsis

ABSTRACT

Background and Objective: Bifidobacteria are part of the natural intestinal flora of neonates, but their role as a single probiotic in reducing sepsis and necrotizing enterocolitis (NEC) is still under investigation. The aim of this study was to determine the effect of Bifidobacterium breve M-16 V on morbidity and mortality in preterm and low-birth-weight neonates.

Methods: A randomized controlled trial was conducted >18 months on infants with gestational age between 28 and 36 weeks and 6 days or birth weight between 1000 and 2499 grams in whom enteral feeding was initiated within the first week. They were randomly divided to receive the probiotic or placebo. The primary endpoint was the incidence of neonatal sepsis or mortality. Secondary endpoints included the occurrence of NEC, jaundice, length of hospital stay, and weight gain.

Findings: Among the 63 infants analyzed as the test group and 61 as the control group, no statistically significant differences were found between the groups in the incidence of neonatal sepsis (11.1% versus 14.7%; RR 0.75; [95% CI 0.3 to 1.8], p =0.54), NEC, jaundice, or length of hospital stay with probiotic supplementation. The mean weight gain was 982 ± 336 grams in the probiotic group, which was significantly higher than 848 ± 340 grams in the control group (p=0.02).

Conclusion: Supplementation with Bifidobacterium breve M-16 V indicated no significant effect on most parameters studied. However, infants supplemented with Bifidobacterium breve M-16 V showed a significantly higher weight gain after 6 weeks.

Cite this Article: Padar C, Rajan A, Oommen R. Role of Probiotics in Preterm and Low Birth Weight Infants: A Randomised Controlled Trial. Caspian J Pediatrs June 2025; 11: e13.

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Introduction

Preterm birth affects an estimated 15 million infants globally each year, with India contributing to one of the largest shares worldwide. Complications arising from prematurity account for close to one million childhood deaths annually [1]. Premature neonates face several problems due to immaturity of the organ systems. Sepsis, necrotizing enterocolitis (NEC), feed intolerance, anemia of prematurity, and neonatal jaundice are among the major early problems of a preterm baby [2].

In contrast to term newborns, preterm infants have an altered intestinal microbial colonization, increasing their susceptibility to infections [3]. It has been demonstrated that preterm infants have fewer protective and more pathogenic bacterial strains in their intestinal microbiota as compared to term infants [4]. This can result in intestinal dysbiosis, which can predispose them to NEC. Probiotics promote intestinal health by modulating dysbiosis, which improves nutrient metabolism and leads to the production of protective metabolites [5]. There is evidence that *Bifidobacterium breve* M-16V may reduce the risk of complications associated with prematurity, like NEC or late-onset sepsis [6]. Bifidus flora rarely establishes in early life and may be delayed, especially in very low birth weight (VLBW) infants [7]. By stimulating the colonization of bifidobacterial species, it may enhance overall intestinal health and thereby prevent the colonization of pathogenic bacteria [6]. Although many studies have been conducted, the heterogeneity in strains used, dosing protocols, and differences in population limit the generalizability of the findings. There still remains a need for strain-specific evidence in the context of neonatal care in South India.

By reducing the risk of sepsis and NEC through various mechanisms, probiotics strengthen intestinal barrier function, alleviate hypoxemic injury, suppress pathogenic bacteria, and overall regulate host immunity [8]. Consequently, intervention with probiotics is receiving significant attention as a non-invasive method of improving the infant's gut microbiome. Despite the obvious role of probiotics in the prevention of morbidity in preterm infants, there are no standard guidelines formulated, and there is a reluctance to use them. Further studies have been recommended to fill gaps in knowledge about probiotics, which might bridge the gap [9, 10]. The importance and uniqueness of this study lie in deducing the effect of a specific probiotic strain in an Indian neonatal intensive care unit (NICU), where its relevance has not been explored. This, in turn, may bridge the gap between global research and clinical applicability. The aim of this study was to evaluate the role of probiotics in reducing the morbidity and mortality of preterm and low birth weight (LBW) infants.

Methods

Study design

A single-center single-blinded randomized controlled trial was conducted at the A.J. Institute of Medical Sciences, Mangalore, Dakshina Kannada, India, over 18 months (November 2018–May 2020) comparing two groups of preterm infants receiving either supplemental probiotics or placebo.

Ethical Clearance

Approval for the study was obtained from the Institutional Ethics Committee vide letter number AJEC/REV/201/2018 dated 2/11/2018. Written informed consent was taken from the patient's parents/ guardian before enrolment into the study.

Source of data

All preterm and LBW infants hospitalized at NICU during the study period were eligible to participate in the present study. Inclusion criteria: (a) preterm infants a with gestational age between 28 weeks and 36 weeks and 6 days or (b) low-birth-weight babies with a birth weight between 1000 grams and 2499 grams in whom enteral feeding could be initiated within the first week. Infants with contraindications to enteral feeding (e.g., suspected or diagnosed NEC, severe gastrointestinal malformations, or severe medical or surgical conditions) were excluded from the study. Furthermore, neonates of parents who withdrew their consent to participate in the study before the study was completed were excluded.

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Group Allocation and Randomisation

Participants were stratified by gestational age: early preterm birth: 28–33+6 weeks, and late preterm birth: 34–36+6 weeks and birth weight: VLBW: 1000–1499 g, and LBW: 1500–2499 g. Infants were randomly assigned to the treatment group (Group A) or control group (Group B) pre-established randomization list that was stratified according to gestational age with a block size of two blocks. Patients were allocated to one of the two treatment groups using sequentially numbered, sealed, opaque envelopes. There were prepared by a researcher who was not involved in recruitment or outcome assessment.

Intervention

The preterm infants were supplemented either with a probiotic or a placebo. The probiotic used in the present study was *Bifidobacterium breve* M16-V. The formulation used was granules available as RESCUNATE™ with each 0.5 g sachet containing 1 x 10^9 CFU of *Bifidobacterium breve* M16-V manufactured by Allianz Biosciences Pvt Ltd, India. The contents of the sachet were mixed with 1 ml of expressed breast milk and mixed bedside by the nurses immediately before administration. It was given once a day just before the first feed in the morning. The ones who didn't receive the probiotic were set to receive 1 ml of expressed breast milk only, without the supplementation of probiotics.

Feeding practices

Feeding practices were standardized in the NICU. Enteral feeding was initiated with expressed breast milk (EBM) as soon as clinically feasible, usually within the first 24–48 hours of life. EBM was initially started at 1ml every fourth hour via an orogastric tube for infants unable to suck effectively and then gradually advanced to 20-30ml/kg/day as per their tolerance. - If the mother did not produce sufficient milk, a preterm formula was provided, either in addition to the mother's milk or alone.

When the infants were discharged from the hospital, RESCUNATE™ was provided to families, which was to be continued for a period of 2 weeks or till a gestational age of 37 weeks, whichever is later.

Weighing procedures

Infant weights were measured using a calibrated digital weighing scale (sensitivity: 5 g; brand: Phoenix Baby Weighing Scale, India). Babies were weighed without diapers and with minimal clothing. Weight gain was calculated as the difference between birth weight and weight at the 6-week follow-up visit.

Phototherapy and jaundice assessment

All infants were monitored for jaundice clinically and with serum bilirubin estimation as required. Phototherapy was initiated using standard LED phototherapy units according to the American Academy of Pediatrics guidelines, and duration was recorded in hours. The type of jaundice (physiological, breast milk, or haemolytic) was documented for each infant.

Antibiotic therapy

Antibiotic regimens followed the NICU protocol. Empirical therapy for suspected sepsis typically consisted of ampicillin and gentamicin; in cases of clinical deterioration or confirmed Gram-negative sepsis, escalation to piperacillin–tazobactam or cefotaxime was undertaken as per culture sensitivity reports.

Outcomes

The first primary outcome was the incidence of at least one episode of sepsis during the hospital stay, while the second one was mortality. Sepsis was diagnosed to be present if the septic screen was positive and documented as culture-negative or culture-positive sepsis after obtaining the culture report. A septic screen was said to be positive if the baby had any two of the five parameters as mentioned [2]:

a) Total leukocyte count < 5000/mm³
b) Absolute neutrophil count below age-specific reference (Manroe chart for term, Mouzinho chart for VLBW)
c) Immature-to-total neutrophil ratio > 0.2
d) Micro-ESR > 15 mm in the first hour
e) C-reactive protein > 1 mg/dl

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Secondary outcomes assessed were (a) the incidence of NEC which was diagnosed if the neonate had abdominal distension, occult blood in stools and unstable vital parameters like apnea, bradycardia or tachycardia and temperature instability with or without abnormal radiographic findings and was classified according to the Bell's staging; (b) occurrence and severity of jaundice, and the duration of phototherapy required; (c) duration of hospital stay starting from the day of NICU admission up to discharge from the hospital (d) weight gain which was documented at a follow up visit at six weeks and the gain in weight since birth was calculated.

Sample size

A minimum of 42 infants per group was calculated to achieve 90% power ($\alpha = 0.05$, two-sided test, continuity correction) to detect a 34% reduction in mortality, allowing for a 10% dropout rate. An additional 20 infants were recruited per arm to increase the representation of VLBW infants.

Statistical analysis

An overall comparative analysis was made of the outcome between the treatment and the control group. The outcome was further compared between subgroups under treatment and control groups based on gestational age (early preterm was considered from 28 weeks to 33 weeks 6 days and late preterm was considered from 34 weeks to 36 weeks 6 days) and birth weight (VLBW between 1000grams and 1499 grams and LBW between 1500 grams and 2499 grams)

Statistical analysis was made using the software R-Studio v1.3.2. Fisher's exact test for count data was used to compare the occurrence of sepsis, NEC, jaundice, and death, and the ANOVA test was used to compare weight gain and duration of phototherapy between the subgroups. A value of $p< 0.05$ was considered significant.

Results

During the study period of 18 months, a total of 261 premature and LBW babies were examined for their suitability. Of these, 132 babies who met the inclusion criteria were included in the study after informed consent. The participants were randomly divided into a treatment group (Group A) and a control group (Group B). The distribution of cases is depicted in the CONSORT diagram (Figure 1).

The baseline characteristics of the study population are illustrated in Table 1. 33 term babies whose weight fell into the LBW category were also included. However, the mean birth weight was similar in both groups, 2179 grams in group A and 2072 grams in group B. A large majority of babies in both groups fell into the LBW category (between 1500 and 2499 grams) in both groups.

Among the study population, 36% of the babies required admission to NICU predominantly due to respiratory distress secondary to hyaline membrane disease and/or patent ductus arteriosus, causing pulmonary flooding and pulmonary artery hypertension. Other causes were sepsis, preterm care and requirement of phototherapy.

Primary outcomes depicted in Table 2 showed there was no significant difference between the groups in occurrence of at least one episode of neonatal sepsis ((11.1% in Group A vs. 14.75% in Group B; relative risk [RR] 0.76, 95% confidence interval [CI] 0.3–1.9, p=0.57) with the supplementation of probiotic. This remained unchanged when the incidence of early versus late onset sepsis was studied (p = 0.52, 0.96). Only one culture positive early onset sepsis was seen (0.8 %), which grew *Acinetobacter baumannii* and it belonged to the group receiving probiotics. Higher culture positivity (2.4%) was noted for late onset sepsis, two *Klebsiella pneumoniae* in the control group and one in the probiotic group, which grew *Citerobacter koseri*. Mortality before discharge occurred in one infant in each group. The baby in the test group died on the 15th day of life, while the other died on day 10 of life. Both deaths were attributed to neonatal sepsis. Only one baby, who was an early preterm, developed NEC in the control group, while none in the test group developed NEC and hence was not considered to be significant (p=0.491).

Secondary outcomes studied are listed in Table 3 and showed 46% of the babies in the test group and 60% of the babies in the control group developed jaundice with comparable mean serum bilirubin values (14.51 ± 6.3 versus 15.37 ± 4.6 mg/dl, p =

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0.318) as well as duration of phototherapy (p = 0.212). On average, the duration of hospital stay was similar in both groups, with a mean of 10.1 ± 6.2 days in the test group and 10.8 ± 6.5 days in the control group. The mean weight gain was noted as the increase in weight from birth at six weeks of life as 982 ± 336 grams in the probiotic group and 848 ± 340 grams in the control group, which was significantly higher in the probiotic group with a p value of 0.02. The weight gain did not vary depending on the gestational age; however, the weight gain was significantly higher in the LBW group supplemented with probiotics.

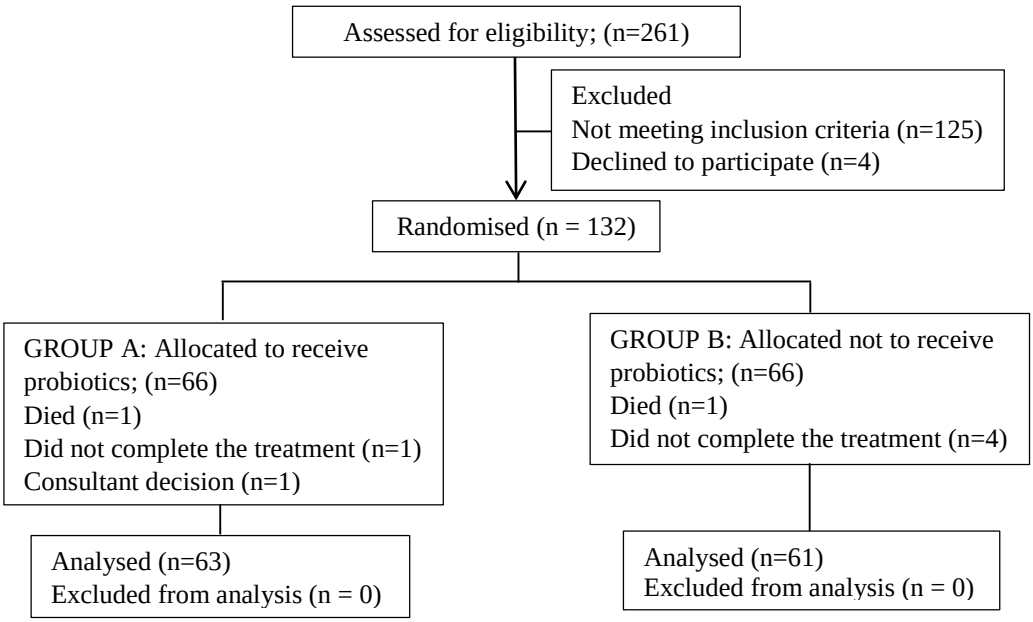

Figure 1. CONSORT diagram showing patient enrolment

Table 1. Comparison between baseline characteristics of the two groups.

Baseline parameters	Category	Group A, (N = 63)	Group B, (N = 61)	P-value
Gender	Female	32 (50.8)	36 (59)	0.373
	Male	31 (49.2)	25 (41)	
Gestational age in weeks, n (%)	28 – 34	9 (14.2)	16 (26.2)	0.09
	34 - 36	36 (57.1)	30 (49.2)	0.38
	≥ 37	18 (28.7)	15 (24.6)	0.6
Gestational age in weeks, mean (SD)	-	35.57 (2.2)	35.02 (2.24)	0.163
Birth weight in grams, n (%)	1000 – 1499	2 (3.2)	3 (4.9)	0.66
	1500 – 2499	57 (90.4)	54 (88.5)	0.73
	≥ 2500	4 (6.4)	4 (6.6)	0.96
Birth weight in grams, mean, (SD)	-	2179.3 (325.7)	2072.6 (376.6)	0.094
Use of antenatal steroid, n (%)	Yes	34 (54)	39 (64)	0.26
	No	29 (46)	22 (36)	
Presence of risk factors for sepsis	Yes	6 (9.5)	10 (16.4)	0.262
	No	57 (90.5)	51 (83.6)	
APGAR score, mean (SD)	-	7.17 (1.2)	7.29(1.27)	0.585
Type of feed, n (%)	Breast milk only	52 (82.5)	55 (90.1)	0.22
	Breast milk and formula feed	11 (17.4)	6 (9.8)	

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Table 2. Comparison of primary outcomes and subgroup analysis between Group A and B

Outcome variables N (%)	Category	Group A (N = 63)	Group B (N = 61)	Adjusted Relative Risk (95% Confidence Interval)	P_value
Neonatal sepsis	-	7 (11.1)	9 (14.75)	0.76 (0.3 – 1.9)	0.57
Early onset sepsis	Culture positive	1 (1.5)	0 (0)	4.2 (0.21 – 88.3)	0.347
	Culture negative	3 (4.8)	6(9.8)		
	Overall	4 (6.3)	6 (9.8)	0.64 (0.19 – 2.14)	0.526
	Early preterm	3/9 (33.3)	1/16 (6.25)	5.33 (0.647 – 44)	0.116
	Late preterm	1/36 (2.7)	3/30 (10)	0.28 (0.03 – 2.53)	0.322
	Low birth weight	2/57 (3.5)	5/54 (9.2)	0.38 (0.07 – 1.87)	0.262
	VLBW	1/2 (50)	1/3 (33.3)	2.00 (0.22 – 17.8)	0.535
Late onset sepsis	Culture positive	1 (1.5)	2 (3.3)	0.5 (0.08 – 2.99)	0.447
	Culture negative	2 (3.1)	1 (1.6)		
	Overall	3 (4.8)	3 (4.9)	0.97 (0.20-4.62)	0.968
	Early preterm	2/9 (22.2)	3/16 (18.75)	1.18(0.24 – 5.82)	0.83
	Late preterm	1/36 (2.77)	0/30 (0)	0.12 (0.005 – 3)	0.20
	Low birth weight	3/57 (5.2)	2/54 (3.7)	1.42 (0.24 – 8.17)	0.69
	VLBW	0/2 (0)	1/3 (33.3)	0.55 (0.03 – 9.7)	0.68

Table 3. Comparison between secondary outcomes between the two groups

Outcome variables	Category	Group A (N=63)	Group B (N=61)	P value
NEC	-	0 (0)	1 (1.6)	0.491
Jaundice; N (%)	-	29 (46)	37 (60.6)	0.572
Mean S. Bilirubin level in mg/dl, mean, (SD)	-	14.51 (6.3)	15.37 (4.6)	0.318
Duration of phototherapy in hours, mean, (SD)	-	31.75 (14.4)	35.04 (12.7)	0.212
Duration of hospital stay in days, mean, (SD)	Early preterm	18.2 (8.01)	16.4 (7.3)	0.59
	Late preterm	17 (4.74)	11 (4.34)	0.457
	Low birth weight	9.98 (6.2)	10.25(5.1)	0.478
	VLBW	15 (0.7)	26.67 (10)	0.217
	Overall	10.11(6.2)	10.87 (6.5)	0.465
Weight gain in grams, mean (SD)	Early preterm	762.78 (210.1)	695.93(320.4)	0.64
	Late preterm	977.46 (345)	899 (346.7)	0.353
	Low birth weight	989.91 (340)	858.09 (321)	0.03
	VLBW	695 (282)	338.33 (324)	0.213
	Overall	982.68 (336.5)	848.07 (340.4)	0.02

Discussion

Bifidobacterium breve M-16V is a commonly used probiotic strain in infants for modulation of gut microbiota, thereby playing a role in the prevention of neonatal sepsis and NEC [11].

In our cohort, the relatively high use of antenatal steroids in both groups may have contributed to the overall low rates of NEC (0.8%) and sepsis (11–15%), potentially masking any additive protective effect of probiotic supplementation. Similarly, the prevalence of recognized risk factors for sepsis, such as prolonged rupture of membranes, maternal intrapartum fever, or perinatal asphyxia, was relatively low in both groups (9.5% in Group A and 16.4% in Group B). This low baseline risk profile could also explain the absence of a statistically significant difference in sepsis incidence between the probiotic and control groups. This study did not demonstrate a significant effect of *Bifidobacterium breve* M-16V supplementation on the incidence of neonatal sepsis or mortality in preterm and low-birth-weight infants. This lack of effect was consistent for both culture-confirmed sepsis and clinically diagnosed early- and late-onset sepsis. The overall incidence of early onset sepsis was only around 8% (10 cases), of which 40% were in the test group. Late-onset sepsis was recorded in 4.7% of infants in the probiotic group compared with 4.9% in the control group, with statistical analysis showing no significant difference. Subgroup analysis also did not

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reveal any statistically significant differences in the incidence of early onset or late onset sepsis depending on the gestation or birth weight. Only one case of NEC was noted in the control group and none in the test group, and hence, not statistically significant. Studies have shown that oral administration of *B. breve* M-16V leads to its colonization in the infant gut for at least several weeks after administration and potentially contributes to improved gut microbiota establishment [12]. Patole et al. [6] in a large randomised controlled trial involving 1755 neonates conducted in the year 2016, supplemented preterms with B*ifidobacterium breve* M-16V and showed a decrease in NEC stage 2 and 3 as well as all-cause mortality in preterm babies <34 weeks. Subsequent randomized control trials (RCT)s and meta-analyses (fixed effects model) which used bifidobacterium breve or bifidobacterium species did not show significant benefits on higher stages of NEC, late-onset sepsis, mortality or time to achieve full enteral feeds, [8, 13, 14] but recommended the need for further studies to formulate guidelines for the same [15, 16]. A 2020 Cochrane review of 56 RCTs concluded that evidence for the effect of probiotics on NEC and related morbidity and mortality in very preterm or very low-birth-weight infants remains of low to moderate certainty, with even less certainty for extremely preterm or extremely low-birth-weight populations [17].

Incidence of jaundice was studied as it is hypothesised that the dearth of natural probiotics in the neonates increases the enterohepatic circulation and results in hyperbilirubinemia [18]. Incidence of jaundice was similar in both groups (p=0.5). Relatively higher incidence (46%) of jaundice was noted in the late preterms that were given probiotics in comparison with the control group (37%); however, it didn't garner any statistical significance. To our knowledge, no prior studies have examined the effect of *B. breve* M-16V on neonatal jaundice. One report on prophylactic *Bacillus clausii* given for three days showed a reduction in both the requirement for and duration of phototherapy [18].

The overall average duration of hospital stay in the test group was 10.1 days and in the control group was 10.8 days. This short duration may be attributed to the majority of the study population included being late preterm LBW babies. It may appear as though the VLBW babies in the control group stayed longer and had a mean duration of stay as high as 26.6 ± 10 days compared to the test group which had a mean stay of only 15 ± 0.7 days, however since the number of LBW babies in each group were only two and three in the test and control group respectively, the p value was not significant.

Mean weight gain calculated from birth to 6 weeks was one of the significant findings in the probiotic group, where a higher mean of 982.68 ± 336.5 grams versus the control group, which had a mean of 848.07 ± 340.4 grams (p=0.02) was found. It was further noted that there was a significantly higher weight gain in the children in the LBW category, although this could be due to the VLBW category having a very small number of babies. Kitajima et al. [7] had studied 66 VLBW neonates after supplementing them with probiotics and noted their mean weight gain at 6 weeks to be 600 grams in the test group against 350 grams in the control group (p = <0.001), which is consistent with our findings. Sun et al. [19] likewise found that probiotics in this population could reduce the risk of NEC and sepsis, lower mortality, shorten hospitalization, and promote weight gain. In contrast, the present study did not find significant differences in weight gain within the very-low-birth-weight category.

Strengths

Since this study, was a randomized, double-blind design, selection and observer error were minimized. By assessing a single probiotic strain, *Bifidobacterium breve* M-16V, the study addresses the variability seen in previous probiotic studies combining multiple strains or formulations. Most importantly, this appears to be the first randomized controlled trial in a neonatal unit in South India evaluating this specific probiotic strain, thereby contributing region-specific findings to the global literature.

Limitations

The present study was limited by a small sample size, and the majority of the sample fell in the LBW or late preterm category. Fewer cases were obtained

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from the VLBW and early preterm groups, as many cases in this category were excluded due to hemodynamic instability and the requirement of mechanical ventilation. The quality of patient compliance and adherence to the treatment could be variable in those babies who were sent home on the probiotic. The benefit of the probiotic may be limited by the strain of probiotic used, dose, or timing of initiation; however, current literature suggests no standard guidelines for the choice of probiotic, what dosage should be used, when they should be started, or the duration of administration [20]. Hence, larger, high-quality trials are still needed to produce robust and widely applicable evidence [17].

Conclusion

Supplementation of the probiotic Bifidobacterium breve M-16 V as a single probiotic did not reveal any significant effect on preterms or LBW in terms of prevention of the occurrence of sepsis, NEC, or jaundice; nor did it decrease the length of hospital stay in these babies. However, the babies fed with Bifidobacterium breve M-16 V showed a significantly higher weight gain after 6 weeks. Future studies with a larger sample size and in multiple centers are required to validate the results of the current study.

Acknowledgements

None.

Ethical approval

The research was reviewed and approved by A.J. Ethics Committee, A. J. Institute of Medical Sciences, Mangalore, Dakshina Kannada, Karnataka [DCGI Reg.No.ECR/348/Inst/KA/2013/RR-16] via letter number AJEC/REV/201/2018 dated 2/11/2018. Written informed consent was taken from the patient's parents/ guardian before enrolment in the study.

Funding

There was no financial support for this research.

Conflict of interest

There is no conflict of interest.

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