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A randomized control study on the effect of probiotics on feed tolerance in very low birth weight neonates

Senthil Kumaran G[1], Chairman Muthu Prem Kumar L[2], Jeyarama Krishnan R[3]

[1]Associate Professor, [2]Assistant Professor, [3]Postgraduate Resident, Department of Pediatrics, Government Thoothukudi Medical College, Thoothukudi, Tamil Nadu, India

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ABSTRACT

Background: Probiotics are live microbial supplements that increase feed tolerance, colonize the gut of these newborns with beneficial flora, and promote growth in these infants. **Aims and Objectives:** This study was planned to compare the role of probiotics in low birth weight (LBW) infants in the time taken to reach full feeds, episodes of feed intolerance, weight gain, duration of hospital stay, incidence of necrotizing enterocolitis (NEC) stage 2 or more, and morbidity and mortality during hospital stay. **Materials and Methods:** This interventional two-arm blinded randomized control study was conducted in Thoothukudi Government Medical College Hospital, Thoothukudi, from November 2019 to October 2020. The selected sample of babies was randomly divided into two groups, the probiotic and the no-probiotic group. Bifidobacterium breve M-16 was administered to infants in the probiotic group at a dose of 0.5 g/day once a day in breast milk. Only breast milk was used to feed babies in the no-probiotic group. **Results:** The time to reach full enteral feed was shorter in the probiotic group (9.21 ± 1.74 days) than in the no-probiotic group (12.43 ± 3.74 days). Better feed tolerance (12%) was seen in the probiotic group than in the no-probiotic (44%) group. A low incidence of sepsis (12%) was seen in the probiotic group than in the non-probiotic group (40%). A lesser duration of hospital stay (10.42 ± 1.77 days) was seen in the probiotic group than in the probiotic group (13.78 ± 4.18 days). **Conclusion:** Very LBW neonates who received probiotic supplements along with their feeds have shorter times to reach full feeds, greater feed tolerance, lower rates of sepsis, and shorter mean hospital stays.

Key words: Probiotic; Feed tolerance; Sepsis; Hospital stays; Feeding; Low birth weight

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INTRODUCTION

In India, the prevalence of low birth weight (LBW) decreased during the past 10 years from 20.4% to 16.4%. As neonates' survival rates have increased due to cutting-edge obstetric and neonatal care 6, the emphasis is now on enteral nutrition and encouraging growth. Due to poor oral feed tolerability, necrotizing enterocolitis (NEC), nosocomial sepsis, and extended hospital stays take longer to reach full enteral feedings. According to research, this is one of the main causes of a worse mental outcome in these infants.[1-4]

NEC is a significant cause of morbidity and mortality in preterm infants in neonatal intensive care units (NICU) worldwide. The incidence of NEC is 1–3 cases/1000 live births. NEC makes up about 1–8% of admissions to NICUs overall. In India, the incidence for newborns under 32 weeks is 5.2%. In addition to its physical component, the intestinal barrier has a microbiological component.[5] The gut microbiota creates the gut barrier's innermost layer. The healthy gut microbiota competes with infections for resources such as space and energy to digest the chemicals and preserve the integrity of the mucosa. Symbiotic interactions occur between it and the human body. The maintenance of epithelium integrity and production of vitamins and micronutrients are the other benefits of gut microbiota.[6-8]

Address for Correspondence:
Dr. Jeyarama Krishnan R, Postgraduate Resident, Department of Pediatrics, Government Thoothukudi Medical College, Thoothukudi, Tamil Nadu, India. **Mobile:** +91-8870717416. **E-mail:** jramlegend@gmail.com

Recent studies have shown the usefulness of probiotics in reducing the time required to reach complete enteral feeds, improving feed tolerance, and reducing the occurrence of NEC and late-onset sepsis. A systematic evaluation of 25 randomized controlled studies revealed improved weight gain and growth velocity, a shorter duration from orogastric to breastfeeding, and higher postprandial mesenteric flow.[9-12]

As the standard of care for LBW neonates, the use of probiotics is not yet recommended; irrespective of these reviews, most of the studies reviewed have observed the effect of probiotics on reducing NEC and mortality. There are very few studies on the role of probiotics in achieving full enteral feeds, weight gain, and episodes of feed intolerance as the primary outcome.

Aims and objectives

This study aimed to compare the role of probiotics in LBW infants in time taken to reach full feeds, episodes of feed intolerance, weight gain, duration of hospital stay, incidence of NEC stage 2 or more, and morbidity and mortality during hospital stay.

MATERIALS AND METHODS

This interventional two-arm blinded randomized control study was conducted in the Department of Paediatrics, Thoothukudi Government Medical College Hospital, Thoothukudi, from November 2019 to October 2020. The study population included all the LBW neonates admitted in the NICU (inborn as well as outborn) in the NICU who met the inclusion and exclusion criteria of the study.

Inclusion criteria

All neonates with a birth weight of 750 g–1499 g admitted to the NICU where enteral feeds were started were eligible for the study.

Exclusion criteria

Gastrointestinal anomalies, major congenital malformation, very LBW (VLBW)babies on parenteral antibiotics, sick babies on mechanical ventilation, and those not started on enteral feeds by day 14 of life were excluded from the study.

Ethical consideration

Informed consent was sought from the parents before enrolment. The ethical committee of Thoothukudi Government Medical College Hospital, Thoothukudi, approved this study.

Fifty LBW neonates who were randomly allocated as group A (probiotics group) (n=25)-VLBW neonates on orogastric feeds who received probiotics and their feeds belong to this group. Group B (no probiotics group) (n=25) VLBW neonates on orogastric feeds received no probiotics; their feeds belong to this group.

Methodology

Blinding

The resident physicians were kept unaware of the group allocations. The feeding, whether containing probiotics or not, was meticulously prepared by a single staff nurse who was not directly engaged in the care of the study infants. This preparation took place in an area separate from the patient care zone to maintain blinding. Subsequently, the prepared feed was transferred to the resident or staff nurse on duty.

Randomization

A researcher who had no direct involvement in the study selected the subjects. The allocation of subjects into both study arms was achieved using random numbers generated by a computer.

Feeding protocol

According to the unit protocol, feeding was started, advanced, interrupted, and restarted throughout the study. The protocol was included with each research case file to ensure compliance. Hemodynamically stable infants received breast milk or formula (non-probiotic) to start trophic feeds, 10–20 mL/kg/day at two hourly intervals. 20 mL/kg/day more food was added to the diet. Babies receiving gavage feeds had their abdomens measured. Every 2 h, feeds were provided. Any indications of feed intolerance, suspected NEC, hemodynamic instability, or sepsis were grounds for withholding feeding. Feed intolerance was defined as the presence of any of the following three features: abdominal distension ≥2 cm from the previous measurement, blood-stained or bilious vomiting, and vomiting ≥2 episodes in the past 6 h.

Neonates were investigated for these signs. Feeding was restarted after the indicators listed above were all resolved. Until 110 mL/kg/day (75% of full feeds) of feeds were reached, I/V fluids were continued. Full feeding was tolerated at 150 mL/kg/day. Oral feeding was initiated in infants older than 30–32 weeks who exhibited a healthy sucking reflex and other physical characteristics. A calibrated digital weighing scale with a sensitivity of 5 g was used to assess the weight each day. Bell's staging was updated and used to define and stage NEC. The neonates were monitored for further morbidities, such as sepsis, patent ductus arteriosus, and intraventricular hemorrhage and treated accordingly. Neonates who maintain a normal body temperature in an open crib and have stable hemodynamics were discharged following the unit's policy.

Administration of probiotics

Bifidobacterium breve M-16V probiotic formulation was given to the probiotic group as 0.5 g powdered sachets. Within 24 h of starting the feeding, the probiotic was given once a day at a dose of 1 billion colony forming unit. It was offered in powder form. In breast milk or formula milk, it was dissolved. Every study infant received it from 10 a.m. to 2 p.m. during the morning shift. Up until discharge, the probiotic supplementation was continued. Probiotic was given after 2 h of antibiotic administration. Probiotics were discontinued whenever feeding was interrupted for any reason. The only milk given to the probiotic-free group was breast milk or formula.

Statistical analysis

The recorded data were compiled and entered into a computer spreadsheet (Microsoft Excel 2010). Then, the recorded data are exported to the data editor page of SPSS version 20 (SPSS Inc., Chicago, Illinois, USA). Computation of percentages, means, and standard deviations were the descriptive statistics. Student t-test and Chi-square test were the statistical tests applied for the analysis. For all tests, the P-value was set at ≤0.05.

RESULTS

Among 50 neonates, 56% were female and 44% were male. There is no statistically significant difference in gender between groups P=0.569.

94% of neonates are enrolled on day 1, and 6% on day 2. There is no statistically significant difference in age at enrollment between groups P=0.552 (Table 1).

Neonates born preterm were categorized according to gestational age. Very preterm neonates were the maximum in both groups. There is no statistically significant difference between gestational age and groups P=0.311 (Figure 1).

The mean Appearance, pulse, grimace, activity, and respiration (APGAR) 1 min in the probiotic group is 6.36, and in the no-probiotic group is 6.48. There was no statistically significant difference in APGAR 1 min between groups P=0.673. The mean APGAR 5 min in the probiotic group is 8.36, and in the noprobiotic group, it is 8.44. There is no statistically significant difference in APGAR 5 min between groups P=0.646 (Table 2).

Anemia was noted in 28% of probiotic and no-probiotic groups, respectively. However, there is no statistically significant difference in anemia between groups P=1.000. Pre-eclampsia was noted in 4% and 12% of probiotic and no-probiotic groups, respectively. However, there was no statistically significant difference in pre-eclampsia between groups P=0.297. Pregnancy-induced hypertension (PIH) was noted in 20% and 28% of probiotic and no-probiotic groups, respectively. However, there is no statistically significant difference in PIH between groups P=0.508. Leaking per vaginum was noted in 20% and 32% of probiotic and no-probiotic groups, respectively. However, there is no statistically significant difference in leaking per vaginum between groups P=0.333 (Table 3).

The mean time to reach the full feed-in probiotic group is 9.21 days, and the no-probiotic group is 12.43 days. There was a statistically significant difference in time to reach full feed between groups P<0.0001 (Figure 2).

The mean birth weight in the probiotic group was 1188.6 g, and in the no-probiotic group was 1209.0 g. There was no

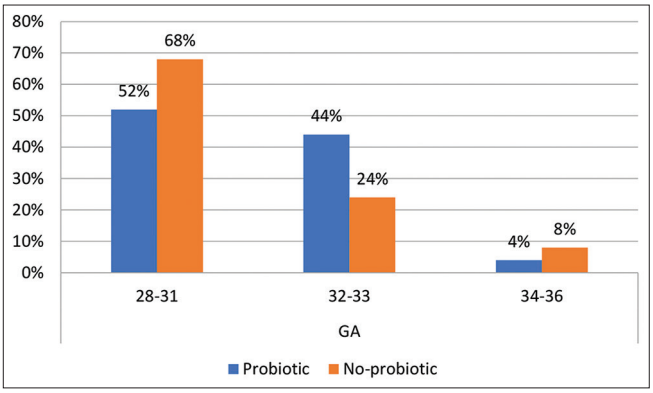

Figure 1: Distribution of gestational age between groups

Table 1: Sex distribution and age at enrollment between groups

Group	Sex		Sex ratio (M: F)	P-value
	FCH	MCH		
Probiotic	13 (52%)	12 (48%)	1.08:1	0.569
No- probiotic	15 (60%)	10 (40%)	1.5:1	
Group	**Age at enrollment**		**Age at enrolment (days)**	**P-value**
	1	2		
Probiotic	23 (92%)	2 (8%)	1.00±0.00	0.552
No- probiotic	24 (96%)	1 (4%)	1.023±0.17	

MCH: Mean corpuscular hemoglobin, FCH: Family and child health concentration

Table 2: Mean APGAR score at 1 and 5 min between groups

Group	Mean±SD	P-value
APGAR 1 min		
Probiotic	6.36±0.99	0.673
No-probiotic	6.48±1.00	
APGAR 5 min		
Probiotic	8.36±0.57	0.646
No-probiotic	8.44±0.65	

SD: Standard deviation, APGAR: Appearance, pulse, grimace, activity and respiration

Table 3: Maternal risk factors between groups

Maternal risk factors	Group		P-value
	Probiotic (%)	No probiotic (%)	
Anemia	7 (28)	7 (28)	1
Pre-eclampsia	1 (4)	3 (12)	0.297
PIH	5 (20)	7 (28)	0.508
LPV	5 (20)	8 (32)	0.333

PIH: Pregnancy induced hypertension, LPV: Low plasma volume

statistically significant difference in birth weight between groups P=0.686. The mean discharge weight in the probiotic group was 1192.20 g, and in the no-probiotic group was 1197.0 g. There was no statistically significant difference in discharge weight between groups P=0.921 (Figure 3).

28% of neonates had regurgitation of feed. There was a statistically significant difference in regurgitation of feed between groups P=0.012 (Figure 4).

Mean episodes of probiotic feed intolerance were 0.20, and no probiotics were 0.54. There was a statistically significant difference in an episode of feed intolerance between groups P=0.040 (Figure 5).

In 50 neonates, 26% had sepsis; 12% had sepsis in the probiotic group. In the no-probiotic group, 40% had sepsis. There is a statistically significant difference in sepsis between groups P=0.024.

In the probiotic group, 12% of neonates had NEC stage 2; in the no-probiotic group, 20% had NEC stage 2. No statistically significant difference in NEC stage 2 between groups P=0.701 (Table 4).

In 50 neonates, 4% of neonates had the requirement of ventilation. No statistically significant difference in the ventilation requirement between groups P=1.000 (Figure 6).

In 50 neonates, 30% had undergone antibiotic treatment; 12% underwent antibiotic treatment in the probiotic group, whereas 48% underwent antibiotic treatment in the no-probiotic group. There is a statistically significant difference

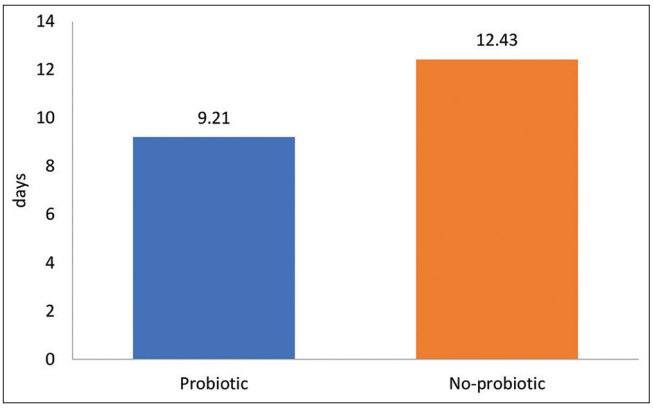

Figure 2: Time to reach full feed comparison between groups

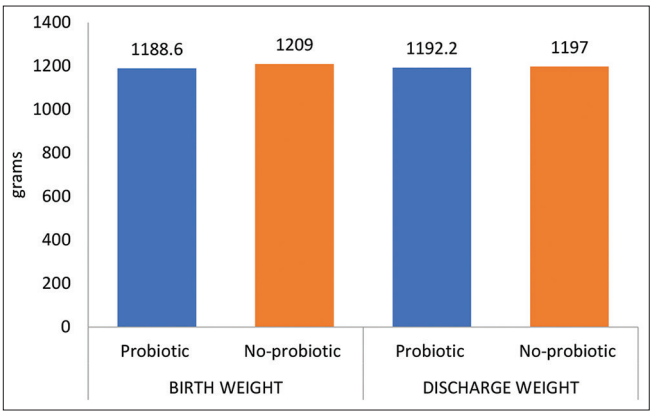

Figure 3: Mean birth weight and discharge weight comparison between groups

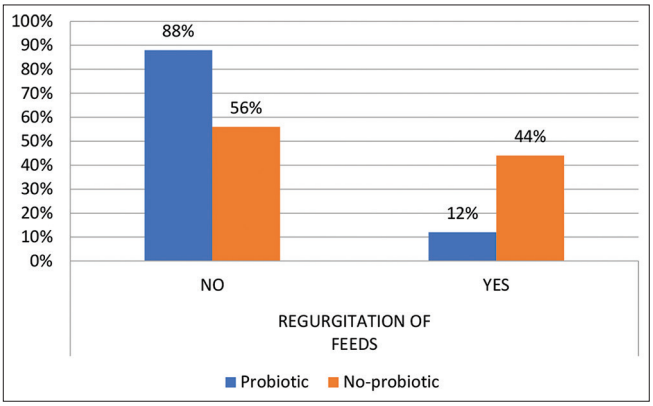

Figure 4: Regurgitation of feeds between groups

in antibiotic treatment between groups P=0.005 (Table 4). Mortality incidence in this study is 6%. In the probiotic group, the mortality rate is 4%, whereas in the no-probiotic group, the mortality rate is 8%. There is no statistically significant difference in mortality between groups P=0.552 (Figure 7).

The mean duration of hospital stay in the probiotic group is 10.42 days, and in the no-probiotic group is 13.78 days. There is a statistically significant difference in the duration of hospital stay P=0.001 (Figure 8).

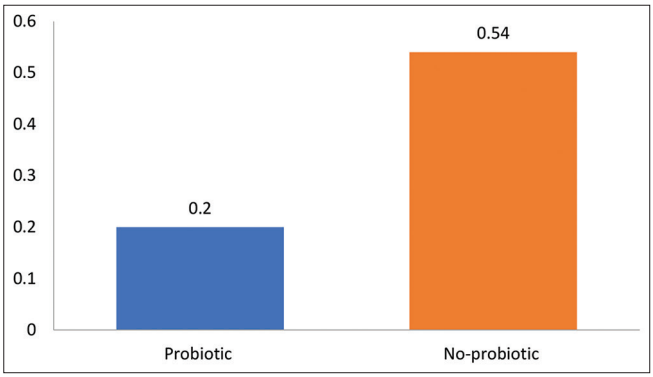

Figure 5: Episode of feed intolerance between groups

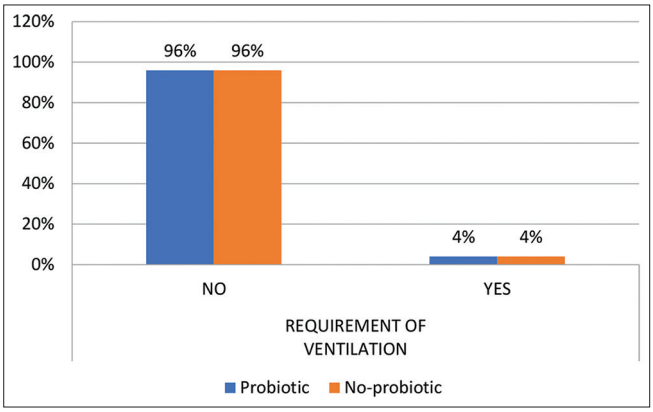

Figure 6: Requirement of ventilation between groups

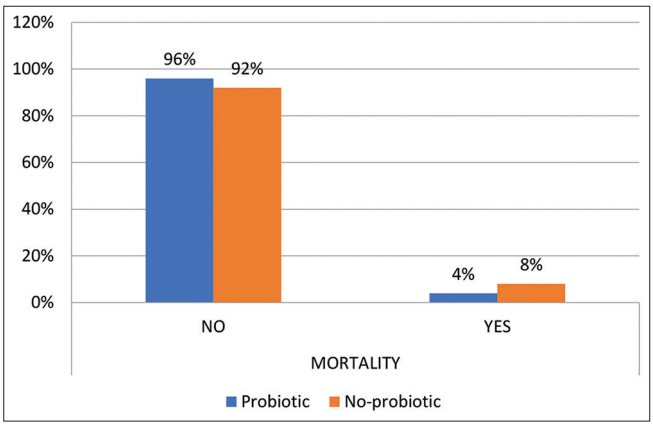

Figure 7: Mortality incidence between groups

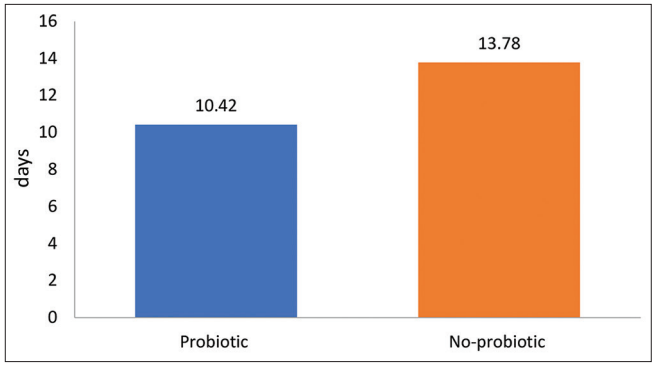

Figure 8: Duration of hospital stay between groups

Table 4: Incidence of sepsis, NEC stage, and requirement antibiotics between groups

Group	Sepsis		P-value
	No (%)	Yes (%)	
Probiotic	22 (88)	3 (12)	0.024
No-probiotic	15 (60)	10 (40)	
Group	**NEC stage ≥ 2**		**P-value**
	No (%)	**Yes (%)**	
Probiotic	22 (88)	3 (12)	0.701
No-probiotic	20 (80)	5 (20)	
Group	**Antibiotics**		**P-value**
	No (%)	**Yes (%)**	
Probiotic	22 (88)	3 (12)	0.005
No-probiotic	13 (52)	12 (48)	

NEC: Necrotizing enterocolitis

DISCUSSION

The present study was conducted to study the role of probiotics in feed tolerance, weight gain, and time to reach full feeds and further analyze their effect on the duration of hospital stay, mortality during hospital stay, incidence of NEC stage 2 or more, and sepsis. In our study, In the probiotic group, the male–female ratio was 1.08:1. In no probiotic group, it was 1.5:1. Shashidhar et al.,[13] did a study where the male–female ratio was 1.08:1 in the probiotic group and 0.62:1 in the no probiotic group. Moni et al.,[14] conducted a study where the male-female ratio was 1.5:1 in the probiotic group and 1.6:1 in the no-probiotic group.

In the present study, there were no significant differences in the age at enrolment (P=0.552). The median time of initiation of enteral feeds in the probiotic group and no probiotic group in the study done by Shashidhar et al.,[13] was 15 and 17 h, respectively. In the present study, there was no significant difference in the mean birth weight in the probiotic and no probiotic groups. This is comparable with studies conducted by Indrio et al.,[15] and Sreenivasa et al.[16]

In the present study, according to gestational age, the very preterm were 52% versus 68%, Moderate preterm were 44% versus 24%, and Late preterm were 4% versus 8% in probiotic and no probiotic groups, respectively (P=0.311). Only 2.86% of neonates were enrolled in the probiotics group and 4.29% in the no-probiotic group in the <28 weeks group in a gestational age-wise distribution study by Chandrashekar et al.[17] Similarly, in the study, only 8% of neonates in the probiotic group and 10.66% of neonates in no probiotic group were enrolled in the category of 28–32 weeks gestation (P=0.807) in a similar study by Arora et al.[18] The mean Apgar scores at 1 and

5 min in the probiotic and no-probiotic groups were comparable to the study by Shashidhar et al.[13]

Further, there was no significant difference in maternal risk factors like pre-eclampsia, anemia, pregnancy-induced hypertension, and leaking per vaginum. This aligns with previous studies conducted by Samanta et al.,[19] and Chandrashekhar et al.[17]

In the present study, the time to reach full feeds (in days) in the probiotic group was significantly less than in the no-probiotic group. This is in line with other studies, including Samanta et al.,[19] Shashidhar et al.,[13] Arora et al.,[18] and Sreenivasa et al.[16] We found that the weight change per day (in grams) was 3.60±46.24 g in the probiotic group and 12±30.24 g in the no-probiotic group (P=0.165). Due to the natural physiology in preterm babies up to 14 days of life, there was weight loss in the neonates in the initial few days, which is indicated by the negative sign. We found that the weight loss in the probiotic group was more than in the no-probiotic group, although the difference was insignificant in the present study. The neonates in the no-probiotic group did not reach their birth weight at the time of discharge, whereas those in the probiotic group almost regained their birth weight at discharge.[1,4,13,14]

A few studies have commented on weight gain per day and weight at discharge, while others have commented on weight gain per week. Results on weight gain are varied. Most studies reported a positive change in weight over days or weeks. The results cannot be compared in the present study since neonates were discharged even before regaining birth weight. However, Sonawane et al.,[20] Cui et al.,[21] Moni et al.,[14] and Indrio et al.,[15] reported only a statistically significant difference in weight gain in the probiotic group, which reported weight at discharge, similar to our study. However, they have not given mean birth weight like in our study, which cannot be compared.

In the present study, the number of neonates who developed feed intolerance was more significant than in the no-probiotic group (12% vs. 44%) (P=0.012). The number of neonates with feed intolerance in the probiotic group was 7%, and in the no-probiotic group was 10.6% (P=0.08, NS) in the study done by Rojas et al.[22]

In our study, the incidence of culture-proven sepsis was 12% and 4% in the probiotic and no-probiotic groups, respectively (P=0.024). Statistically significant differences in the incidence of sepsis were observed by Samanta et al.,[19] Arora et al.,[18] and Sreenivasa et al.[16] In contrast to our study, Rojas et al.,[22] Chandrashekhar et al.,[17] Al-Hosni et al.,[23] Lau et al.,[24] and Cui et al.,[21] did not find any significant difference in the incidence of sepsis.

In the present study, we found the % of deaths in the probiotic and no probiotic groups was 4% and 8%, respectively (P=0.552). However, in studies conducted by Samanta et al.,[19] Shashidhar et al.,[13] and Arora et al.,[18] it was 4.4%, 1.9%, and 0% in the probiotic group, and 14.7%, 5.7%, and 2.6% in the no-probiotic group, respectively.

In the present study, we found that the duration of hospital stay in the probiotic group was significantly lower than in the no-probiotic group. Most authors reported shorter hospital stays in the probiotic group than in the no-probiotic group. Similarly, statistically significant results were reached by Samanta et al.,[19] Arora et al.,[18] Chandrashekhar et al.[17], Moni et al.,[14] Indrio et al.,[15] and Cui et al.[21] The study by Sreenivasa et al.,[16] reported an increased duration of hospital stays in the probiotic group, in contrast to all studies. Discharge protocols followed by various authors and differences in the morbidity profile of the study population could be the reason for variable results.

Limitations of the study

The present study has some limitations. The exact dosage of probiotics to be administered was unclear, and analysis of adverse effects of probiotics was not done.

CONCLUSION

VLBW neonates who received probiotic supplements along with their feeds have shorter times to reach full feeds, better feed tolerance, lower incidence of sepsis, and shorter mean hospital stays. Before recommending its routine use in neonatal feeding protocols, more research is needed on specific strains and dosages of probiotics.

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Authors Contribution:
GSK - Writing manuscript; **LCMPK** - Editing manuscript; **RJK** - Study design, Data collection, Data analysis.

Work attributed to:
Department of Pediatrics, Government Thoothukudi Medical College, Tamilnadu, India.

Orcid ID:
Dr. Senthil Kumaran G - https://orcid.org/0000-0002-2007-5494
Dr. Chairman Muthu Prem Kumar L - https://orcid.org/0009-0002-7537-4536
Dr. Jeyarama Krishnan R - https://orcid.org/0009-0008-3713-8501

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