

Impact of Probiotics Supplementation on Enteral Feed Tolerance in Very Low Birth Weight Neonates: An Open Label Randomised Controlled Trial

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ABSTRACT

Introduction: Probiotics are live microorganisms recognised for their potential health benefits. While the evidence regarding their effectiveness in improving feed tolerance among very low birth weight (VLBW) newborns remains inconclusive, this study seeks to investigate whether probiotic supplementation can significantly reduce the time it takes for VLBW neonates to achieve full feeding.

Aim: To study the impact of probiotics supplementation on enteral feed tolerance in very low birth weight neonates.

Materials and Methods: An open-label, randomised-controlled trial was conducted at the Neonatal Intensive Care Unit of a tertiary care center, PGIMS, Rohtak, Haryana. All the study participants were screened and enrolled based on the eligibility criteria from September 2022- January 2024. A total of 100 participants were recruited and divided equally into two groups (n=50 each): the probiotic group and the control group. The probiotic group received 1 gm of multistrain probiotics in

breast milk. The control group received breast milk with 1 gm of formula milk powder and no probiotics. Statistical analysis was done using appropriate tests for baseline characteristics, and primary and secondary outcomes, and a p-value <0.05 was considered to be statistically significant.

Results: Neonates in the probiotic group achieved full feeds much earlier, averaging 4.22±2.88 days as compared to 9.56±3.56 days in the control group (p-value <0.001). They also had a shorter hospital stay of 17.68±3.48 days versus 29.6±2.59 days. Moreover, the incidence of necrotising enterocolitis (NEC) and sepsis was significantly lower in the probiotic group (p-values of 0.05 and 0.04), underscoring the positive health effects of probiotics on neonatal well-being.

Conclusion: This study concluded that probiotics should be used in very low birth weight neonates as soon as the feed is started which can reduce the time to attain full feeds, duration of hospital stay, and also preventing from potential complications such as sepsis, necrotising enterocolitis.

Keywords: Probiotics, Preterm neonates, Very low birth weight, Necrotising enterocolitis, Neonatal sepsis

INTRODUCTION

Various problems like- feed intolerance, necrotising enterocolitis, nosocomial sepsis, and the need for prolonged NICU care are significant hindrances in achieving optimal outcomes for low-birth-weight babies [1,2]. Necrotising enterocolitis (NEC) is one of the most common acute and fatal gastrointestinal emergencies in very low birth weight (VLBW) preterm neonates with mortality ranging from 15 to 30%. [1] NEC is likely to be due to multifactorial processes such as prematurity, dysbiosis, hypoxia-ischemia, and non-breast milk feeds [3]. Extended hospitalisation affects the development and stability of the gut microbiota in preterm babies, preventing their ability to establish a gut microbiota similar to that of term neonates [4]. Before late-onset sepsis, there is an accumulation of bacilli and their fermentation products which can lead to intestinal dysbiosis [5].

To prevent colonisation of pathogenic bacteria and altered flora due to antibiotics in the bowel of low birthweight babies we can administer the 'desirable flora' or probiotics. Probiotics are defined as "live microorganisms, which when given in adequate amounts may lead to health benefits for people with specific illnesses" [6]. They were initially introduced for the management of a range of diseases of the intestinal tract, such as antibiotic-associated

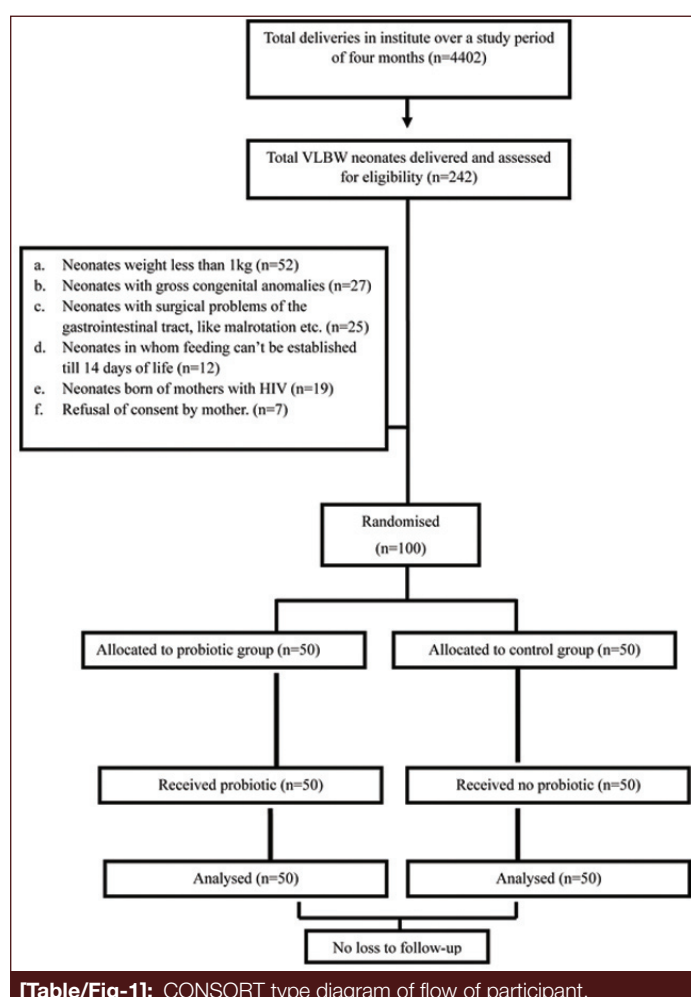
diarrhoea, irritable bowel syndrome, etc. Long-term benefits may also be present and may depend on the type of probiotic strain used [7-9]. Mercer et al. [10] pointed out in his review the need for RCTs evaluating the optimal timing of initiation, dosing, duration, mode of delivery, and composition of probiotic formulations. However, there are many issues raised regarding the efficacy and the safety of this therapeutic intervention in immunocompromised individuals [11].

Balasubramaniam et al. [12] concluded that "Current evidence from RCTs support probiotic supplementation for optimising outcomes of preterm neonates in India". Panchal et al. [13] suggested that "Probiotics did not affect the length, head circumference, long-term growth, and neurodevelopmental outcomes of preterm neonates. Rath et al [14] opined that "Limited evidence suggests a higher dose might improve gut colonisation in preterm neonates. Further studies are needed to address this gap in the knowledge considering the increasing use of probiotics for preterm neonates". Many authors remained unclear about the benefits of probiotic supplementation in improving feed tolerance among VLBW newborns. [15-16]. Therefore the current study was planned to determine the impact of probiotics on feed tolerance and the time taken by VLBW babies to reach full enteral feeding.

MATERIAL AND METHODS

An open-label randomised controlled trial was conducted over a period of one and a half years duration in the Neonatal intensive care unit of the Department of Paediatrics and Neonatology, Pt B D Sharma PGIMS, Rohtak. The study was approved from Institutional Ethics Committee- [IEC no: BREC/22/TH/Ped.07] and the trial was registered with the Clinical Trial Registry of India (Clinical Trial registration no.-CTRI/2023/04/051455).

We included intramural hemodynamically stable very low birth weight neonates, weighing between 1000 to 1500 grams at the time of birth irrespective of gestational age. Neonates weighing <1000 or >1500 grams or those with gross congenital anomalies, any surgical problem of the gastrointestinal tract, like malrotation, etc, or major liver problems that are known to interfere with feeding, born of mothers with HIV were excluded. The composite flowchart of recruitment and analysis of patients has been depicted in the CONSORT-type diagram [Table/Fig-1].



Sample size: Sample size calculation was done based on the prevalence of NEC (taken as 6% to 10% in neonates) in previous studies. $Z (1-\alpha/2)$ was taken as 1.96 at 95% Confidence Intervals or 5% level of significance. The sample size (n) was computed to be 87. Assuming a 5% attrition, the total number was taken as 100 (50 in each group) [15].

Data collection: All the participants were screened and enrolled in the study consecutively based on the eligibility criteria. Randomisation was performed by using a computer-generated random sequence number (Version 4.0 of research randomiser). The allocation ratio was 1:1. Allocation concealment was achieved by using opaque, sealed envelopes that were serial-numbered and contained group codes. Envelopes were opened at the time of

randomisation and patients were allocated to either probiotics or control group.

Feeding was initiated, advanced, stopped, and restarted as per unit protocol for the study. The protocol algorithm was attached to the study case files to ensure compliance. Trophic feeds were initiated at 10 to 20 mL/kg/day at 2 hourly intervals. This was either breast milk or formula feeds in stable neonates. Feeds were advanced by 20-30 ml/kg/day. Feeds were given every 2 hourly, and abdominal girth was measured among babies on gavage feeds. Feed intolerance was defined as the presence of either abdominal distension >2 cm from previous measurement, vomiting > 2 episodes in 6 hours, or Bloodstained or bilious vomiting. Accordingly, feeding was withheld if feed intolerance, hemodynamic instability (respiratory distress, shock), or features of NEC or sepsis were noted. Feeding was restarted when the above-mentioned signs were resolved [17]. Intravenous fluids were continued till 100 mL/kg/day or 2/3rd of the total feeds was reached. From an intervention point of view, the probiotic group received a multicomponent probiotic formulation of *Lactobacillus acidophilus*, *Lactobacillus rhamnosus*, *Bifidobacterium longum*, and *Saccharomyces boulardii* in the form of powdered sachets of 1 gram (Darolac, manufactured by ARISTO Pharmaceuticals Pvt. Ltd.) containing 1.25 billion cells. It was available in powder form which was dissolved in breast milk. Milk plus probiotics were prepared individually under strict asepsis by staff nurses for each neonate. If the volume of feed was 2 ml or more, the probiotic was administered 1 gm once a day (starting within 24 hours of initiation of feeds) and in four divided doses (i.e. 250 mg each) if the baby received < 2 mL feed two hourly [16]. The probiotics supplementation was continued till discharge. The control group received 1 gm of formula milk powder daily dissolved in breast milk without probiotics. Time to achieve full enteral feeds was defined if neonate tolerated enteral feeds of 100 mL/kg/day with stoppage of intravenous fluids. The weight of the neonates was checked daily using a calibrated digital weighing machine scale. NEC was defined and staged as per modified Bell's staging criteria [17]. Other morbid conditions such as intraventricular haemorrhage, patent ductus arteriosus, sepsis, etc, were managed as per standard unit protocol. A neonate was discharged on full feeds after ensuring all the vital parameters as normal with definitive weight gain (at least 10 gm/kg/day) and proper follow-up advice for growth, mile stones assessment and vaccination. Advise to continue breastfeeding and kangaroo mother care with a special emphasis on danger signs explained for seeking immediate care.

STATISTICAL ANALYSIS

Data was analysed using Microsoft Excel Stat Pac V365. Descriptive data was presented as Mean and Standard deviation, or median and Interquartile range, as the case may be. Data was subjected to a normality test using the Kolmogorov-Smirnov test. All comparisons were performed between the intervention and control groups. A p-value of <0.05 was taken as statistically significant.

RESULTS

There were 27 males and 23 females in the probiotic group and 24 males and 26 females in the control group respectively. The baseline characteristics (such as Gravida, Maternal risk factors, Delivery Mode, Nature of Liquor, Gestational age, etc.) of the neonates did not show any statistically significant difference between the groups [Table/Fig-2]. Maximum neonates were born out of normal vaginal delivery to multiparous mothers. Anaemia and Premature rupture of membranes were considered to be the most common maternal risk factors.

Parameters	Probiotic group (n=50)	Control group (n=50)	p-value
Gravida distribution			
G1	8	10	0.89 Not statistically significant
G2	23	18	
G3	14	18	
G4 and above	5	4	
Maternal risk factors			
Anaemia	6	11	0.28
Hypertensive disorder of pregnancy	5	4	1
Antepartum haemorrhage	5	3	0.715
Prolonged Preterm Premature rupture of membranes	7	3	0.317
Delivery mode			
Normal delivery	31	35	0.526 (not statistically significant)
Caesaeran section	19	15	
Nature of liquor			
MSL	6	9	0.89 (not statistically significant)
Clear liquor	44	41	
Gestational age (weeks)			
28-28.6	3	3	0.13 (not statistically significant)
29-29.6	5	3	
30-30.6	5	8	
31-31.6	12	13	
32-32.6	7	9	
33-33.6	4	7	
>=34	14	7	
Birth asphyxia			
Yes	2	3	0.66 (not statistically significant)
No	48	47	
Anthropometric parameters at birth			
Birth weight (Kg)	1.3±0.13	1.227±0.152	0.067
Birth length (cm)	39.44±0.99	39.28±0.60	0.33
Occipitofrontal circumference (cm)	28.18±0.92	28.63±1.82	0.12

[Table/Fig-2]: Comparison of baseline characteristics between the groups.

Most of the outcome parameters (Time to reach full feed, day of discharge, the day at which feed restarted etc) were in favour of probiotic group. The Mean time to reach full feeds (in days) was 4.22±2.8 in the probiotic vs. 9.56±3.59 in the control group and showed a statistically significant difference (p-value <0.001). Similarly, the difference in mean days of discharge 17.68±3.48 vs. 29.6±2.59 (p-value <0.001) was significant statistically [Table/Fig-3]. A higher proportion of neonates in the probiotic group experienced only one episode of feed intolerance (18% of neonates). Very few neonates in the probiotic group had two episodes (8%) or three episodes (6%) of feed intolerance. Time (in days) at which symptoms appeared was delayed in the probiotic group as compared to the control group (2.22±1.25 vs. 0.94±1.26, p-value <0.001). The days at which feed restarted 1.64±2.14 vs. 6.88±3.43 was too early for probiotic group and volume achieved so far 23.2±14.2 vs. 11.2±17.23 was higher. This suggests that probiotics may help reduce the frequency of

Primary outcomes	Probiotic group	Control group	p-value
Time to reach full feed (in days)	4.22±2.88 (n=50)	9.56±3.59 (n=50)	<0.001
Feed volume (in ml) before which symptom appeared	12.34±11.8 (n=16)	13.6 ±9.89 (n=27)	0.17
Days at which symptoms appeared	2.22±1.25 (n=16)	0.94 ±1.26 (n=27)	<0.001
Days at which feed restarted	1.64±2.14 (n=16)	6.88±3.43 (n=27)	<0.001
Volume achieved after feed restarted	23.2±14.2 (n=16)	11.2±17.23 (n=27)	<0.001
Days of discharge	17.68±3.48 (n=16)	29.6±2.59 (n=27)	<0.001

[Table/Fig-3]: Comparison of primary outcomes between the groups.

feed intolerance episodes. However, the difference between the groups was not statistically significant, with a p-value of 0.754. This suggests the utility of probiotics in reducing the frequency of feed intolerance episodes. However, the difference between the groups did not reach statistical significance (p-value=0.754).

The incidence of necrotising enterocolitis (NEC) was significantly lower in the probiotic group, with a rate of 2% compared to 4% in the control group (1 vs. 4; p-value=0.05) [Table/Fig-4]. Additionally, the occurrence of sepsis was 16% in the probiotic group as against 34% in the control group (8 vs. 17; p-value=0.046). However, there were no significant differences in the rates of respiratory distress syndrome (RDS) or mortality between the two groups (p-values exceeded 0.05).

Secondary outcomes	Probiotic group (n=50)	Control group (n=50)	p-value
NEC	1	4	0.05
Sepsis	8	17	0.046
RDS	8	14	0.2270
Mortality	1	2	0.89

[Table/Fig-4]: Comparison of secondary outcomes between the groups. NEC: Necrotising enterocolitis; RDS: Respiratory distress syndrome

DISCUSSION

The present study was a randomised controlled trial (RCT) that assessed the effectiveness of administering probiotics to preterm neonates compared with a control group receiving no intervention. Due to the nature of the probiotic supplement, this was an open-label RCT, making it impossible to blind participants or caregivers to the treatment.

Our findings indicated that symptoms of feed intolerance appeared later in the probiotic group compared to the control group (2.2±1.25 days vs. 0.9±1.26 days, p<0.001), which was statistically significant. Chandrashekhar et al. [15] (10.55±2.14 days vs. 9.9±2.62 days, p=0.18) and Arora et al. [16] (12.0±0.0 days vs. 8.5±2.92 days, p=0.295) also noticed late onset of symptoms in the probiotic group, but these findings were not statistically significant.

Notably the time taken to reach full feeds was significantly shorter in the probiotic group compared to the control group (4.2±2.8 days vs. 9.5±3.6 days, p<0.001). Similar results have been reported by Chandrashekhar et al. (15.8±3.15 days vs. 20.2±2.14 days, p<0.001), Indrio et al. [17] (4.2±1.1 days vs. 7.5±3.2 days, p<0.001), and Xu et al. [18] (0.37±0.13 days vs. 1.7±0.45 days, p<0.01), all of which showed that neonates were able to achieve full feeds earlier when probiotics were used.

Feeding was restarted significantly earlier in the probiotic group (1.6 ± 2.14 days vs. 6.8 ± 3.43 days, $p < 0.001$). In contrast, the study by Shashidhar A et al. [19] found no significant difference between the groups (9.5 ± 8.3 days vs. 10.5 days, $p = 0.5$). Furthermore, neonates in the probiotic group were discharged earlier than those in the control group (17.6 ± 3.48 days vs. 29.6 ± 2.59 days, $p < 0.001$). This aligns with findings from Arora et al. (16.0 days vs. 20.0 days, $p = 0.001$), Indrio et al. (13.4 days vs. 22.4 days, $p < 0.01$), Xu et al. (18 days vs. 23.3 days, $p = 0.035$), and Zahed et al. [20] (12.77 days vs. 31.17 days, $p = 0.0005$), all demonstrating the positive effect of probiotics on reducing hospital stay duration. However, Shashidhar A et al. (27.6 ± 18.5 days vs. 31.2 ± 22.9 days, $p = 0.4$), Sinha et al. [21] (29 days vs. 44 days, $p = 0.075$), and Sreenivasa et al. [22] (13.66 ± 4.9 days vs. 13.55 ± 5.09 days, $p = 0.87$) did not report similar findings. Regarding the occurrence of sepsis, our study showed a significantly lower rate in the probiotic group (16% vs. 34%, $p < 0.01$). This finding was consistent with Sinha et al. (12.6% vs. 15.9%, $p = 0.08$), Sreenivasa et al. (28% vs. 42%, $p = 0.038$), and Xu et al. (7.8% vs. 12.2%, $p = 0.06$), all highlighting the potential for probiotics to reduce the risk of sepsis, a major cause of neonatal mortality.

The incidence of necrotizing enterocolitis (NEC) was also significantly lower in the probiotic group (2% vs. 4%, $p = 0.05$). This aligns with findings from Arora et al. (1.33% vs. 16%, $p = 0.06$), Chandrashekhar et al. (3% vs. 12%, $p = 0.04$), and Sreenivasa et al. (2% vs. 10%, $p = 0.017$), strongly suggesting that probiotics play a beneficial role in preventing NEC. However, Shashidhar A et al. (4.1% vs. 12.5%, $p = 0.3$) and Zahed et al. (3.3% vs. 3.3%) did not find similar results.

Lastly, the mortality rate in our study was 2% in the probiotic group compared to 4% in the control group. Other studies, such as Chandrashekhar et al. (1.43% vs. 5.7%, $p = 0.44$), Arora et al. (1.3% vs. 0%, $p = 0.75$), Shashidhar A et al. (1.9% vs. 5.7%, $p = 0.6$), Zahed et al. (6.7% vs. 0%, $p = 0.492$), and Sinha et al. (0.65% vs. 1.2%, $p > 0.05$), did not observe significant differences in mortality rates between the groups. Given the low absolute numbers of mortality, it seems that the sample sizes in these studies may not have been adequate to draw definitive conclusions regarding the impact of probiotics on neonatal mortality.

Although the field of probiotics has advanced considerably in recent years, there is still a need for clear communication with consumers and healthcare providers on how to differentiate probiotic products [23]. Given the low to moderate certainty of evidence for the effects of probiotic supplements on the risk of NEC and associated morbidity and mortality for very preterm or VLBW infants, and particularly for extremely preterm or ELBW infants, there is a need for further large, high-quality trials to provide evidence of sufficient validity and applicability to inform policy and practice [24].

Limitation(s)

- Single strain of probiotics could not be studied.
- Intermediate and long-term outcomes were not addressed in this study.
- Cost-benefit analysis was not performed.
- Effect of low/high doses of probiotics was not studied in this study.

CONCLUSION

Based on the findings in this study, we recommend administering probiotics to preterm neonates at the start of feeding which reduces the time required to achieve full feeds and lessens the chances of

feed intolerance thereby enhancing the volume of tolerated feeding and shortening the length of hospital stay.

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