

Evaluating the Impact of Probiotic Supplementation on Mortality in Preterm and Low Birth Weight Neonates in a Tertiary Care Center: A Randomized Controlled Study

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ABSTRACT

Background: Preterm birth (before 37 weeks of gestation) and low birth weight (under 2500 grams) are major contributors to infant mortality worldwide, particularly in developing countries. India alone sees around 12% of births as preterm and 18% as low birth weight, making this a significant public health concern.

Aim: To assess the role of probiotics usage on the mortality in preterm and low birth weight neonates in a tertiary care centre-a randomized control study.

Methodology: The study involved newborns between 28–36 weeks of gestation or weighing less than 1800 grams, admitted to the NICU at Sharda Hospital and meeting specific inclusion criteria. After obtaining informed consent from parents, data was collected using a structured case form. Participants were randomly assigned to two equal groups (A and B) through a computer-generated block randomization method, with allocation concealed in sealed, numbered envelopes. To ensure objectivity, both the medical team and investigators were blinded to group assignments. The probiotic (*Bacillus clausii*) and placebo (sterile water) were coded and packed separately, with only the designated nurse aware of which was which. Each baby received 2.5 mL of either the probiotic or placebo orally every 12 hours along with feeds, continued until discharge or death, and paused if feeds were stopped.

Results: A total of 112 neonates were enrolled, equally divided into placebo (n=56) and probiotic (n=56). 9 neonates died in placebo group, 1 died in probiotic group and 102 were discharged.

- Demographics: Gestational age, gender, and birth weight were comparable in both groups.
- Mortality: Significantly lower in the probiotic group.

Conclusion: Based on the findings, the administration of probiotics was associated with reduced mortality rates. Mortality was notably higher in the placebo group compared to the probiotic group.

Keywords: Probiotics, pre-term, neonates, low birth weight, mortality, randomized study

1. INTRODUCTION

Globally, approximately 15 million premature births^{1,2} and over 20 million infants are born with LBW each year³. The prevalence of PTB worldwide is 10.6%, with South Asia accounting for more than one-third of the burden. In India, Approximately 12% of children were born preterm, and 18% had low birth weight during 2019–21. Additionally, nearly 3 million stillbirths occur annually worldwide, with 98% happening in developing countries⁴.

Preterm infants face a higher risk of serious health issues, such as metabolic imbalances, sepsis, death, and long-term neurodevelopmental and cognitive challenges. One of the most severe gastrointestinal conditions they may develop is necrotizing enterocolitis (NEC), marked by damage to the intestinal lining, bacterial invasion, and in severe cases, tissue death and bowel perforation—most commonly affecting the terminal ileum and proximal colon.⁵

Systematic reviews of randomized controlled trials (RCTs) and non-RCTs have shown that probiotic supplementation significantly reduces the risk of all-cause mortality, NEC $\geq$ Stage II, LOS, and feeding intolerance in preterm, very low birth weight (VLBW) infants⁶.

A number of prominent international health bodies, including the European Society for Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN), the World Health Organization (WHO), the American Academy of Pediatrics, and the Canadian Paediatric Society, have reviewed available evidence and issued guidelines or recommendations supporting the use of probiotics in neonatal care, particularly for preterm and low birth weight infants⁷. Importantly, research indicates that the clinical benefits of probiotics—such as improved survival and reduced complications—are not limited to specific regions or economic settings, with comparable outcomes observed in both high-income countries and low- to middle-income countries (LMICs)⁷. Preterm and low birth weight infants represent a highly vulnerable group with an increased risk of mortality. While probiotic supplementation has shown promise in improving survival rates in this population, there remains considerable uncertainty regarding its consistent effectiveness and safety, especially in varied clinical settings. Additionally, there is a lack of robust, localized data on how probiotics influence mortality in preterm neonates. Considering these gaps, our study was designed to evaluate the impact of probiotic use specifically on mortality in preterm and low birth weight neonates admitted to our tertiary care center.

Indian Epidemiology

Between 2019 and 2021, about 12% of births in India were preterm, and 18% of newborns had low birth weight.⁸

Punjab recorded the highest proportion of low birth weight infants at 22%, followed closely by Delhi, Dadra & Nagar Haveli, Madhya Pradesh, Uttar Pradesh, and Haryana.

When it comes to preterm births, higher rates were observed in states like Himachal Pradesh, Uttarakhand, the Andaman & Nicobar Islands, Rajasthan, Nagaland, and Delhi. The prevalence showed wide variation—ranging from as high as 39% in Himachal Pradesh to just 2% in Mizoram.⁹

TABLE 1. The common problems associated with prematurity and low birth weight neonates

General	Hypothermia, trans epidermal fluid loss
CNS	Apnea, intraventricular bleed, birth asphyxia
Lung	Respiratory Distress Syndrome, Bronchopulmonary Dysplasia (BPD), chronic lung disease
CVS	PDA
GIT	Feed intolerance, NEC, cholestasis, intraabdominal bleed, and hyperbilirubinemia.
Hematology	Anemia of prematurity
Immune system	Infections (bacterial,viral,fungal)
Eye	Retinopathy of prematurity (ROP)
Metabolic	Hypoglycemia, hyperglycemia, hypocalcemia, hyperkalemia, acidosis

Gut Microbiome in Preterm Infants

Being born prematurely plays a key role in shaping how a baby's gut microbiome develops. Unlike full-term babies, preterm infants are often admitted to the NICU soon after birth, where they are more likely to be exposed to hospital-acquired bacteria rather than beneficial microbes passed from the mother.¹⁰

Their early environment, combined with medical interventions like ventilation, artificial feeding, antibiotics, and frequent use of medical devices (such as feeding tubes and catheters), disrupts the natural process of microbiome formation. Adding

to this, preterm infants have underdeveloped digestive systems and immature immune responses.¹⁰

Unlike full-term babies—who tend to have a gut microbiome rich in beneficial bacteria like *Bifidobacterium* and *Lactobacillus* thanks to maternal transfer and breastfeeding—preterm babies have a less diverse microbiome. Their gut is often dominated by *Staphylococcus* species, such as *S. epidermidis* and *S. aureus*, while beneficial *Bifidobacterium* is often lacking. This imbalance is further worsened by the frequent use of broad-spectrum antibiotics in preterm care.¹¹

Bifidobacterium is particularly important because it helps protect against conditions like necrotizing enterocolitis (NEC) and supports overall gut health. Unfortunately, preterm babies—especially those fed formula instead of breast milk—often experience delayed colonization of this vital bacteria. The NICU environment itself can also contribute to an imbalance in the gut microbiota, as babies are exposed to bacteria from surfaces, equipment, and the surrounding air.^{10,11}

In a 2012 study titled "Probiotics, Prebiotics, and Infant Formula Use in Preterm or Low Birth Weight Infants," researchers Mary N. Mugambi and Alfred Musekiwa concluded that there was insufficient evidence to support that supplementing exclusively formula-fed preterm infants with probiotics or prebiotics leads to better growth or clinical outcomes.¹²

In 2022, P. Namratha and colleagues conducted a double-blind randomized controlled trial to assess the effect of *Bacillus clausii* probiotics on reducing the incidence of late-onset sepsis (LOS) in preterm neonates. The study found no statistically significant difference between the probiotic and placebo groups in terms of LOS incidence or length of hospital stay ($p > 0.05$). However, the probiotic group showed a significantly lower rate of feed intolerance (11.11%) compared to the placebo group (26.47%), with a p -value < 0.05 .¹³

Despite growing global interest in the use of probiotics in neonatal care, there is a notable lack of Indian data specifically addressing their role in reducing mortality among preterm and low birth weight infants. While several international studies have explored this area, findings have been inconsistent, and their applicability to the Indian context remains unclear. Recognizing this gap, and following the Indian Academy of Pediatrics' recent endorsement of the scientific rationale behind probiotic use, this study was designed as a double-blind, block-randomized controlled trial to evaluate whether probiotic supplementation can help improve survival outcomes in this high-risk neonatal population.

2. METHODOLOGY

This study was conducted as a double-blinded, block randomized controlled trial over a duration of 18 months, from May 2023 to November 2024. The research was carried out in the Neonatal Intensive Care Unit (NICU) at Sharda Hospital, Greater Noida, Uttar Pradesh. The study population comprised preterm neonates born between 28 and 36 weeks of gestation or with a birth weight of less than 1800 grams, who were receiving nutrition via orogastric (OG) tube or katori/spoon (K/S) feeding methods. Prior to the initiation of the study, ethical clearance was obtained from the Institutional Ethics Committee. A total of 112 neonates who met the eligibility criteria were enrolled in the study.

Inclusion Criteria:

Preterm neonates born between 28 to 36 weeks of gestational age or with a birth weight of less than 1800 grams, who were admitted to the NICU at Sharda Hospital, were included in the study. Only those neonates who were being fed through an orogastric tube or by katori/spoon feeding methods were considered eligible for participation.

Exclusion Criteria:

Neonates who had been shifted to the mother's side for routine care were excluded from the study. Additionally, newborns who were clinically unstable and kept nil per oral (NPO) due to medical indications were also excluded from participation.

After identifying eligible neonates, informed consent was obtained from the parents or legal guardians. The methodology, purpose, and potential benefits of the study were explained to them in detail prior to enrollment.

Gestational age assessment was performed using the Dubowitz method, as described in the annexures. Each enrolled neonate was then weighed using a calibrated electronic pan balance machine with a sensitivity of 10 grams, ensuring accuracy by recording nude birth weight. All relevant demographic and clinical information was systematically documented in a predesigned case record form for consistency in data collection.

Double-blinded block randomization was employed for allocation of participants. A computer-generated sequence was used to create blocks of four participants, resulting in 14 blocks and allowing for an equal distribution of 112 neonates into two groups—Group A and Group B—each consisting of 56 participants. The randomization sequence was generated using the Sealed Envelope platform [<https://www.sealedenvelope.com/>]. Allocation concealment was ensured through the use of sequentially numbered, opaque, sealed, and stapled envelopes. The envelopes were handled exclusively by the in-charge nurse of the NICU, who was the only individual aware of the group assignments.

The intervention involved administration of either a probiotic or a placebo. The probiotic used was *Bacillus clausii*, with one respule containing 2 billion spores in 5 mL of suspension. The placebo consisted of 5 mL sterile water in identical respules. Both the probiotic and placebo bottles were identically coded, with labeling concealed to maintain blinding. They were

packed into two separate containers labeled as Group A and Group B. The NICU investigators, staff, and nurses were all blinded to group allocation. The administration of either the probiotic or placebo was carried out by designated personnel other than the head nurse, and any unused portions were discarded to preserve dosing integrity. Decoding of the intervention assignments was carried out only after the completion of data analysis.

Neonates in the probiotic group received *Bacillus clausii* at a dose of 2.5 mL orally every 12 hours, mixed with enteral feeds administered via orogastric tube or orally, depending on feeding status. The placebo group received 2.5 mL of sterile water orally every 12 hours with feeds. Throughout the intervention, a detailed performa was maintained, recording the dosage administered, start and stop dates of the intervention, and the final clinical outcome.

The probiotic or placebo administration continued until either the neonate was discharged from the NICU or until death. The intervention was discontinued if the neonate was made nil per oral (NPO) for any clinical reason. The primary parameters observed during the study included gestational age, birth weight, gender and final outcome, specifically whether the neonate survived to discharge or succumbed during the hospital stay.

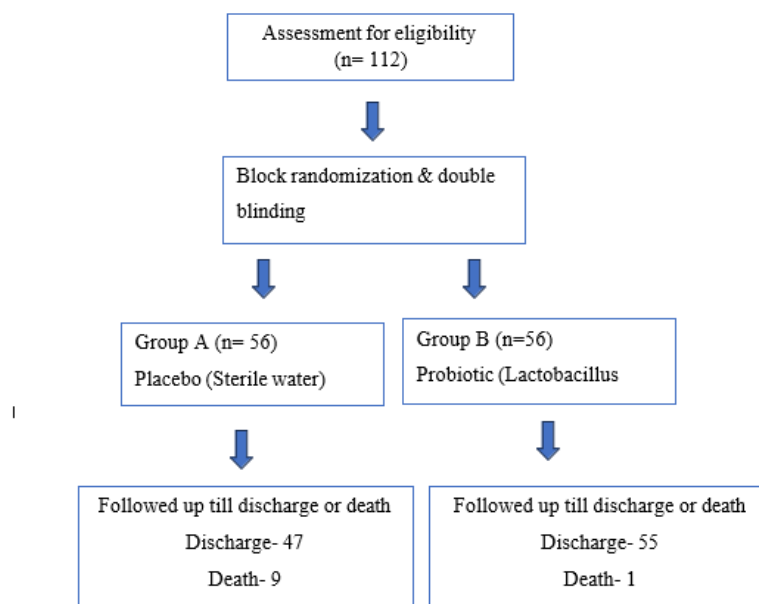


Fig1- Flowchart of study

3. RESULTS AND OBSERVATIONS

During our study period, a total of 112 neonates were enrolled in the study with equal distribution of neonates in both the groups i.e. Group A- placebo (n=56) and Group B- Probiotic (n=56). Among these, 10 neonates died and 102 were discharged.

4. DEMOGRAPHIC CHARACTERISTICS- GENDER

The study population included 48 males (45.28%) and 58 females (54.71%) neonates.

Table 2- Demographic characteristics based on gender

GROUPS	Male	Female	Total	χ^2 value	df	P value
Control Group (A)	27	29	56	0.0358	1	0.850
	24.1%	25.9%	50.0%			
Study Group (B)	26	30	56			

	23.2%	26.8%	50.0%			
Total	53	59	112			
	47.3%	52.7%	100.0%			

GESTATIONAL AGE (Weeks)

Gestational Age was comparable in both the groups.

Table 3- demographic characteristics based on gestational age (weeks)

Gestational Age	Control Group (n=56)	Study Group (n=56)
Mean	33.6	33.8
Median	34.0	34.0
Standard deviation	2.09	2.07
Minimum	29.3	28.3
Maximum	38.3	39.4

Independent Samples T-Test

		Statistic	df	p
Gestational Age(weeks)	Student's t	-0.652	109	0.516

BIRTH WEIGHT

Table 4- demographic characteristics based on birth weight

	GROUP	N	Mean	Median	SD	SE
Birth weight	Control	56	1.74	1.65	0.430	0.0574
	Study	56	1.84	1.80	0.374	0.0500

Independent Samples T-Test				
		Statistic	df	p
Birth weight	Student's t	-1.29	110	0.201

Birth weight was comparable in both the groups.

OUTCOME

Mortality was significantly higher in Control group as compared to study Group with a p- value of 0.02.

Table 5- Outcome in control and study groups

Outcome			
GROUP	discharge	expired	Total
Control	47	9	56
	41.9%	8%	50.0%
Study	55	1	56
	49.1%	0.9%	50.0%
Total	102	10	112
	91%	9%	100.0%

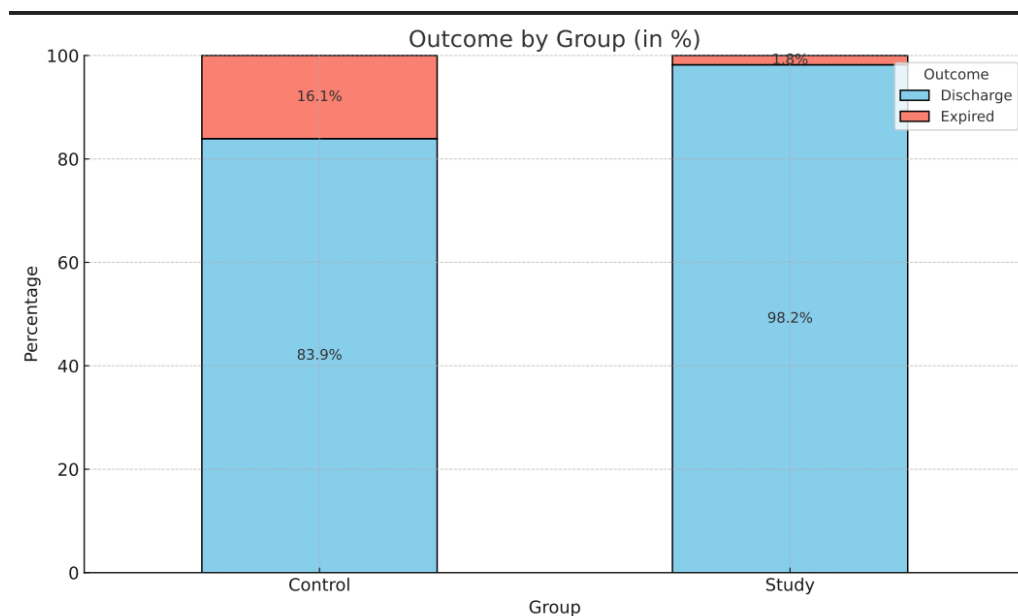


fig 2- Outcome in control and study groups

5. DISCUSSION

Preterm neonates with low birth weight are particularly vulnerable to harmful bacterial colonization in the gut, which can trigger inflammation and potentially lead to serious conditions like sepsis or necrotizing enterocolitis (NEC). Factors such as early antibiotic exposure and extended hospital stays further reduce the diversity of beneficial gut microbes. This study aimed to evaluate the effects of probiotic supplementation versus placebo in this high-risk group. There is limited research specifically assessing the use of *Bacillus clausii* in such infants. *B. clausii* is a spore-forming, heat-stable probiotic approved for use in breastfed neonates. It is safe, can be stored at room temperature, withstands stomach acidity, and comes in a liquid form—allowing for easy and accurate administration without the need for reconstitution.

Mary N Mugambi, Alfred Musekiwa, conducted a study in the year 2012 named Probiotics, prebiotics infant formula use in preterm or low birth weight infants concluded that there is not enough evidence to suggest that supplementation with probiotics or prebiotics results in improved growth and clinical outcomes in exclusively formula fed preterm infants¹².

Wei-Hung Wu in 2024 retrospectively examined 330 extremely low-birth-weight (ELBW) infants in neonatal intensive care units amongst them 206 received probiotics (60 early, 146 late), while 124 did not. Probiotic supplementation was associated with lower overall mortality (adjusted OR 0.22, 95% CI 0.09–0.48) and decreased mortality from necrotizing enterocolitis (NEC) or late-onset sepsis (LOS) (adjusted OR 0.12, 95% CI 0.03–0.45). Early probiotics reduced overall mortality, NEC/LOS-related mortality, and NEC/LOS-unrelated mortality. Late probiotics decreased overall mortality and NEC/LOS-related mortality. Early probiotic use also expedited full enteral feeding achievement¹⁵.

Table 6. Studies evaluating effect of probiotics in preterm and low birth weight neonates on mortality is highlighted below.

Author	Year	Sample		Interventions		Mortality	
		T	C	T	C	T	C
Present Study	2025	56	56	Lb. Clausii	Placebo	1	7
Wei-Hung Wu [15]	2024	206	124	Probiotic	Placebo	9	24
Paolo Manzonil[16]	2014	247	258	BLF	Placebo	1	18
Gamze Demirel[17]	2013	135	136	S.b	Placebo	5	6
Kate Costeloe[18]	2015	650	660	B.b	Placebo	54	56
Hung-Chih Lin[19]	2014	217	217	B.bi and L.a	Placebo	4	20
Mehmet Yekta Oncel[20]	2014	200	200	L.r	Placebo	20	27
Stephane Hays[21]	2015	150	52	B.I	Placebo	1	1
Dilek Dilli[22]	2015	100	100	B.I	Placebo	3	12
Kate Costeloe[23]	2016	611	619	B.b	Placebo	54	56
Ipek Güney-Varal[24]	2017	70	40	LGG, L.p, L.c and B.l	Placebo	1	9
Ozge Serce Pehlevan[25]	2019	104	104	LGG, L.p, L.c and B.l	Placebo	6	3
Gayatri Athalye-Jape[26]	2022	86	29	B.b	Placebo	18	0
Erik Wejryd[27]	2019	68	66	L.r	Placebo	5	5
Nancy Patricia[28]	2015	24	20	L.r	Placebo	1	/

The lower mortality in probiotic group in our study was similar to the findings of Paolo Manzonil et al 2014¹⁶, Gamze Demirel 2013¹⁷, Mehmet Yekta Oncel 2014²⁰ and Ipek Güney-Varal 2017²⁴.

6. CONCLUSION

The results of the study highlight a potential life-saving benefit of probiotic supplementation in preterm and low birth weight neonates. Infants who received probiotics showed a lower mortality rate compared to those given a placebo, suggesting a protective role against fatal outcomes in this high-risk group. While other clinical outcomes were observed, the most notable difference was in survival rates. The findings indicate that probiotics may contribute significantly to reducing neonatal deaths, reinforcing their possible role as a supportive intervention in neonatal care. These results emphasize the need for broader consideration of probiotics in improving neonatal survival.

7. LIMITATIONS

- Small sample size – One of the primary limitations of this study is the small sample size, which may limit the generalisability of the findings to a larger population.

- Single-Center Study – As the research was conducted at a single center, the findings may not be fully generalisable to other healthcare settings or broader populations.
- Lack of Long-Term Follow-Up – Long-term outcomes of the neonates were not assessed, limiting insights into their developmental trajectory and overall prognosis.

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