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# Role of probiotics in prevention of bronchopulmonary dysplasia in preterm infants: A double-blind randomized controlled trial

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**Abstract**
**Background and Objective:** Bronchopulmonary dysplasia is a relatively common and severe complication of prematurity, and its pathogenesis remains ambiguous. Revolutionary advances in microbiological analysis techniques, together with the gut-lung axis hypothesis, have resulted in more studies linking gut microbiota dysbiosis to the occurrence and development of bronchopulmonary dysplasia. The present article based on findings to examine the intrinsic associations between gut microbiota and bronchopulmonary dysplasia. The gut microbiota affects bronchopulmonary dysplasia via several potential mechanisms including alteration of the gut-lung axis, promotion of inflammation and the ensuing growth effects. By evaluating the potential mechanisms, new therapeutic targets and therapeutic modalities for BPD can be identified from a microecological perspective.
**Methods:** This was a prospective single center, double-blinded, placebo controlled, randomized trial done in department of Neonatology, NICU, BSMMU over 12 months period. Infants born ≤ 35 completed weeks, weighing ≤ 2000 gm admitted in NICU were included consecutively in this study. The probiotic - Each capsule contains (500 mg blend): Lactobacillus acidophilus: 2 billion cfu, Lactobacillus bulgaricus: 1 billion cfu, Bifidobacterium bifidum: 1 billion cfu, Fructo-Oligosaccharide: 100 mg and Placebo- Each capsule contains (500 mg blend) Pregelatinised Starch (Starch-1500) and/or Lactose. The study drug was dispenced in blister having one of the two identification number. The study drug provider group was assigned for the identification number and supply the study drug, which was of the same batch production. Study drug was introduced once daily along with first feeding (mixed with distilled water) by dropper or OG/NG tube and was continue till discharge. After intervention, decoding was done by drug provider group. Results was found as probiotics and placebo group. The number of study samples 59 and 60 in probiotics and placebo group. The primary outcome was the development of Bronchopulmonary dysplasia (BPD). Secondary outcomes include: feeding intolerance, mortality, time to establish full enteral feeds, days required to physiological weight gain, patent ductus arteriosus, intraventricular hemorrhage, retinopathy of prematurity, duration of hospital stay.
**Results:** Rates of development of BPD, mortality, feeding intolerance were statistically significant low in probiotics group than the placebo group. There was less hospital stay, less days required to reach full enteral feeds and more weight gain in probiotics group and it is statistically significant.
**Conclusions:** This randomized, double blinded, placebo controlled trial has demonstrated clinically significant effects of the chosen probiotic mixture on the rate of development of BPD in LBW infants. A large clinical trial is required to address outstanding issues regarding safety and efficacy in this vulnerable population.

**Keywords:** Bronchopulmonary, preterm infants, controlled trial

## Introduction
World health organization estimates more than 20 million babies born with low birth weight annualy and around 80% of neonatal deaths are due to low birth weight [1]. Bronchopulmonary dysplasia (BPD), a chronic lung disease of prematurity, is considered one of the major complications of premature birth [2, 3]. The incidence of BPD is inversely proportional to gestational age, with rates reaching up to 60–90% in extremely preterm infants (22–25 weeks gestation). Infants suffering from BPD are at increased risk of death and long-term pulmonary and neurodevelopmental morbidities [4, 5].

The pathogenesis of BPD is initiated by the arrest in alveolar and lung vascular development, due to premature birth, and sustained by inflammatory events that play a paramount role in the progression of BPD. The initiation of the inflammatory response can already occur in utero, in the setting of chorioamnionitis [4-7]. Nevertheless, postnatal stimuli, such as the ex-utero higher oxygen partial pressures, the need for oxygen administration or mechanical ventilation, and the occurrence of postnatal infections including late onset sepsis (LOS) and necrotizing enterocolitis NEC, perpetuate inflammation and lead to the establishment of BPD [8]. Several treatments, most of which focused on anti-inflammatory or homeostasis-restoring properties, have been attempted in order to prevent or treat BPD. However, meta-analyses could confirm a reduction of BPD only for vitamin A and dexamethasone. Moreover, vitamin A showed only a modest effect, while the use of dexamethasone is limited in preterm infants by its well-known long- and short-term side effects. Adequate timing, dose, and formulation of steroid therapy is still under investigation in preterm infants at risk for BPD [9]. However, the knowledge of stem cell therapy is still incomplete, and further studies are needed to elucidate the impact of several manufacturing aspects that may determine the success or failure of this therapy. In summary, despite the continuous advances in neonatal care, BPD remains a significant burden for the premature population, lacking a safe, effective and easily available treatment [10]. Probiotics are defined as live micro-organisms which, when administered in adequate amounts, confer a health benefit on the host [11, 12]. Several meta-analyses combined these RCTs and demonstrated that probiotic supplementation reduces mortality, NEC, and LOS, as well as the time to achieve full enteral feeding in preterm infants [13-16]. Although until now limited studies have been performed to analyze the effect of probiotics on BPD as primary outcome, a number of RCTs included BPD as a secondary outcome. There are several hypothetical mechanisms by which probiotic may exert a protective effect against BPD: (1) by reducing postnatal inflammatory processes such as NEC and LOS; (2) by modulating the immune function; (3) by improving the nutritional status and growth of the infants; and (4) through the antioxidant properties of probiotics [17-19]. The most frequently used probiotics are *Lactobacillus* and *Bifidobacterium*. There is increasing interest in the potential health benefits of protective colonization of the gastrointestinal tract of preterm infants [20]. It has been suggested that the overgrowth of pathogens might be prevented by inducing the colonization of the bowel with nonpathogenic bacteria (probiotics) of species normally resident in the gut of preterm and full-term infants. In particular, probiotics compete with other microbes for binding sites and substrates in the bowel and produce a wide range of antimicrobial substances such as bacteriocins, microcins, reuterin, hydrogen peroxide and hydrogen ions [21]. Probiotics safety record renders it an attractive alternative to many of the more aggressive therapeutic options; it represents a simple, non-invasive attempt to recreate a natural or normal flora rather than a disruption of nature; and it appears to be effective in preventing a major source of morbidity in low birth weight infants. Postulated mechanisms by which they may protect the host from infections and inflamations include: increasing resistance of the mucosal barrier to migration of bacteria and their toxins by strengthening intestinal cell junctions, modification of host response to microbial products, augmentation of immunoglobulin. A mucosal responses, enhancement of enteral nutrition to inhibit the growth of pathogens; production of bacteriocins (small proteins which kill bacteria); and competitive exclusion of potential pathogens [22]. There are limited studies done in Bangladesh showing the efficacy of probiotics in the prevention of BPD. So the primary objective of this study was to determine the role of oral probiotics in the prevention of Bronchopulmonary dysplasia in preterm infants.

## Material and Methods

### Study Design

This RCT was conducted in Department of Neonatology of BSMMU after approval by institutional review board over a period of eighteen months. A written informed consent was taken from parents and assurance about confidentiality was given. Between 2019 and 2021, 119 infants born ≤ 35 weeks gestation, weighing ≤ 2000 g were randomized to the probiotics group (n = 59) or the placebo group (n = 60). Thorough history of these newborn including demographic information was obtained at the time of enrollment. On admission enrolled newborns were randomly assigned into two groups. Criteria for exclusion were the presence of major congenital malformations, chromosomal anomalies, and lack of parental consent.

### Randomization and Study intervention

Study newborns were assigned either Group A or Group B. Group A was the intervention group which received probiotics along with regular breast feeding and standard care; and Group B was the control group which received placebo with regular breast feeding and standard care. Computerized randomization was done. Participants and investigators were unaware about group allocation. After completion of study, the study drug provider group revealed that, which group got probiotics.

The probiotic volume was 0.5ml containing $3\times10^9$CFU and introduced once daily from first feeding by dropper or tube till discharged. Each probiotic capsule contains Lactobacillus acidophilus- 2 billion cfu, Lactobacillus bulgaricus- 1 billion cfu, Bifidobacteriumbifidum-1 billion cfu, Fructo-Oligosaccharide- 100 mg and each placebo capsule contains Pregelatinised Starch (Starch-1500) which was nontoxic. The study drugs introduced once daily from first feeding mixed with milk by dropper or NG/ OG tube.

To identify factors affecting survival, clinical, biological and microbiological data was obtained from each infant's medical records. Documented data of pregnancy included number of fetus, use of antenatal steroids, presence of prolong rupture of membrane, maternal diabetes, maternal hypertension. Documented clinical data of the newborn included gestational age, birth weight, sex and type of delivery were recorded. The diagnosis of BPD was made by clinical and radiological evidence. BPD was defined as patients on any respiratory support at 36 weeks post menstrual age along with radiological evidence (Stage 1: radiographically indistinguishable from severe RDS; stage 2: marked radiopacity of the lungs; stage 3: clearing of the radiopacity into a cystic, bubbly pattern; stage 4: hyperexpansion, streaks of abnormal density and areas of emphysema with variable cardiomegaly). The principal investigator and the research assistant were in charge in

caring of the infants during their hospital stay. All the clinical care was given as per protocol.

**Primary and Secondary Outcomes**

Infants born ≤ 35 completed weeks, weighing ≤ 2000 g admitted in NICU are included in this study. The primary outcome was the development of BPD. Secondary outcomes include: feeding intolerance, mortality, time to reach enteral feeds of 120 ml/kg per day for ≥ 3 days, days required to physiological weight gain, patent ductus arteriosus, intraventricular hemorrhage, retinopathy of prematurity, duration of hospital stay.

**Sample Size Statistical Analysis:** Probiotics group (n = 59) and the placebo group (n = 60) included in this study. After collection, data were entered into a personal computer then edited, analyzed, plotted and were presented in tables. Quantitative data was expressed as mean ± SD and categorical data was presented as proportion. Categorical scale was analyzed by using Chi square test and continuous scale was analyzed by t test. Data was analyzed using the statistical package for social sciences (SPSS) version 25. P value <0.05 was considered as level of significance.

**Results**

Between 2019 and 2021, 119 infants born ≤ 35 weeks gestation, weighing ≤ 2000 g were randomized to the probiotics group (n = 59) or the placebo group (n = 60). The baseline characteristics of the two groups are shown in Table 1.

**Table 1:** Baseline Characteristics of enrolled neonates (N=119)

| Characteristics | Probiotics group, n= 59 | Placebo group, n= 60 | P value |
|---|---|---|---|
| Gestational age, wk, mean (SD) | 31.49 ±2.18 | 31.82 ± 1.90 | 0.39 |
| ≤32 wk, n (%) | 36(61) | 37(61.7) | 0.99 |
| >32- 34wk, n (%) | 22(37.3) | 22(36.7) | |
| >34 wk, n (%) | 1(1.7) | 1(1.7) | |
| Birth weight, g, mean (SD) | 1417.80 ± 306.91 | 1502.03 ± 265.19 | 0.11 |
| <1500 g, n (%) | 35(59.3) | 30(50) | 0.59 |
| 1500- 1800 g, n (%) | 19(32.2) | 24(40) | |
| ≥ 1800 g - ≤ 2000g, n (%) | 5(8.5) | 6(10) | |
| Male, n (%) | 24(40.7) | 32(53.3) | 0.17 |
| Multiple births, n (%) | 13(22) | 15(25) | 0.70 |
| Cesarean delivery, n (%) | 47(79.7) | 48(80) | 0.96 |

**Table 2:** Baseline Characteristics of mothers (n=119)

| Characteristics | Probiotics group, n= 59 | Placebo group, n= 60 | P value |
|---|---|---|---|
| **Maternal age, n (%)** | | | |
| < 30 yr | 14 (23.73) | 10 (16.66) | 0.40 |
| >30 yr | 45 (76.27) | 50 (83.34) | |
| Premature rupture of membrane (PROM) | 22 (37.20) | 26 (43.33) | 0.23 |
| Received antenatal corticosteroid | 52 (88.13) | 55 (91.66) | 0.54 |
| Maternal diabetes | 20 (33.89) | 32 (53.33) | 0.32 |
| Maternal hypertension | 31(52.54) | 35 (58.33) | 0.38 |

**Table 3:** Primary outcome of infants (N=119)

| Development of BPD | Probiotics group, N=59, n (%) | Placebo group, N=60, n (%) | P value |
|---|---|---|---|
| Yes | 1(1.7%) | 8(13.3%) | **0.016** |
| No | 58(98.3%) | 52(86.7%) | |
| Total | 59(100.0) | 60(100.0) | |

There was significant difference in the development of BPD (1.7 vs 13.3%, P = 0.016) in probiotics and placebo group (Table 3).

**Table 4:** Other secondary outcomes and morbidities (N=119)

| | Probiotics group, n= 59 | Placebo group, n=60 | P value |
|---|---|---|---|
| Mortality, n (%) | 8(13.6) | 17(28.3) | 0.048 |
| Hospital stay, days, mean ± SD | 12.66 ± 6.69 | 17.85 ± 10.28 | 0.016 |
| Days to full enteral feeds, mean (SD) | 7.96 ± 4.63 | 13.60 ± 7.55 | 0.003 |
| Weight gain, n (%) | 29 (49.2) | 12(20.0) | 0.001 |
| Feeding intolerance, n (%) | 7 (11.9) | 17(28.3) | 0.025 |
| PDA, n (%) | 5(8.5) | 5(8.3) | 0.978 |
| IVH, n (%) | 3(5.1) | 3(5.0) | 0.983 |
| ROP, n (%) | 8(13.6) | 9(15) | 0.822 |

Mortality, time to reach full enteral feeds, feeding intolerance and duration of hospital stay were less in probiotics group and it is statistically significant. Weight gain was statistically significant in probiotics group. There was no significant difference in patent ductus arteriosus, intraventricular hemorrhage and retinopathy of prematurity between two groups (Table 4).

## Discussion

In our study, we found a protective effect of probiotics on BPD in preterm infants with gestational age less than 35 weeks. Probiotics are supplements of living micro-organisms that colonize the gut. Proper probiotics can confer a benefit on the host by regulating local and systemic immunity and increasing anti-inflammatory cytokines [22]. We did the study to observe the effect of probiotics on BPD as the primary outcome. We found that the use of probiotic was associated with reduced BPD in preterm infants < 35 weeks of age. Several meta-analyses of randomized controlled studies have shown that the probiotics supplementation can reduce neonatal mortality, necrotizing enterocolitis, and late-onset sepsis, as well as the time to achieve full enteral feeding in preterm infants [23–25]. Inflammatory events such as necrotizing enterocolitis and late-onset sepsis are also important influencing factors of BPD, so the preventive effect of probiotics on BPD is also worth expecting. Recently, a meta-analysis reported that available evidence could not support any significant effect of probiotics on reducing the incidence of BPD [26]. The protective effect of probiotics on BPD may have several hypothesized mechanisms: 1. Premature infants have immature immune systems that cannot balance the pro-infammatory responses, leading to a decrease in the number of regulatory T cells (Tregs) that constitute anti-inflammatory lymphocyte subsets and a higher proportion of activated pro-inflammatory T cells, which is an important cause of BPD. Probiotics appear to improve T cells production, expansion, and activity while reducing the activation of pro inflammatory lymphocyte subsets [27, 28]; 2. Probiotics can reduce the occurrence of BPD by regulating intestinal flora (29); 3. In the NEC experiment, the combined effect of hyperoxia and suboptimal nutrition had an adverse effect on the level of lung vascular endothelial growth factor (PVEGF). Probiotics can improve the nutritional status of infants, help to improve lung vasculogenesis and prevent BPD [25, 27]. 4. In addition, the performance of probiotics also help to reduce the incidence of BPD [30]. Other favourable effects reported include reduced time to full enteral feeds, improved weight gain in the probiotic versus placebo group (Mohan R, et al, 2008). In this study we found feeding intolerance and hospital stay were less in probiotics group which was statistically significant. More days required to reach full enteral feed in case of placebo group. Weight gain is significantly more in probiotics group in this study group. This result was similar to the study of Deshpande *et al*., where the time to full oral feeds was significantly shorter in the probiotic group (weighted mean difference -2.74 days, 95% CI -4.98 to -0.51) than in controls. Bin Nun *et al*. did not find any difference between the study and control group in terms of early oral feeding (p=0.13). In this study, the mean duration of hospital stays was significantly shorter in study group compared to control group (p = 0.016). This result was similar to that of the study by Samanta *et al*. where the duration of hospital stay was significantly shorter in probiotic group than that of control group 17.17 ±3.23 days versus 24.07 ±4.00 days. Though, Lin *et al*. did not find any significant difference in the hospital stay between case (46.7 ±27.1days) and control (46.5 ±26.1 days) in his study. Lin *et al*. set 34 weeks (not less than that) as preterm and 1500 grams as low birth weight which might produce the probable result. It requires extended research to find out the exact reasons behind this.

## Conclusions

Our study showed that oral supplementation of probiotics is effective in reducing the incidence of Bronchopulmonary dysplasia in preterm infants. We also found feeding intolerance and mortality is less in probiotics group. Time to reach full enteral feeding and hospital stay also more in placebo group.

## Conflict of Interest

Not available

## Financial Support

Not available

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