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Research Article

Role of Probiotics in Prevention of Necrotizing Enterocolitis in Preterm Infants: A Double-Blind Randomized Controlled Trial

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Abstract

Background and objective: Necrotizing Enterocolitis is a common complication of prematurity, causing morbidity and mortality. There is scarcity of documentation on the safety or efficacy of routine use of probiotics. Therefore, incidence of NEC, feed intolerance, and all-cause mortality, can be decreased by using probiotic supplementation is the aim of the study.

Methods: This prospective double-blinded, placebo controlled, randomized trial was conducted in a single center which compared routine administration of a probiotic with a placebo. The composition of each probiotic capsule was (500 mg blend)- Lactobacillus acidophilus- 2 billion cfu, Lactobacillus bulgaricus-1 billion cfu, Bifidobacteriumbifidum-1 billion cfu, Fructo-Oligosaccharide- 100 mg and each placebo capsule was (500 mg blend) Pregelatinised Starch (Starch-1500). The NICU admitted infant who were ≤ 35 completed weeks, weighing ≤ 2000 gm were included in this study. The development of NEC (stage II and III) was the primary outcome. Feeding intolerance, mortality, time to establish full enteral feeds, days required to physiological weight gain, development of patent ductus arteriosus, intraventricular hemorrhage, retinopathy of prematurity, bronchopulmonary dysplasia, duration of hospital stay were the secondary outcome.

Results: Among 119 preterm infants from NICU, BSMMU between 2019 and 2021, randomization was done. Probiotics group had statistically significant low incidence of NEC, mortality, feeding intolerance than the placebo group. Whether in placebo group, there were statistically significant more hospital stay, more days to reach full enteral feeds and less weight gain.

Conclusions: This randomized, double blinded, placebo-controlled trial has a proven clinical significant effects of probiotics on the rate of development of NEC in low birth weight infants. Further large clinical trial is required to establish the safety and efficacy of probiotics in this vulnerable population.

Keywords: Probiotics; Prevention; Necrotizing enterocolitis; Preterm infants

Introduction

World Health Organization estimates the number of babies born with low birth weight, currently 25 million babies annually [1] and more than 80% of neonatal deaths were in low-birth-weight babies [2]. Necrotizing Enterocolitis (NEC) is a serious gastrointestinal comorbidity of preterm low birth weight babies [3]. NEC is a worldwide problem in very low birth weight infants, with highly variable incidence affecting 2.6% to 28%, and causing 1% to 5% of admissions to the Neonatal Intensive Care Unit (NICU) [4]. Prematurity and low birth weight is the most frequent risk factors of NEC. Preterm accounts over 90% of neonates having NEC. The global incidence of NEC is 1% to 5% of the live births [2]. The exact pathogenesis of NEC is unknown but multiple factors are contributing like gastrointestinal immaturity, enteral feeding (especially formula feeding), presence of bacteria, and inflammation in the gastrointestinal tract. Inflammation in the gut is triggered by host-pathogen interactions that result in bowel injury, leading to the pathogenesis of the disease [5]. Despite potent antimicrobial agents mortality (Attributable mortality of 15% to 30%) and morbidity (including surgery in 20% to 40% of infants and delayed neurodevelopment) are significantly increased by NEC. Therefore, the agents that can modulate inflammation and enhance host defences may improve the outcome of infants with neonatal sepsis or NEC [6]. Researchers are trying different preventive strategies like probiotics, exclusive breast milk feedings, steroids, platelet activating factor and their receptor antagonistic [7]. Probiotics can be defined as live exogenous micro-organism delivered enterally that improve mucosal defences of the gastrointestinal tract and potentially provide

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benefit to the host. *Lactobacillus* and *Bifidobacterium* are the most frequently used probiotics. Interest in the potential health benefits of protective colonization of the gastrointestinal tract of preterm infants is increasing [8]. The overgrowth of pathogens might be prevented by inducing colonization of the bowel with nonpathogenic bacteria (probiotics) species which are normal resident of the gut of preterm and full-term infants. Particularly, probiotics compete with other microbes for binding sites and substrates in the bowel and a wide range of antimicrobial substances such as bacteriocins, microcins, reuterin, hydrogen peroxide and hydrogen ions are produced [9]. Probiotics can be an attractive alternative to many of the more aggressive therapeutic options; it is a simple, non-invasive attempt to recreate a normal flora without any disruption of nature; and it appears to be effective in preventing a major cause of morbidity in low-birth-weight infants. The mechanisms by which probiotics protect the host from gastrointestinal and urinary infections 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 [10]. As there is the limited number of clinical trials defining the optimal strains, timing, dosage, and duration of probiotics administered to preterm infants, these issues need to be evaluated in trials. Few studies of Bangladesh showed significant efficacy of probiotics in the prevention of NEC [11,12]. But the dose, count of organism, and exact duration of treatment were not specified by those studies. There is also scarcity of regional studies on this issue. So, the primary objective of this study was to determine the role of oral probiotics in the prevention of necrotizing enterocolitis in preterm infants.

Methodology

Patients and study design

This RCT was conducted in Department of Neonatology of BSMMU after approval by institutional review board over a period of eighteen months. Between 2019 and 2021, 119 infants born ≤ 35 weeks gestation, weighing ≤ 2000 g was randomized to the probiotics group (n=59) or the placebo group (n=60). 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 infants were assigned to either Group A or Group B. Group A was the intervention group who received probiotics along with regular breast feeding and standard care; and Group B was the control group who 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, pharmaceutical company revealed that, which group got probiotics.

The probiotic volume was 0.5 ml containing 3×10^9 CFU and introduced once daily from first feeding by dropper or tube till discharged. Each probiotic capsule contained *Lactobacillus acidophilus*- 2 billion cfu, *Lactobacillus bulgaricus*- 1 billion cfu, *Bifidobacteriumbifidum*-1 billion cfu, Fructo-Oligosaccharide-100 mg and each placebo capsule contained Pregelatinised Starch (Starch-1500). During hospital stay, in charge of caring the infants was the principal investigator and the research assistant. All the clinical care was given as per protocol. Each infant's gestational age, birth weight, sexes, type of delivery were recorded. Diagnosis of NEC was diagnosed on the basis of modified Bell's classification.

Primary and secondary outcomes

Infants born ≤ 35 completed weeks, weighing ≤ 2000 g admitted in NICU were included in this study. The development of NEC (stage II and III) was the primary outcome. Feeding intolerance, mortality, time to reach enteral feeds of 120 ml/kg per day for ≥ 3 days, days required to physiological weight gain, development of patent ductus arteriosus, intraventricular hemorrhage, retinopathy of prematurity, bronchopulmonary dysplasia, duration of hospital stay were the secondary outcome.

Sample size and statistical analysis

Data were entered into a personal computer then edited, analyzed, plotted and were presented in tables. Statistical Package for Social Sciences (SPSS) version 25 was used; categorical data was analyzed by using Chi square test and continuous data was analyzed by t test. P value <0.05 was considered as statistically significant.

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.

There was significant difference in the development of NEC (1.7 *vs.* 13.3%; (95% CI-0.741 to 0.30.37), P=0.016) in probiotics and placebo group (Table 2).

Mortality, time to reach full enteral feeds, feeding intolerance, duration of hospital stay were statistically significant less in probiotics group where weight gain was more in probiotics group. No significant differences was found in the development of patent ductus arteriosus, intraventricular hemorrhage, retinopathy of prematurity, bronchopulmonary dysplasia, in between two groups (Table 3).

Discussion

Probiotics are live exogenous micro-organism delivered enterally that improve mucosal defences of the gastrointestinal tract and potentially provide benefit to the host [13]. Recent systematic review

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

	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 wk-34 wk, 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 g-1800 g, n (%)	19 (32.2)	24 (40)	
≥ 1800 g- ≤ 2000 g, n (%)	5 (8.5)	6 (10)	
Male, n (%)	24 (40.7)	32 (53.3)	0.17
Multiple births, n (%)	13 (22)	15 (25)	0.7
Cesarean delivery, n (%)	47 (79.7)	48 (80)	0.96

Table 2: Primary outcome of infants (N=119).

Development of NEC	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)	

Table 3: Other secondary outcomes and morbidities (N=119)

	Probiotics group, n= 59	Placebo group, n=60	95% CI	P value
Mortality, n (%)	8(13.6)	17(28.3)	2.52(0.99-6.4)	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)	0.26(0.11- 0.58)	0.001
Feeding intolerance,n(%)	7 (11.9)	17(28.3)	2.93(1.11-7.73)	0.025
PDA, n (%)	5(8.5)	5(8.3)	0.98(0.27-3.59)	0.978
IVH, n (%)	3(5.1)	3(5.0)	0.92(0.19- 5.08)	0.983
ROP, n (%)	8(13.6)	9(15)	1.12(0.40- 3.15)	0.822
BPD, n (%)	1(1.7)	2(3.3)	2(0.18-22.67)	0.569

of probiotic supplementation in preterm infants suggest that enteral probiotics significantly reduces the incidence of severe Necrotising Enterocolitis and mortality [14]. In this study, we found that there is a significant low rate in the development of NEC and low mortality in probiotics group than the placebo group. Similar result is found with the use of probiotics in the study done by Mannan et al. [11]. There is also a lower incidence of NEC in the probiotics group compared to control group in a study of Lin et al. [8]. Similarly Bin-Nun et al. found a significantly lower incidence of NEC in the probiotics group [15]. This is also established by a meta-analysis of 20 randomized, controlled trials, Wang et al. where probiotics supplement was associated with a significantly decreased risk of NEC in preterm VLBW infants which also correlates with the findings of another meta-analysis of 11 randomized, controlled trials Deshpande et al. [16]. But Mihatsch et al. [17] found statistically insignificant result between the probiotics group and the placebo group of their study similar with the study of Sari et al. [18]. As multiple strains were used in present study, their results differed from this. Secondary beneficial effects reported include reduced time to full enteral feeds, improved weight gain [19], less feeding intolerance and hospital stay in the probiotic versus placebo group. Deshpande et al. [16] has the similar findings where the time to full oral feeds was significantly shorter in the probiotic group. But there was no difference between the study and control group in terms of early oral feeding by the study of Bin-Nun et al. Present study shows the mean duration of hospital stays was significantly shorter in study group compared to control group which correlate with the study by Samanta et al. [20] where the duration of hospital stay was significantly shorter in probiotic group than that of control group. Though, no significant difference was found in the hospital stay between case and control in Lin et al. study. As Lin et al. [8] set lower gestational age as preterm and lower birth weight, their result differs from present study. Infants (both case and control) of the study had longer hospital stay than usual due to prematurity and sepsis (in some cases) which need further research to find out the exact reasons.

Conclusions

Oral supplementation of probiotics is effective in reducing the incidence of necrotizing enterocolitis in preterm infants. Feeding intolerance, mortality is also less in probiotics group. Time to reach full enteral feed, hospital stay more in placebo group. However, these results could represent an important preliminary work and justify further evaluation of the clinical effects of probiotics in a population with lower birth weight.

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