

Efficacy of Bifidobacterium Infantis versus Bifidobacterium Bifidum Probiotic in the Prevention of Necrotizing Enterocolitis in Preterm Neonates

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Abstract

Background: To compare the efficacy of Bifidobacterium Infantis with Bifidobacterium Bifidum in terms of frequency of necrotizing enterocolitis in preterm neonates.

Methods: In this comparative cross sectional study 652 preterm Neonates with gestational age of less than 37 weeks of both genders, were included. They were divided in two groups, one group treated with Bifidobacterium Bifidum and other with Bifidobacterium Infantis. Both groups were managed and monitored for the development of clinical evidence of necrotizing enterocolitis during hospital stay.

Results: Comparison of efficacy in both the groups showed that 92.94 % (n=303) in Bifidobacterium Infantis Group and 96.63 % (n=315) in Bifidobacterium Bifidum Group were treated effectively, p value was calculated as 0.03 showing a significant difference.

Conclusion: Efficacy of Bifidobacterium Bifidum is significantly higher when compared with Bifidobacterium Infantis in terms of frequency of necrotizing enterocolitis in preterm neonates.

Key Words: Preterm neonates, Bifidobacterium Infantis, Bifidobacterium Bifidum

Introduction

Necrotizing enterocolitis (NEC) is a devastating intestinal disease of neonates, and clinical evidence suggests the beneficial effect of probiotics in NEC prevention. It is a digestive tract emergency in preterm neonates.¹ It is the varying degree of mucosal or transmural necrosis of intestine.² It affects 15% of very low birth weight preterm neonates.³ Its mortality rate is 15-30%.⁴ Pathogenesis of NEC is multifactorial. Main factors increasing its risk are prematurity, enteral feeding, colonization by pathogenic microorganisms such as E.coli, Klebsiella, Clostridium perfringens, Staphylococcus and Rotavirus.⁵⁻⁷ There is no specific

treatment for NEC. It is managed with supportive treatment.⁸ Probiotics are alive organism when given in adequate amounts and are beneficial to the host.⁹ Probiotics have been recently used in the prevention of NEC in preterm neonates. Commonly used probiotics for this purpose are Bifidobacterium, Lactobacillus, Saccharomyces and Streptococcus thermophilus. Their use has shown reduction in the frequency and mortality caused by necrotizing enterocolitis.¹⁰ A study conducted at CHA Gangnam Medical Center Seoul Korea showed that incidence of NEC without probiotics prophylaxis (control group) was 15.8 % and after giving probiotics prophylaxis (study group) containing Bifidobacterium infantis the incidence decreased to 5.5 %.¹¹ In another study at University of Arizona showed incidence of NEC without probiotics prophylaxis (control group) was 6.45 % and after giving probiotics prophylaxis (study group) containing Bifidobacterium bifidum the incidence decreased to 1.84%.¹² The aim of present study was to compare two groups of probiotics and to establish which one is more effective. The effective probiotic can be used in preterm neonates for the prevention of NEC especially in Neonatal intensive care units.

Patients and Methods

It was comparative cross sectional study conducted at department of Paediatrics Benazir Bhutto Hospital, Rawalpindi from November 2014 to April 2015. A total number of 652 patients were recruited by consecutive (Non probability) sampling. All the Preterm Neonates having less than 37 weeks of gestation of both genders were included in the study. Preterm neonates in which enteral feeding could not be established in first week of life, who already have developed necrotizing enterocolitis, who were made nothing per oral for more than 3 weeks and neonates with other co-morbid conditions like birth asphyxia, cyanotic congenital heart disease and congenital anal atresia were not included. Written informed consent was taken from parents. Patients were divided in two groups. Group

A(326 patients) and Group B(326 patients). Study group (A), receiving probiotic Bifidobacterium Infantis and study group (B) receiving probiotic Bifidobacterium Bifidum. Probiotic used in the study group (A) was Hiflora sachet which is powder for oral suspension containing 0.75×10^9 viable cells. Neonate in group (A) received probiotic Hiflora ½ TSF or 0.35×10^9 viable cells two times a day mixed with milk. Probiotic used in control group (B) was Bifedo syrup, powder for oral suspension containing viable cells 1×10^6 . The neonates in study group (B) received probiotic Bifedo ½ TSF or 0.5×10^6 viable cells two times a day mixed with milk. Both groups were managed with same supportive care including incubator care, intravenous fluids electrolytes and calories, maintenance of thermo neutral environment, prevention of hypoxia, acidosis, scheduled touch times except for different probiotics in both groups and monitored for the development of NEC during hospital stay which was diagnosed if 4 of the following 6 criteria will be there including bradycardia(HR< 80/min), nasogastric aspiration, abdominal distension, occult blood in stool, thrombocytopenia, Pneumatosis Intestinalis on abdominal radiographs. Efficacy was determined by the frequency of neonates who were given probiotics and prevented from developing necrotizing enterocolitis within 14 days of hospital stay. Chi square test was applied to compare both groups for presence of NEC i.e. efficacy. p-value < 0.05 was significant.

Results

Three hundred and twenty six patients were included in Group A and B having mean age 4.08 ± 2.41 and 4.15 ± 2.44 hours of life respectively. Gender distribution showed that 64.11 % (n=209) in Group-A and 66.56% (n=217) in Group-B were male while 35.89% (n=117) in Group-A and 33.44% (n=109) in Group-B were females. Mean gestational age was calculated as 33.32 ± 2.41 and 33.46 ± 2.43 weeks in Group-A and B respectively (Table I).

Table 1. Comparison of efficacy in both groups (n=652)

Efficacy	Group-A (n=326)		Group-B (n=326)	
	No of patients	%	No of patients	%
Yes	303	92.94	315	96.63
No	23	7.06	11	3.37
Total	326	100	326	100

p value=0.03

Discussion

In present study comparison of efficacy in both groups showed that 92.94% (n=303) in Group-A and 96.63% (n=315) in Group-B were treated effectively (p= 0.03; showing significant difference). A recent study has shown that incidence of necrotizing enterocolitis without probiotics prophylaxis was 15.8% and after being treated with probiotics prophylaxis containing Bifidobacterium Infantis the incidence decreased to 5.5%.¹ Study by Khailova L et al showed that oral administration of B. bifidum reduces severity and incidence of NEC. Ileal damage was significantly reduced , with $p \leq 0.01$ to a median histological score of 1.0 as compared 2.0 in the NEC group, and the incidence of NEC was markedly decreased to 17% in the NEC and B.¹² bifidum group compared with the NEC group with an incidence of 57%. B.Bifidum increases intestinal expression of Toll-like receptors-2 in NEC. In the intestine, interaction between enteric bacteria and the host is mediated in part by Toll-like receptors. Appropriate bacterial colonization and the activation of these receptors play a key role in the pathogenesis of NEC, and administration of probiotics increases the expression of these receptors in the intestinal epithelium. B. bifidum treatment of NEC not only stimulates expression of these receptors in the ileal epithelium but also significantly reduces the incidence of NEC (from 57 to 17%).¹²

Ability of bacteria to cross epithelial cell layers is thought to be a crucial step in the cascade of events leading to the development of NEC.^{13,14} Bacterial interactions with the premature intestine play a major role in the pathogenesis of NEC. Studies found a strong relationship between delay and low colonization of commensal flora and proliferation of pathogenic flora in the immature gut, predisposing preterm infants to develop NEC.^{13,17} Caplan et al and But el et al showed that bifidobacterial supplementation resulted in intestinal colonization and subsequent reduction in NEC-like lesions.^{18,19} Bifidobacteria and lactobacilli have been shown to inhibit intestinal colonization of pathogenic microorganisms, to produce protective nutrients, and to prevent translocation of other bacteria.²⁰

A study by Riedel CU et al showed that B bifidum not only have role in down regulation of pro-inflammatory cytokines but also have role in intervention in inflammatory disorders of the gastrointestinal tract. Bifidobacteria acts by locking of lipopolysaccharide induced NF-κB activation and prevention of amplification of the pro-inflammatory signal after exposure to lipopolysaccharide. Ability to

inhibit lipopolysaccharide induced NF- κ B activation is strain-dependent and strains of *B. bifidum* are promising candidates for probiotic intervention in inflammatory disorders of the gastrointestinal tract.²¹ In another study Lin HC et al incidence of necrotizing enterocolitis without probiotics prophylaxis (control group) was 6.45% and after giving probiotics prophylaxis (study group) containing *Bifidobacterium Bifidum* the incidence decreased to 1.84%.¹²

Wu SF et al observed lower mortality rate in groups treated with *B Bifidum* compared with controls. Research evidence indicates that the intestine of preterm infants appears far more sensitive to stimuli that induce interleukin-8 production .IL-8 is a critical component of systemic inflammatory responses in neonates resulting from NEC and studies showed that probiotics could inhibit IL-8 production.²²

In a study conducted by Repa A et al showed that the probiotic *B. infantis* had no significant impact on the overall NEC rates when compared with other *Bifidobacterium* strains in a prospectively followed middle European cohort of very low birth weight (VLBW) infants. In a subgroup analysis, *B. infantis* significantly reduced NEC in infants fed breast milk but was ineffective in infants exclusively fed formula. Author concluded that the efficacy of *B. Infantis* varies strongly between centers and was of low efficacy in population of VLBW infants. A preventive effect against NEC was only present in infants fed breast milk in the first 2 week of life, but not in infants exclusively fed formula, suggesting that the efficacy of probiotics is strongly influenced by feeding practices.²³ Studies reported a decrease in mortality and severity of NEC, following probiotics *L. acidophilus* and *B. infantis*, prophylaxis.^{24,25, 26}

Conclusion

Efficacy of *Bifidobacterium Bifidum* is significantly higher when compared with *Bifidobacterium Infantis* in term of frequency of necrotizing enterocolitis in preterm neonates.

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