

EFFECTS OF PROBIOTICS ON NECROTIZING ENTEROCOLITIS IN VERY LOW BIRTH WEIGHT INFANTS

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Summary

NEC is the most commonly occurring gastrointestinal emergency in preterm infants. This prospective study was carried out in Neonatal unit of Bangabandhu Sheikh Mujib Medical University, Dhaka from June 2006 to May 2007 to see the effect of probiotics on Necrotizing Enterocolitis (NEC) in very low birth weight. In this study total 120 very low birth weight (VLBW) newborn enrolled among them 60 were cases and 60 were control. Out of 120 study population 17 (14%) newborn development NEC in this study. Stage II NEC developed in 4 (6%) babies among cases and 11 (18.33%) neonate among control. Two (3.3%) stage III NEC among the control group but none in the probiotics group. In this study death occurred in 2 (3.3%) were of cases and 7(11%) in control group. Sepsis developed in 35 babies (58%) among cases and 40 (66%) babies in control group. Thus probiotics inhibit growth of pathogens and has preventive role in NEC fatality.

Introduction

Necrotizing enterocolitis (NEC) is an acquired neonatal disorder representing an end expression of serious intestinal injury after a combination of vascular, mucosal and metabolic insults to a relatively immature gut. NEC is predominantly a disorder of preterm infants, with an incidence of 6-10% in infants weighing <1500g¹. The incidence increases with decreasing gestational age. 70% to 90% of cases occur in high-risk low birth weight infants^{1,2}. The precise pathogenesis of NEC is unknown but widely considered as multi-factorial disease. Three major factors have been proposed: the presence of a pathogenic organism, the challenge of enteral feeding and altered enteric mucosa integrity².

The presentation may vary from feeding intolerance, abdominal distension, grossly bloody stools, peritonitis, and perforation. NEC may also present with labile temperature, apnea, bradycardia and other signs of suspected sepsis^{2,3}. Strategies for prevention of NEC are enteral antibiotics, human milk feeding, enteral administration of IgG and IgA together and oral administration of probiotics is an appealing strategy for preventing NEC^{2,4}. Probiotics bacteria are defined as live microbial supplements that colonize the intestine and provide benefit to the host^{5,6}. To be a probiotics, a bacterial strain must fulfill several criteria. It must be healthy, resist acid and bile, adhere to the intestinal epithelial cells, modulate immune responses and resist technological processes^{3,6}. Probiotics organism consist primarily of strains of Lactobacillus, Bifidobacterium and Streptococcus^{6,7,8}. Probiotics have been advocated for prevention or treatment of variety of disorders including rota virus infection, antibiotics associated diarrhea and traveler's diarrhea^{7,8}.

Lin et al.⁵ demonstrate that prophylactic administration of probiotics mixture of Lactobacillus acidophilus and Bifidobacterium infantis given to very low birth weight (VLBW) infants reduces the incidence of all cases NEC as well as severe stage III NEC. VLBW infants often have paucity (oligocolonization) of normal enteric bacterial species and delayed onset of colonization compared with term infants. The aseptic NICU environment, which paradoxically has many resistant enteric organisms, may predispose VLBW infants to the development of aberrant fecal flora⁹. In addition, the most VLBW infants receive prophylactic parenteral broad-spectrum antibiotics after birth, which contributes to delayed, aberrant and antimicrobial-resistant bacteria or fungal colonization^{8,9}. The potential mechanisms by which probiotics may protect high risk infants from developing NEC include reduced colonization by potential pathogens, increased barrier to bacterial and toxin translocation, altered intestinal inflammatory response enhanced enteral nutrition^{10,11}.

Aims and objectives

1. To see the efficacy of probiotics in prevention of NEC in VLBW infants.

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2. To observe duration of hospital stay.

Inclusion Criteria : 1. VLBW babies 2. who started to feed and stable 7 days after birth.3. Male and female babies.

Exclusion criteria : 1. Any congenital anomaly 2. Severe perinatal asphyxia 3. Ventilated baby 4. Critically ill newborn

Variables : 1. Birth wt. 2. clinical features of NEC: abdominal distension, malena, abdominal wall erythema, visible peristalsis or mass .3. Radiological parameter pneumatosis intestinalis, free air under diaphragm or portal vein

Materials and methods

It is a prospective randomized control trial study. Period of study: Jun 2006 to May 2007. Place of study: Neonatal unit, Department of Paediatrics, Bangabandhu Sheikh Mujib Medical University, Dhaka. Sample size was 120 VLBW infants were included in the trial. They were divided into two groups : 60 VLBW infants, who were fed with probiotics with breast milk(case), 60 VLBW infants, who started to feed enterally and survived beyond the seventh day after birth (control).

Procedure

After taking informed parental consent, VLBW infants were randomized into case or control groups by a randomized number table sequence. The cases were fed with (*Lactobacillus*, *Bifidobacterium* and *Streptococcus*) 125mg/kg/dose twice daily with breast milk until discharge. Probiotics was given from the initiation of milk feed^{12,13,14}. The control group was fed with breast milk without probiotics. Feeding was started when infant's vital signs will be stable, active bowel sound without abdominal distension, no bile or blood from the nasogastric tube, and no indwelling umbilical venous catheter for at least 24 hours. Depending on the birth weight and gestational age of the infant, a certain amount of breast milk was started as test feed. Feeding was advanced slowly if tolerated, with no more than 20ml/kg/day increment^{15,16}. Feeding was stopped if there was any sign of feeding intolerance (defined as the presence of gastric aspirate in amount that will more than 30% to the previous feeding, repeated vomiting and significant abdominal distension). NEC is categorized by modified Bell's classification. All statistical analysis is performed with the software SPSS 12 for windows.

Treatment

Initial management is conservative. Medical treatment with stopping feeds and providing enteric decompression. Blood cultures sent prior to antibiotics therapy. Empirical antibiotics cefotaxime and amikasin along with metronidazole given in all cases. Antibiotic regime change according to culture sensitivity. Nutrition is provided parenterally with glucose, essential amino acid for ten to fourteen days. Surgical treatment is required for perforation and intestinal necrosis^{17,18}.

Results

Table I : Distribution of newborns depending on inborn or outborn.

	Inborn	Outborn
Case (n=60)	46	14
Control(n=60)	49	11

Table I : Shows most of the babies among cases and control was inborn.

Fig 1: Distribution of sex in enrolled affected newborns

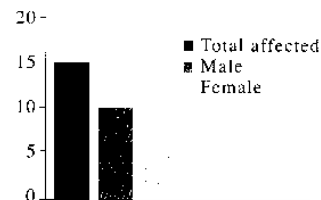


Fig 1: shows among 17 affected newborn 10 (88%) were male & 7 (12%) were female.

Table II: Distribution of case and controlled in NEC stage II

	NEC Stage-II	(%)	P Value
Case (n=60)	4	6.6	<.009
Control(n=60)	11	18.3	

Table II: Shows among 60 cases stage-II NEC developed in 4 (6.6%) cases 11(18.3%) babies developed stage-II NEC in control (n=60)group. P<.009 which is statistically significant.

Table III : Distribution of NEC in stage-III

	NEC Stage-III	(%)	P Value
Case (n=60)	0	0	<.001
Control(n=60)	2	3.3	

Table III: Shows none of the cases developed NEC stage-III and 2 (3.3%) of the control group developed stage- III NEC. $P < .001$ which is statistically significant.

Table IV: Distribution of Death among case and control

	Death	(%)	P Value
Case (n=60)	2	3.3	0.009
Control(n=60)	7	11	

Table IV: Shows among 60 cases 2 (3.3%) babies died and 7 (11%) newborn died in control group. $P < 0.009$ which is statistically significant.

Table V: Distribution of Sepsis in enrolled neonates

	NEC Stage-III	(%)	P Value
Case (n=60)	35	58	0.03
Control(n=60)	38	63	

Table V: Shows among 60 cases 35(58%) babies developed sepsis. In control group 38 (63%) neonate developed sepsis. P value is 0.03 which is not statistically significant.

Discussion

NEC is one of the most serious and devastating disease encountered in the neonatal intensive care unit (NICU). Intestinal microbiologic flora is an important factor in the host defense mechanism against bacterial infections. Un Hc et al⁴ demonstrated that gut colonization with limited numbers and species of bacteria is delayed in a sterile environment. They speculated that lack of an aseptic environment in the NICU resulted in intestinal colonization with absorption of intact bacterial toxin, which may damage the immature ileum, resulting in the development of NEC. Hoy et al⁷ and Millar et al observed both a quantitative and qualitative change in the fecal flora before the onset of NEC. Gewolb et al¹ reported that Bifidobacterium and Lactobacillus are found in the stool of <5% of extremely low birth weight infants within the first month of life. These data suggest that low colonization of Bifidobacterium and Lactobacillus in VLBW infants may serve as a predisposing factor in microbial infection. Potential mechanisms by which probiotics may protect high risk infants from developing NEC include an increased barrier to translocation of bacteria and bacterial products across mucosa, competitive exclusion of potential pathogens, modification of host response to microbial products and enhancing enteral nutrition

that inhibits the growth of pathogens such as Klebsiella pneumoniae, Escherichia coli, and Candida albicans. The incidence of NEC was lower in Probiotics group when compared with the control group 4 of 60 (6.6%) vs. 13 of 60 (21%) respectively. This findings is consistent with the findings of Lin HC et al⁴. Four (6.6%) babies in probiotics group and 11 (18.3%) in control group developed stage II NEC, Lin HC et al in their study found similar result. Stage III NEC developed in 2 (3.3%) babies in control and none in probiotics group which is consistent with the result of other study done by Lin HC. Study done by Lin HC et al⁴, they found death occurred from NEC was 9 (5%) which consistent with the result of our study. In our study death occurred in 2 (3%) in control 7 (11%) probiotics group. In a recent multi center double-blind study, 585 infants of <33 weeks gestational age or birth weight <1500g who survived >2 weeks were randomized to receive either placebo or Lactobacillus rhamnosus GG once a day from the start of feeds to the time of discharge. We used a live probiotics containing L acidophilus and B infants. Another difference is the age of study infants at enrollment: 1 week in our study and > 2 weeks in their trail. In this study showed that the study group has a lower incidence of NEC. The mechanism for the efficacy of probiotics in reducing the incidence of sepsis in VLBW neonate is probably similar to NEC and possibly a result of increased colonization of desirable microflora such as Streptococcus salivarius. Although Wagner et al suggested that safety issues of probiotics treatment need to be addressed in immuno deficient hosts such as neonates, we did not observe complications due to probiotics. However, our trail was not powered to evaluate safety in regards to the possible risk for Lactobacillus or Bifidobacterium sepsis.

Prior experience in VLBW infants treated with different probiotics preparations has sometimes suggested benefit. Kitajima et al⁶, administered Bifidobacterium to 150 infants and demonstrated high colonization rates and enhanced weight gain. Hoyos AB, 1999 in his study observed a significant reduction of NEC associated death in probiotics treated infants. Similar findings are also observed by Bin-Num et al⁸, that probiotics reduces the incidence and severity in the study group. In all of the most recent trials of probiotics, no adverse effects have been reported.

Conclusion

NEC remains one of the major challenges in neonatology, much knowledge has been accrued explaining its etopathogenesis and opening fresh eyes to its management and prevention. Breast milk in the prevention and treatment of NEC is every more firmly based. The worth of probiotics may be realized with additional data on its effect on immature gut of low birth weight babies.

Disclosure

All the authors declared no competing interests.

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