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Research Article

Role of synbiotics in the prevention of necrotizing enterocolitis in preterm neonates: a randomized controlled trial

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ABSTRACT

Background: Although survival of preterm neonates has improved in the surfactant era, necrotizing enterocolitis (NEC) continues to be a major cause of mortality and morbidity. A proposed strategy for the prevention of NEC is the administration of oral synbiotics. We evaluated the role of synbiotics in reducing the incidence and severity of NEC in preterm babies.
Methods: A prospective randomized control trial was conducted in preterm neonates <34 weeks of gestation. They were randomized into two groups. The neonates in the test group were fed with synbiotic sachet with breast milk, twice daily till they reach full feeds. The neonates in the control group were fed with breast milk alone. The primary outcome was incidence and severity of NEC.
Results: 200 preterm neonates were enrolled, 100 in the test group and 100 in the control group. The demographic and clinical variables were similar in both groups. The incidence of NEC was significantly lower in the test group (2 of 100 vs. 10 of 100). The incidence of stage 2 NEC was nil in the test group but 5 in control group. There were 2 cases of severe NEC (stage 3) in the control group and none in the test group. Incidence of sepsis was also significantly lower in the test group (28 of 100 vs. 42 of 100). Other secondary outcomes like age reached full feeds and duration of hospital stay were similar in both test and control groups.
Conclusions: Synbiotics fed enterally with breast milk reduced both the incidence and severity of NEC.

Keywords: Synbiotics, Necrotizing enterocolitis, Sepsis, Preterm

INTRODUCTION

Necrotizing enterocolitis is the most common and frequently dangerous gastrointestinal emergency in premature infants in the neonatal Intensive Care Unit (NICU).[1] Although 90% of infants who develop NEC are born premature, full-term and near-term infants also develop the disease.[2] Modern technology and advances in clinical care have improved our ability to sustain and support infants born prematurely, but the prevalence of NEC has not decreased.[2,3]

The maturity of the gastrointestinal system is directly proportional to gestational age. The preterm infant's gut is immature in multiple functions including motility, digestion, barrier defense function, intestinal permeability, immune defense and anti-inflammatory control.[4] Unlike the micro biome of the term infant, the preterm infant micro biome is less diverse and is predominated by Staphylococcus species, with Bifido bacterium species being less well represented.[5] This is due to the fact that preterm infants are primarily treated with a course of broad spectrum antibiotics.[6] Another

cause of disequilibrium in the intestinal micro biota is bacterial colonization from the intensive care environment.[7] These changes in the composition of the micro biome of the preterm infant can further alter the development of epithelial barrier mechanisms and gut immune function. Therefore, synbiotics, a group of organisms capable of improving this clinical picture, had been studied in order to fight disease progression.

Probiotics have been described as living organisms which, when included in the diet in adequate amounts, can bring health benefits to the host. Prebiotics are non-digestible dietary ingredient, usually polysaccharides and oligosaccharides that selectively promote the proliferation of beneficial bacteria. Combination of probiotics and prebiotics are known as synbiotics.[8] As microorganisms able to colonize the digestive tract by adhering to the intestinal epithelium, producing antimicrobial substances, and modulating the immune response and host metabolism, synbiotics have been discussed regarding their usefulness in necrotizing enterocolitis.[9,10]

The number of studies published that have evaluated the role of Lactobacillus and Bifidobacteria in the prevention of NEC is extremely low. Considering that the effects of synbiotics are species specific, it remains to be determined whether there are any synbiotic strains more suitable for preventing NEC in preterm infants.

METHODS

The present study was a prospective randomized controlled trial conducted at NICU of Basaveshwara medical college and hospital, Chitradurga, during the period July 2012 to December 2014. A sample size of 200 was selected by simple random sampling. Inclusion criteria were preterm neonates (gestational age <34 weeks), hemodynamically stable. Exclusion criteria were gestational age > 34 weeks, cardiorespiratory illness.

Synbiotic preparation used: RUBIC sachets manufactured by TIDAL health care limited. Each sachet of 1 g contains Lactobacillus acidophilus 300 million, Bifidobacterium longum 150 million, Bifidobacterium Bifidum 150 million, Streptococcus thermophiles, 150 million and fructo Oligosaccharide 100mg.

Two hundred babies were selected based on inclusion and exclusion criteria. Ethical approval from ethics committee has taken. Preterm neonates (gestational age <34weeks) who survived to feed enterally were eligible for the study. Of the 200 babies, 100 were in test group and 100 in control group. After informed parental consent, test group babies received regular feeds plus daily synbiotic supplement 125 mg/kg/dose twice daily mixed with expressed breast milk from the onset of enteral feedings till the baby reaches full feeds. The control group was fed with breast milk without the addition of synbiotics. Feeding was started when the infant had stable vital signs, normal bowel sounds without abdominal distension and no bile or blood from nasogastric tube.

A strict feeding protocol was followed for all study neonates. Depending on the birth weight and gestational age of the neonate, expressed breast milk is started at 10-20 ml/kg/day. The amount of feeding was advanced slowly if tolerated with no more than a 20 ml/kg increment per day upto 150-180 ml/kg/day. Feeding was stopped if there was any sign of feeding intolerance (defined as the presence of gastric aspirate in the amount that was more than half of previous feeding, or with abdominal distension). Standard practice guidelines as followed in our NICU for the care of these babies were carried out in both groups. On admission to NICU a septic work up which included complete blood count, C-reactive protein and blood cultures were done for all the babies. Whenever a study infant was suspected to have NEC, clinical status and abdominal films were reviewed and if the diagnosis of NEC was established, the newborn was assigned a score according to the Bell's staging criteria.

Results were analyzed by 't' test and one-way ANOVA for primary outcomes like incidence and severity of NEC in test vs. control groups and secondary outcomes like neonatal mortality, time to establish full enteral feeds (days) and duration of hospitalization (days).

RESULTS

There was no significant difference in the age of the patients between the test and the control groups. Both groups were similar with respect to age distribution. The number of male babies to female babies in test group was 60 and 40 and in control group was 55 and 45.

Study and control groups were compared for their age at admission, sex, birth weight, gestational age, mode of delivery, antenatal risk factors and age of initiation of feeds.

The infant's demographic and clinical characteristics did not differ between two groups. In the present study, majority of neonates were between 1.010-1.499 kg (67% in the test vs. 54% in the control). The mean weight in test group was 1.50 ± 0.89 kg and in control group was 1.43 ± 0.32 kg but did not show statistically significant difference between groups. Majority of neonates were between 28-32 weeks of gestations in both test and control groups. The mean gestational age in test group was 31.12 ± 1.93 weeks and in control group was 31.57 ± 2.05 weeks but did not show statistically significant difference between groups. Out of 200 babies 90% were appropriate for gestational age but did not differ between two groups. Antenatal risk factors also did not differ between two groups.

Table 1: Showing clinical outcome in both groups.

Parameter	Test group (n=100)	Control group (n=100)	P value
Weight (Mean ± SD)	1.50 ± 0.89 kg	1.43 ± 0.32 kg	0.485
Gestational age (Mean ± SD)	31.12 ± 1.93 weeks	31.57 ± 2.05 weeks	0.106
Development of NEC	2 (2%)	10 (10%)	0.017
Age of onset of NEC (Mean ± SD)	4 ± 1.41 days	3.8 ± 1.98 days	0.200
Stages of NEC			
Stage 1	2	3	0.023
Stage 2	None	5	
Stage 3	None	2	
Mortality	None	3	0.371
Development of sepsis	28%	42%	0.038
Duration of hospital stay (Mean ± SD)	13.66 ± 4.99 days	13.55 ± 5.09 days	0.878
Age reached for full feeds	9.78 ± 2.68 days	9.53 ± 3.24 days	0.554

Development of NEC and sepsis was significantly lower in test (synbiotic) group compared to controls. Among the test group which developed NEC is only stage 1 (2 cases) according to Bell's staging, whereas stage 1 (3 cases), stage 2 (5 cases), and stage 3 (2 cases) was noted in control group. And mortality was seen in control group. Sepsis was more in control group than test group.

DISCUSSION

Our study shows that oral synbiotics helps not only in reducing the incidence of NEC in preterms, but also the severity of NEC. Synbiotics will also help in decrease in NEC related mortality, neonatal sepsis in preterm babies.

A growing body of evidence from clinical trials has shown that administration of common synbiotics may reduce the incidence of NEC.[11-14] However, some studies have not shown such effects.[15,16] For example, Dani et al. conducted a multicentre randomized controlled trial in which the probiotic Lactobacillus GG [6×109 Colony-Forming Units (CFU)] was administered once daily from first feed to discharge day.[16] Although the probiotics group tended to have less NEC, urinary tract infection and sepsis compared with the control group, the differences were not statistically significant (1.4% versus 2.8%; 3.4% versus 5.2%; and 4.7% versus 4.1%, respectively). In contrast, Lin et al. found that the probiotic mixture of Lactobacillus acidophilus and Bifidobacterium infantis significantly reduced the severity and incidence of NEC (5% probiotics versus 12.8% control), however, there were some signals that probiotics may increase the risk of sepsis in infants weighing less than 750 g.[12] The variation among study results may be related to the differences in NEC incidence around the world because the incidence is lower in European countries compared with Asian countries.[17]

Necrotizing enterocolitis is a devastating condition that still has no exact etiology and no specific therapy. Prematurity is a predisposing risk factor for NEC. Preterm infants are known to have altered intestinal flora. Synbiotics are promising therapy in establishing normal intestinal flora in the preterm infant. The clinical trials to date have shown some benefit in the use of synbiotics for the prevention of NEC in preterm infants. The problem is that each clinical trial has treated different populations, used different outcome measures and used different synbiotic organisms. FDA approval of synbiotic preparations that have proven to decrease the incidence of NEC could significantly help to reduce this devastating disease. Synbiotics have the potential to become a clinical breakthrough in the prevention of necrotizing enterocolitis in the preterm infant.

Synbiotics hold real promise as an effective and safe preventive strategy, and this approach may soon become the standard of care for NICUs worldwide.

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