



Role of Oral Probiotics in Prevention of Necrotising Enterocolitis in Preterm Neonates in Hi-Tech Medical College and Hospital, Bhubaneswar

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Submitted: 01-03-2021

Revised: 07-03-2021

Accepted: 10-03-2021

ABSTRACT: BACKGROUND: Necrotising enterocolitis (NEC) is primarily a disease of premature infants, but may also be present in 10% of term and near term babies. It is the most common gastrointestinal (GI) medical/surgical emergency occurring in Preterm neonates.

OBJECTIVE: The objective was to study the role of oral probiotics in prevention of necrotising enterocolitis in preterm neonates.

METHOD: Prospective randomized controlled trial was done in Hi-Tech Medical College and Hospital, Bhubaneswar from September 2019 to August 2020. 150 preterm neonates were taken in the study period, out of which 75 in the test group and 75 in the control group were studied. The neonates in the test group were fed probiotics with breast milk twice daily till they reached Direct Breast Feeding. The neonates in the control group were fed only breast milk. Incidence and severity of NEC were measured.

RESULT: 150 neonates (study group n = 75, control group n = 75) were randomized. The incidence of NEC was lower in test group (6.6%) than the control group (16%). The severity of NEC was reduced in test group (stage 2 and 3 seen in 1.3%) than the control group (stage 2 and 3 seen in 9.3%). The mortality was also significantly lower in the test group compared to control group (0% versus 17%).

CONCLUSION: Probiotic supplementation has reduced the incidence and severity of necrotising enterocolitis in preterm neonates.

KEYWORD: Necrotising enterocolitis, Oral probiotics, Preterm neonate

I. INTRODUCTION:-

Necrotising enterocolitis (NEC) is primarily a disease of premature infants, but may also be present in 10% of term and near term

babies. It is the most common gastrointestinal (GI) medical/surgical emergency occurring in neonates.

NEC is an acute inflammatory disease of large intestine with a multiple factors and unclear etiology. The condition is characterized by intramural gas (pneumatosis) and variable damage to the intestinal tract ranging from mucosal injury to full-thickness necrosis and perforation.¹

Infants with NEC have a variety of signs and symptoms and may have an insidious or sudden catastrophic onset. The onset of NEC is usually in the 2nd or 3rd week of life but can be as late as 3 month in VLBW infants. Age of onset is inversely related to gestational age. The 1st signs of impending disease may be nonspecific, including lethargy and temperature instability, or related to gastrointestinal pathology, such as abdominal distention and gastric retention. Grossly bloody stools may be an indication for NEC and approximately 60% of neonates will have Hemocult-positive stools. The spectrum of illness is broad, ranging from mild disease with only guaiac-positive stools to severe illness with bowel perforation, peritonitis, systemic inflammatory response syndrome, shock, and death.

A very high index of suspicion in treating preterm at-risk infants is crucial. Plain abdominal radiographs are essential to make a diagnosis of NEC. The finding of pneumatosis intestinalis (air in the bowel wall) confirms the clinical suspicion of NEC and is diagnostic; 50-75% of patients have pneumatosis when treatment is started.²

Rapid initiation of therapy is required for suspected as well as proven cases of NEC. There is no definitive treatment for established NEC, so, therapy is directed at giving supportive care and preventing further injury with cessation of feeding, nasogastric decompression, and administration of intravenous fluids. Careful attention to respiratory



status, coagulation profile, and acid-base and electrolyte balances are important.

The mortality rate in NEC ranges from 10% to more than 40% in infants who weigh less than 1500 g, depending on the severity of disease, compared with a mortality rate of 0- 20% in babies who weigh more than 2500 g. This study aimed at evaluating the use of oral probiotics in prevention of NEC.¹

A meta-analysis was performed by Deshpande G et al. in 2010 to update the 2007 systematic review of randomized controlled trials of probiotic supplementation for preventing NEC in preterm VLBW neonates. A total of 11 (n = 2176) including 4 new (n = 783) trials were included in the meta-analysis. The risk for NEC and death was significantly lower. Risk for sepsis did not differ significantly. No significant adverse effects were reported. Trial showed 30% reduction in the incidence of NEC.³

A meta-analysis of probiotics for preventing necrotizing enterocolitis in preterm neonates was done by Yang Y et al which incorporated 27 RCTs. A total of 6655 preterm infants, including the probiotic group (n = 3298) and the placebo group (n = 3357), were eligible for inclusion. This meta-analysis has shown that, regardless of gestational age and NEC stage, probiotic supplementation could significantly reduce the risk of NEC in preterm infants. Analysis also indicated that such supplementation did not increase the incidence risk of sepsis or of mortality.⁴

A Cochrane meta-analysis study for the use of probiotics for prevention of necrotizing enterocolitis in preterm infants was done by Robinson J et al which included 24 trials. In a meta-analysis of trial data, enteral probiotics supplementation significantly reduced the incidence of severe NEC (stage II or more) (typical relative risk 0.43, 95% confidence interval 0.33-0.56; 20 studies, 5529 infants) and mortality (typical relative risk 0.65, 95% confidence interval 0.52-0.81; 17 studies, 5112 infants).⁵

The aim was to study the role of oral probiotics in reducing the incidence and severity of necrotising enterocolitis (NEC) in preterm neonates.

II. METHODS:-

A prospective randomized controlled trial of duration 18 months was conducted in 150 preterm neonates ≤ 35 weeks of gestation admitted in neonatal intensive care unit (NICU) in department of paediatrics, Hi-Tech medical hospital. They were randomised into two groups after obtaining informed parental consent. The

neonates in the test group were fed oral probiotics along with breast milk twice daily till they achieved full feeds.

The neonates in the control group were fed breast milk alone. The primary outcome was incidence and severity of NEC.⁶

After approval from the Ethical Committee the data was collected from patients admitted in NICU on day to day basis through rounds and register entries. After giving complete explanation of the process to the parents, informed consent was obtained. 150 babies were strictly selected according to exclusion and inclusion criteria in a 12 months study duration. Preterm neonates (≤ 35 weeks gestation and hemodynamically stable) who survived to feed enterally were eligible for the trial. Babies were randomized to test group and control group after obtaining informed parental consents. Babies in the test group received probiotics and were compared to control group. Probiotic used: 'BIFILAC GG DUO' sachets. Each sachet of 1 g contains *Saccharomyces boulardii* (5.0 Billion Cfu), *Lactobacillus rhamanosus* (6.0 Billion Cfu). The test group received their regular feeds plus their daily probiotic supplements twice daily mixed with expressed breast milk from the onset of enteral feedings till the baby reached full feeds. The control group was fed breast milk without the addition of probiotics.^{7,8}

Feeding was started when the infant had stable vitals, normal bowel sounds without any 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 was started at 10-15 ml/kg/day. The amount of feeding was increased slowly, if tolerated, with no more than 15 ml/kg increment per day upto 150-180 ml/kg/day.⁸ 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 the previous feed, or with abdominal distension). Standard practice guidelines as followed in our NICU for the care of neonates was followed in both the groups. On admission to NICU, a sepsis work up was done for all the neonates. Whenever a study infant was suspected to have NEC, clinical status and abdominal radiographic films were reviewed and if the diagnosis of NEC was established, the neonate was assigned a score according to the bell staging criteria.⁹

The results were analysed by t-test and one-way ANOVA for primary outcomes like incidence and



severity of NEC in test versus control groups and secondary outcomes like neonatal mortality.

In the present study, 5 babies (6.6%) in the test group and 12 babies (16%) in the control group developed NEC. Incidence of NEC was less in the test group as compared to controls.

III. RESULTS:-

Table 1: Incidence of NEC.

Group	NEC	Percentage
Test	05	6.6%
Control	12	16%
Total	17	11.3%

Table 2: Severity of NEC.

Severity of NEC by stage	Test	Control	Total
Stage- 1	4 (5.3%)	5 (6.7%)	9 (6%)
Stage- 2 and 3	1 (1.3%)	7 (9.3%)	8 (5.3%)

In present study, 9 (6%) babies developed less severe NEC out of which 4 babies were in the test group and 5 babies were in the control group. 8

neonates developed stage II or greater NEC in the study out of which 1 baby was in the test group and 7 babies were in the control group.

Table 3: NEC and bell staging.

Staging	Test	Control	Total
No NEC	70 (93.3%)	63 (84%)	133 (88.7%)
Stage- 1	4 (5.3%)	5 (6.7%)	9 (6%)
Stage- 2	1 (1.3%)	5 (6.7%)	6 (4%)
Stage- 3	0	2 (2.7%)	2 (1.3%)

In present study, out of the 17 babies who developed NEC, 9 babies developed stage I NEC (6%), 6 babies (4%) developed stage II NEC and 2 babies (1.3%) developed stage III NEC. More

severe NEC i.e. stage 2 and stage 3 were seen in control group. NEC was less severe in the probiotic group.

Table 4: NEC and mortality.

	Test	Control	Total
Mortality due to NEC	0/5 (0%)	2/12 (17%)	2/17 (11.8%)

In present study, 2 of the 14 babies with NEC in control group died and no babies died in test group out of 5 babies who developed NEC.

group (stage 2 and 3 seen in 1.3%) than the control group (stage 2 and 3 seen in 9.3%). Similar observations were found in the study done by Bin Nun et al and Manzoni et al.^{10,11} Study done by Manzoni et al. reported a non-significant trend towards less severe NEC in the treatment group. (2.6% versus 4.9%; p = 0.51).¹¹

IV. DISCUSSION:-

150 preterm neonates (gestation \leq 35 weeks) (study group n = 75, control group n = 75) were randomized. 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.

The mortality was also significantly lower in the test group (0% versus 17%). Studies done by Lin et al. and Manzoni et al. reported a significantly lower mortality rate in the probiotic group but did not differentiate between death attributed to NEC versus other cases.^{10,11}

The incidence of NEC was lower in test group (6.6%) than the control group (16%). Similar observations were seen in study by Lin et al. They reported a lower incidence of NEC in the probiotic group (1.1% versus 5.3%; p = 0.04).¹⁰

The severity of NEC was reduced in test

V. CONCLUSION:-

The present study found that probiotic supplementation has reduced both incidence and severity of necrotising enterocolitis in preterm neonates. The limitations of our study is the choice



of probiotic mixture, the dose and the frequency of dosing need to be discussed because each probiotic organism has variable rate of colonization. The adverse effects of probiotic supplementation like probiotic associated sepsis could not be analysed in our study. NEC is a multifactorial disease and the other factors contributing to the development of NEC is not analysed in our study.

Probiotics may offer potential benefits for premature infants. Nevertheless, probiotic treatment provides a promising strategy to prevent NEC in premature neonates.

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