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Evaluation of Probiotics for the Prevention of Necrotizing Enterocolitis in Preterm Neonates

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Abstract

Background: *Necrotizing Enterocolitis (NEC) is the most common life-threatening emergency of the gastrointestinal tract in the newborn period. The disease is characterized by various degrees of mucosal and transmucosal necrosis of the intestine.* ***Methods***: *This trial was conducted to study role of probiotics in reducing the incidence and severity of necrotizing enterocolitis in preterm neonates. Based on the previous study experiences and consultation with experts, sample sizes of 200 were selected by simple random sampling.* ***Results***: *In our study 51.5% were males and 48.5% were females. The number of male babies to female babies in test group is n=52 and n=48 and in control group is n=51 and n=49. There is no statistically significant difference between the two groups in sex distribution. In the present study, 5% were less than 1 kg, 60.5% between 1.01-1.499 kg, 31.5% between 1.5 -2 kg and 3% > 2 kg. In this study 90% babies were associated without any antenatal risk factors, 4% were associated with premature rupture of membranes (PROM), 5.5% were associated with pregnancy induced hypertension or pre-eclampsia (PIH/PE) and 0.5% were associated with gestational diabetes mellitus (GDM).* ***Conclusion***: *The present study found that probiotic supplementation has reduced both incidence and seventy of NEC in preterm neonates < 34 weeks of gestation. Probiotic supplementation has also reduced the incidence of culture proven sepsis in the preterm neonates but there were no significant differences between test and control groups in age reached full feeds and mean duration of hospital stay.*

Keywords: *Probiotics, Necrotizing Enterocolitis, Neonates*

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Introduction

Infant mortality rate is declining over recent years, because of better health care, immunization, oral rehydration therapy, promotion of exclusive breast feeding, maternal and infant nutrition and level 3 care. Despite the declining infant mortality rate, the perinatal mortality rate has not been changed significantly it remains 49% of the total infant deaths. [1] Factors contributing to neonatal mortality are multifactorial which include Prematurity and its complications, Birth asphyxia/intra cranial bleed, Neonatal infections, Intra uterine growth retardation, Respiratory disorders in the neonate like MAS, HMD, and pneumonia, Congenital anomalies and metabolic problems. Necrotizing enterocolitis (NEC) is primarily a disease of premature infants, although up to 10% of cases are found in term and near-term babies. [2] Signs of NEC include abdominal distension, blood or bile-stained emesis, bloody stools, and pneumatosis intestinalis is the pathognomic radiographic sign of the disease. [3] Medical management is largely supportive; however, surgery may be required for intestinal necrosis and mortality may reach up to 35% of all cases. [4] NEC is likely initiated with intestinal mucosal injury from any number of factors. Following this injury, bacteria in the gut proliferate with

formula or breast milk as a substrate. The bacteria invade the damaged mucosa causing inflammation and, ultimately, necrosis of the infected area. [5] Because of the association of feeding and bacterial infection with NEC, prevention strategies have focused on manipulating the feeding of premature infants as well as trying to manipulate the bacterial environment of the intestine. Although some early trials showed a decreased incidence of NEC with slow advancement of feedings, recent randomized studies have shown no difference in the incidence of NEC with fast vs slow or early vs delayed feedings. [6] In an attempt to modulate the immunologic milieu of the intestine, immunoglobulin (Ig)A and IgG have been given orally to infants. Unfortunately, a Cochrane analysis of these studies revealed that there was no significant difference in the incidence of NEC between those who received Ig and those who did not. [7] Recent interest has focused on giving probiotic bacteria to premature infants. Probiotic bacteria, such as Bifidobacteria and Lactobacillus, are live microbial supplements that colonize the intestines and provide benefit to the infant. The hope is to prevent the overgrowth of pathogenic organisms that have been associated with NEC. We in this study tried to evaluate the role of probiotics in reducing the incidence and severity of NEC in preterm neonates. Also study the efficacy and safety profile of enteral probiotics in preterm neonates.

Materials and Methods

The present study is a prospective randomized controlled interventional trial conducted at tertiary care centre NICU, Prathima Institute of Medical Sciences, Nagunur,Karimnagar, This trial was conducted to study role of probiotics in reducing the incidence and severity of necrotizing enterocolitis in preterm neonates. Based on the previous study experiences and consultation with experts, sample sizes of 200 were selected by simple random sampling.

Inclusion criteria

1. Preterm neonates (gestational age <34 weeks)
2. Hemodynamically stable

Exclusion Criteria

1. Gestational age >34 weeks
2. Cardiorespiratory illness
3. Parental refusal

Probiotic used

Saccharomyces boulardi ('ECONORM' sachets. Each sachet of 1 g contains *Saccharomyces boulardi* 250 mg corresponding to 221 mg of yeast). N=200 babies were selected strictly based on inclusion and exclusion criteria. Preterm neonates (gestational age <34 weeks) who survived to feed enterally were eligible for the trial. Of the 200 babies analyzed, 100 babies were randomized to test group and n=100 to control group, after informed parental consents were obtained. Babies in the test group received probiotics and were compared with the control group. The test group received their regular feeds plus daily probiotic 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 probiotics. 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 up to 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 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 were n=200 preterm neonates <34 weeks of gestation admitted to NICU of Prathima Institute of Medical Sciences, Nagunur, Karimnagar. They were assigned randomly to the study or control group. The study group was fed with probiotic and the control group was fed with breast milk without the addition of probiotics.

Table 1: Age at the time of admission

Age At (Days)	Groups		Total	*p*-Value
	Test	Control		
1	99	96	195 (97.5%)	0.550
2	1	1	2 (1%)	
3	0	1	1 (0.5%)	
4	0	1	1 (0.5%)	
5	0	1	1 (0.5%)	
Total	100	100	200 (100%)	

In our study 51.5% were males and 48.5% were females. The number of male babies to female babies in test group is n=52 and n=48 and in control group is n=51 and n=49. There is no statistically significant difference between the two groups in sex distribution. In the present study, 5% were less than 1 kg, 60.5% between 1.01-1.499 kg, 31.5% between 1.5 -2 kg and 3% > 2 kg. There was no significant difference in the birth weight of babies between the test and control group (p>0.05). Out of n=200 babies, 1% babies were <28 weeks of gestational age, 39.5% babies between 28-30 weeks, 38% between 31-32 weeks and 21.5% between 33-34 weeks. There was no significant difference in the gestational age of preterm babies between the test and control group (p>0.05).

Table 2: Comparison of gestational age

Gestational age	Groups		Total	*p*-value
	Test	Control		
AGA	87	93	180	0.333
SGA	12	6	18	
LGA	1	1	2	
Total	100	100	200	

In this study 90% babies were associated without any antenatal risk factors, 4% were associated with premature rupture of membranes (PROM), 5.5% were associated with pregnancy induced hypertension or pre-eclampsia (PIH/PE) and 0.5% were associated with gestational diabetes mellitus (GDM). There was no significant difference in the risk factors of patients between test and control groups (p>0.05). The mean age of initiation of feeds in test group is 2.33±o.711 and in control group is 2.14 ± 0.40 which is statistically significant (P<0.05). In the present study, 2 babies (2%) in test group and 10 babies in the control group (10%) developed NEC. The incidence of Necrotizing Enterocolitis in both groups is statistically significant (p<0.05). Incidence of NEC was less in the test group compared to controls.

Table 3: Stages of NEC in both the groups

Staging	Groups		Total	*p*-value
	Test	Control		
No NEC	98	90	188	0.023*
Stage I	2	3	5	
Stage II	0	5	5	
Stage III	0	2	2	

In the study, (5) 2.5% babies developed less severe NEC out of which 2 babies were in the test group and 3 babies were in the control group. Seven neonates developed stage II NEC in the study out of which all the 7 babies were in the control group, which is statistically significant (p<0.05). In the study, three of the 12 babies with NEC died; all three of the NEC associated deaths were from the control group. There is no significant difference in mortality associated with NEC (p-value >0.05). Although the difference was not significant, it is observed that three babies who died with NEC were from the control group vs no babies from the test group. In our present study, the incidence of sepsis in the test group is 28% and in the control group is 42%. It is found that the incidence of sepsis is less in test group, which is statistically significant (p<0.05). In our study, mean age reached full feeds in test and control groups were 9.78±2.687 and 9.53±3.248 respectively. There is no significant difference in the age reached full feeds in both test and control groups (p>0.05). The mean duration of hospital stay in test and control groups were 13.66 ± 4.99 and 13.55 ± 5.09 respectively. There is no significant difference in the mean duration of hospital stay (p>0.05)

Discussion

Necrotizing Enterocolitis (NEC) is the most commonly acquired neonatal intraabdominal emergency and causes significant mortality and morbidity in preterm neonates with mortality

approaching 30%. Approximately 25% of survivors experience long term sequelae. In our present study, the incidence of NEC was significantly lower in the test group compared with the control group (2 of 100 neonates vs 10 of 100 neonates; p=0.017). Similar observations were seen in study by Lin et al; [8] reported a lower incidence of NEC in the probiotic group (1.1% Vs 5.3%; p=0.04). The study by Bin-Nun et al; [9] found a significantly lower incidence of all cases of NEC in the probiotic group (4% Vs 16.6%; p=0.031). Dani et al; [10] found a lower incidence of NEC (1.4 Vs 2.7%) in the probiotic group, but this did not reach statistical significance. In our study, mean age of onset of NEC in the test group was 4±1.41 and in the control group was 3.80±1.98 which was not statistically significant. Studies done by Lin et al; [8] Hung–Chin et al; [11] showed similar observations in the age of onset of NEC which were statistically non-significant. According to literature, the postnatal age at onset is inversely related to birth weight and gestational age with a mean at onset of 12 days. [2] In this study, out the n=12 babies developed NEC, n=5 babies developed stage I NEC, 5 babies stage II NEC and 2 babies stage III NEC, which was statistically significant (p<0.05). The study by Lin et al; [8] showed similar observations. They reported more severe NEC in the control group it showed NEC ≥ 2 more in the control group (2 Vs 10) and NEC 3 (0 Vs 6). [8, 11] Similar observations were found in the study done by Bin Nun et al; [9] and Manzoni et al; [12]. In the present study, more severe NEC and NEC ≥ 2 were found in the control group (0 Vs 7) which was statistically significant (p = 0.023). Similar observations were found in the study done by Lin et al; [8] They reported n=6 cases of severe NEC (≥ 2) in the control group versus none in the probiotic group (p=0.003). Bin Nun et al; [9] reported similar observations in terms of severe NEC (≥ 2) (1% Vs 14%; p=0.013). In our study, n=3 of the n=12 babies died with NEC were from the control group. There is a non-significant trend to towards less NEC-related mortality in the probiotic group (0 of 2 Vs 3 of 10; p=0.371). Hoyos A [13] showed NEC-associated mortality is more in the non-probiotic group (35/1282 Vs 14/1237; p value<0.005) which was statistically significant. But here the test group was compared with historic controls. Studies done by Lin et al. and Manzoni et al; [12] reported a significantly lower mortality rate in the probiotic group but did not differentiate between death attributed to NEC version other cases. In this study, the incidence of sepsis in the test group is 28% and, in the control, group is 42%. It is found that the incidence of sepsis is less in the test group which is statistically significant (p=0.038). The study by Hung–Chin Lin et al; [8] reported a lower incidence of sepsis in the probiotic group (22/180 Vs 36/183; p=0.03). The mechanism for the efficacy of probiotics in reducing the incidence of sepsis in VLBW infants is probably similar to NEC and possibly a result of increased colonization of desirable microflora supplemented through probiotics. But studies done by Dani et al; [10] and Bin Nun et al; [9] did not show any reduced incidence of sepsis in the probiotic group their studies reported that the pathogens were most often related to catheter related infections in both groups. In the current study, the mean duration of hospital study in test and control groups were 13.66 ± 4.99 and 13.5 ± 5.09 respectively. There was no significant difference in the mean durations of hospital stay (p>0.05). Lin CH et al; [8] Hung–Chin et al; [11] showed similar observations that no significant difference in the hospital stay between test and control group (46.7 ± 27.1 in test and 46.5 ± 26.1 in control group).

Conclusion

Necrotizing Enterocolitis is a worldwide problem in very low birth weight infants (VLBW), causing significant mortality and morbidity. The present study found that probiotic supplementation has reduced both incidence and seventy of NEC in preterm neonates < 34 weeks of gestation. Probiotic supplementation has also reduced the incidence of culture proven sepsis in the preterm neonates but there were no significant differences between test and control groups in age reached full feeds and mean duration of hospital stay. However more research is required involving more sample size to support the use of probiotics in preterm neonates.

Conflict of Interest: *None declared*
Source of Support: *Nil*
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