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Research article

ROLE OF ORAL PROBOTICS IN THE PREVENTION OF NECROTIZING ENTEROCOLITIS IN PRETERM NEONATES

Amith Kumar Ch*[1]., Pradeep Jatoth[2]., Sowmithra[3] and Chandra Kanth Reddy, S[4]

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ABSTRACT

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.

INTRODUCTION

The present study is a prospective randomized controlled interventional trial conducted at tertiary care centre NICU, Prathima Institute of Medical Sciences, Nagunur, Karimnagar, during the period of one and half years between December, 2013 and May 2015. This trial was conducted to study role of probiotics in reducing the incidence and severity of necrotizing enterocolitis in preterm neonates <34 weeks.

Probiotic used: Saccharomyces boulard ('ECONORM' sachets. Each sachet of 1g contains Saccharomyces boulardi 250 mg corresponding to 221 mg of yeast).

RESULTS

Table-1 Age of admission of both test and control

Age of admission (days)	Groups		Total	P-value
	Test	Control		
1	99 (99%)	96 (96%)	195 (97.5%)	0.550
2	1(1%)	1(1%)	2(1%)	
3	0	1(1%)	1(0.5%)	
4	0	1(1%)	1(0.5%)	
5	0	1(1%)	1(0.5%)	
Total	100 (100%)	(100%)	200(100%)	

p-value = 0.550 (NS)

In the present study, out of 200 preterm neonates 99% of babies in the test group and 96% in the control group were admitted on day one of their life. There were 1% babies admitted on day two of life, 0.5% of each at their third day, fourth day and fifth day of life. There was no significant difference in the age of the patients between test and control groups. Both groups were similar with respect to age distribution (p>0.05).

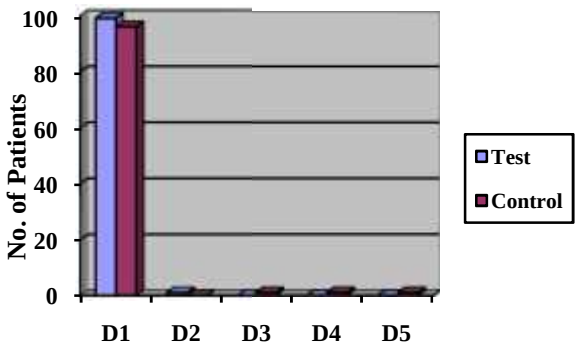

Figure 2 Age of admission of both test and control

Sex distribution

Table-2 Sex wise distribution between study and control group

Sex	Groups		Total	P-value
	Test	Control		
Male	52 (52%)	51 (51%)	103 (51.5%)	0.887
Female	48 (48%)	49 (49%)	97 (48.5%)	
Total	100 (100%)	(100%)	200(100%)	

p-value = 0.887 (NS)

*Corresponding author: *Amith Kumar Ch*

In our study 51.5% were males and 48.5% were females. The number of male babies to female babies in test group is 52 and 48 and in control group is 51 and 49. There is no statistically significant difference between the two groups in sex distribution.

Gestational age

Table3 Distribution of test and control groups according to gestational age.

Gestational age in weeks	Groups		Total	P-value
	Test	Control		
<28	2(2%)	0(0%)	2(1%)	
28-30	44 (44%0	35 (35%)	79 (39.5%)	
31-30	39 (39%)	37 (37%)	76 (38%)	
33-34	15 (15%)	28 (28%)	43 (21.5%)	0.072
Total	100 (100%)	(100%)	200(100%)	

In the present study, out of 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).

Risk Factors

Table 4 Antenatal Risk Factors

Antenatal Risk factors	Groups		Total	P-value
	Test	Control		
Nil	91(91%)	89(89%)	180(90%)	
PROM	4(4%)	4(4%)	8(4%)	
PIH/PE	4(4%)	7(4%0	11(5.5%)	
GDM	1(1%)	0(0%)	1(0.5%)	0.606
Total	100 (100%)	(100%)	200(100%)	

In the present 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).

Age of Initiations of feeds

Table 5 Age of Initiations of feeds

Age of initiation of feeds	Mean		Std. deviation		Sig (2-tailed)
	Test	Control	Test	Control	
	2.3300	2.1400	0.71145	0.40252	0.021

The mean age of initiation of feeds in test group is 2.33 $\pm$ 0.711 and in control groups is 2.14 $\pm$ 0.40 which is statistically significant (p<0.05).

Age of onset of NEC

Table-6 Showing age of onset of NEC

Group	N	Mean	Std. deviation	p. value
Test	2	4.00	1.41421	
Control	10	3.80	1.98886	0.200

In our study, mean age of onset of NEC in the test group was 4 $\pm$ 1.41 and in the control group was 3.80 $\pm$ 1.98. The difference in the age of onset on NEC is not statistically significant (p>0.05).

DISCUSSION

Necrotizing Enterocolitis (NEC) is the most commonly acquired neonatal intraabdominal emergency and causes significant mortality and morbidity in pretem neonates with mortality approaching 30%. Approximately 25% of survivors experience long term sequelae.

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[6].

Probiotic bacteria are defined as live microbial supplements that colonise the gut and provide benefit to the host Emerging evidence suggests that probiotics may have a role in the control or prevention of NEC by

- reducing intestinal colonization with pathogenic organisms,
- reinforcing intestinal barrier,
- changing the intestinal permeability,
- enhanced mucosal lg A activity and
- alleviating intestinal inflammation.

Functions such as promotion of fermentation to produce organic acids and production of antimicrobial bacteriocins and fatty acids and further theoretical support to their role in the protection of NEC. Lastly, their colonization might reduce the pro-inflammatory mediators responsible for the intestinal tissue damage.

Potential use of probiotics could lead to improvements in nutrition, reduced dependence on intravenous nutrition, a reduction in the incidence of sepsis and use of antibiotics and prevention of Necrotizing Enterocolitis[8].

Normalization of the properties of unbalanced indigenous microflora by specific strains of the healthy gut microflora constitutes the rationale of probiotic therapy[9].

Modification of the intenstinal flora by increasing the predominance of specific nonpathogenic bacteria seemed to be a reasonable means of attaining a prophylactic or therapeutic affect against enteropathogens[9].

Selection of strains for clinical trails is based on the microbial characteristics such as ability to survive gastric acid and colonize the gut, products of factors that inhibit the growth of pathogenic bacteria (such as H_2O_2 by lactobacilli) and other desirable (generally metabolic or immunologic) effects[8].

The microorganism most frequently used as probiotic agents are lactic acid bacteria (species of lactobacillus) and nonpathogenic, antibiotic resistant, ascosporic yeasts, such as Saccharomyces boulardi. Lactobacillus rhamnosus GG, which was originally isolated from human intestinal flora, is the most widely studied probiotic agent for adults and children[10].

A neonate is born with a sterile gut that is colonized within 12-24 hours. VLBW preterm neonates usually acquire microbial flora mainly from intensive care vironment rather than from their own mother. Hence they are at risk of gut colonization with pathogens which can alter the permeability of intestine and promote inflammatory cascade which facilitates NEC[11].

An important rationale for the use of probiotics in neonates at risk for Necrotizing Enterocolitis is that very low birth weight infants have aberrant fecal colonization compared with healthy term infants. The predominant facultative species in the fecal flora of preterm infants undergoing intensive care are staphylococci (CONS and Staphylococcus aureus), enterobacteriaceae (Klebsiella) and enterococci. Clostridia are the most common anaerobes and bifidobacteria are less common than the flora of healthy breast fed term infants in whom bifidobacteria predominate[8].

In our study, 200 preterm neonates <34 weeks of gestational age were selected based on inclusion and exclusion criteria. They were assigned randomly to test group (100) and control group (100). Study group was fed with probiotics with breast milk and control group only with breast milk.

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.

Incidence of NEC

In our present study, the incidence of NEC was significantly lower in the test group compared with the control group (2 of 100 nenoates vs 10 of 100 neonates; p=0.017).

Similar observations were seen in study by Lin *et al*. They reported a lower incidence of NEC in the probiotic group (1.1% Vs 5.3%; p=0.04)[12].

The study by Bin-Nun *et al*. found a significantly lower incidence of all cases of NEC in the probiotic group (4% Vs 16.6%; p=0.031)[13].

Dani *et al*. found a lower incidence of NEC (1.4 Vs 2.7%) in the probiotic group, but this did not reach statistical significance[14].

Costalos *et al*. reported a non significant trend lowered less NEC of any severity in the probiotic group (9.8% Vs 16%; p=0.5)[15].

Manzoni *et al*. also reported a non-significant trend towards less severe NEC in the probiotic group (2.6% Vs 4.9%; p=0.51)[16].

Similar studies by Mihatsch *et al*, Braga *et al*, Al-Hosni *et al*, Propems *et al* in last 4 yrs showed significant trend towards less severe NEC in the probiotic group[17,18,19].

Age of onset of NEC

In our study, mean age of onset of NEC in the test group was 4 $\pm$ 1.41 and in the control group was 3.80 $\pm$ 1.98 which was not statistically significant.

Two studies done by Hung-Chin Lin *et al*. showed similar observations in the age of onset of NEC which were statistically non-significant[12].

According to literature, the postnatal age at onset is invesrsely related to birth weight and gestational age with a mean at onset of 12 days[1].

NEC and severity

In the present study, more service NEC and NEC $\geq$ 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*. They reported 6 causes of severe NEC ($\geq$2) in the control group versus none in the probiotic group (p=0.003)[12].

Bin Nun *et al* reported similar observations in terms of severe NEC ($\geq$2) (1% Vs 14%; p=0.013)[13].

According to the study done by Dani *et al*. a lower incidence of NEC $\geq$2 were seen in the probiotic group (1.4% Vs 2.8%) but his did not reach statistical significance. But in this study, patients were not stratified by severity[-14].

Study done by Manzoni *et al*. reported a non-significant trend towards less severe NEC in the treatment group. (2.6% Vs 4.9%; p=0.51)[16].

NEC and Sepsis

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 les in the test group which is statistically significant (p=0.038).

The study published by Hung-Chin Lin *et al*. in 2005 reported a lower incidence of sepsis in the probiotic group (22/180 Vs 36/183; p=0.03)[12].

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.

Age reached full feeds

In our study, the mean age reached full feeds in test and control group were 9.78 $\pm$ 2.687 and 9.53 $\pm$ 3.248 respectively. We found no significant difference in the mean age reached full feeds in both test and control group.

Similar observations were found in the study done by Bin Nun *et al*. They reported that full feeds were reached at similar ages in both test and control group (p=0.13)[13].

CONCLUSIONS

Necrotizing Enterocolitis is a world wide 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.

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