PROBIOTICS IN PREVENTION OF NECROTIZING ENTEROCOLITIS IN PRETERM NEWBORNS

Suman Chirla[1], V.V.S.P. Kumar Appasani[2]

[1]Assistant Professor, Department of Paediatrics, NRIIMS Medical College, Visakhapatnam, Andhra Pradesh.
[2]Assistant Professor, Department of Paediatrics, NRIIMS Medical College, Visakhapatnam, Andhra Pradesh.

ABSTRACT

BACKGROUND

Necrotizing Entero-Colitis (NEC) is the most commonly acquired intra-abdominal emergency and causes significant mortality and morbidity. A proposed strategy for the prevention of NEC, is the administration of oral probiotics. Probiotics have been shown to reduce NEC in experimental rat models and have been used in clinical trials. We evaluated the role of probiotics in reducing the incidence and severity of NEC in preterm neonates.

MATERIALS AND METHODS

A prospective randomized control trial was done in preterm neonates <34 weeks of gestation. They were divided into two groups. The newborns in the test group were fed with a probiotic with breast milk twice daily. The newborns in the control group were fed with breast milk alone. The incidence and severity of NEC were studied in both test and control group.

RESULTS

Two-hundred preterm neonates were enrolled in our study. 100 newborns in the test group and 100 newborns in the control group. The incidence of NEC was significantly lower in the test group (2 of 100 vs. 10 of 100). The incidence of NEC >/= 2nd stage was significantly lower in the test group than in the control group (0 of 100 vs. 7 of 100).

CONCLUSION

Probiotics fed along with breast milk reduced both the incidence and severity of NEC in preterm newborns.

KEYWORDS

Preterm Babies, Probiotics, Necrotizing Enterocolitis.

HOW TO CITE THIS ARTICLE: Chirla S, Kumar Appasani VVSP. Probiotics in prevention of necrotizing enterocolitis in preterm newborns. J. Evid. Based Med. Healthc. 2018; 5(51), 3488-3492. DOI: 10.18410/jebmh/2018/711

BACKGROUND

Necrotizing enterocolitis (NEC) is primarily a disease of premature infants, although up to 10% of cases present in term and near-term babies.[1] 2–5% of all NICU admissions worldwide are due to NEC.[2] 85% of the cases of NEC occurs in premature infants (<1500 g or <32 weeks)[3] while late preterm and term infants contribute to only 7% to 15%.[4] The incidence is inversely related to prematurity and infants born at 22–28 GA have a higher incidence (11%).[5] NEC is characterised by a triad of Abdominal distension, gastro intestinal bleeding and pneumatosis intestinalis (air in bowel wall) on abdominal radiography.[6] Medical management is early recognition and supportive care in intensive care, but surgery is required for intestinal necrosis and late stages.

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.[7]

Some Probiotic bacteria like Bifido bacteria and Lactobacillus, are live microbial supplements that colonize the intestines and may provide benefit to the infant. The idea of these probiotics is to prevent and sometimes replace the pathological overgrowth of pathogenic organisms that have been associated with the pathogenesis of NEC. There have been some studies describing the safety of probiotics in newborns in prevention of NEC.[8]

A Study in 2003 from South America revealed a significant decrease in the incidence of NEC with the introduction of Lactobacillus enteral feeds, but this study used only historical controls.[9]

In summary, although the use of probiotics to prevent NEC appears attractive, at this time it is too early to recommend their general use. Randomized trials of sufficient size are needed to determine whether probiotics decrease the incidence of NEC as well as to identify the possible side effects.

Aims and Objectives

1. The main objective is to determine the role of probiotics in reducing necrotizing enterocolitis among preterm neonates.
2. The other objectives are to see the efficacy of probiotics in reducing the complications of NEC like sepsis and mortality.

Financial or Other, Competing Interest: None.
Submission 29-11-2018, Peer Review 05-12-2018,
Acceptance 08-12-2018, Published 13-12-2018.
Corresponding Author:
Dr. Pradeep Kumar Appasani,
Flat No. A201, Staff Quarters, NRIIMS Medical College,
Sanghivalasa, Visakhapatnam- 531162,
Andhra Pradesh.
E-mail: dr.pradeepkumar.a@gmail.com
DOI: 10.18410/jebmh/2018/711

MATERIALS AND METHODS

The present study is a prospective randomized controlled trial conducted at Neonatal Intensive Care Unit of Anil Neerukonda Hospital, attached to NRI Medical College Visakhapatnam, during the period of one and half years between December 2016 and May 2018.

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.

Materials Used

Probiotic used: 'Pedistine™' sachets. Each sachet of 1 g contains Saccharomyces boulardii 282.50 mg corresponding to 250 mg of yeast, Lactobacillus rhamanosus 0.24 billion, Lactobacillus acidophilus 0.24 billion, Bifidobacterium longum 0.24 billion, Streptococcus thermophilus 0.24 billion. It is manufactured by Wockhardt Limited (India), Wockhardt Towers, Bandra Kurla Complex, Mumbai-400 051, India.

Methods of Collection of Data

A prospective randomized control study was done on preterm neonates in Neonatal ICU. Two hundred babies were selected strictly based on inclusion and exclusion criteria. Preterm neonates (gestational age <34 weeks) who survived to feed enter ally were eligible for the trial. Of the 200 babies analyzed, 100 babies were randomized to test group and 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 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.

Results were analyzed by 't' test and one-way ANOVA for primary outcomes like incidence and severity of NEC in test vs. control groups.

RESULTS

There were 200 preterm neonates <34 weeks of gestation admitted to NICU of Anil Neerukonda Hospital attached to NRI Medical College Visakhapatnam, during the time period between December 2016 and May 2018. 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. The study and control groups were compared accordingly.

Age of Admission (days)	Groups		Total	p-value
	Test	Control		
1	99 (99%)	96 (96%)	195 (97.5%)	.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%)	

Table 1. Age of Admission of both Test and Control

P-value=0.550

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% of 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).

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 (100%)	200 (100%)	

Table 2. Sex Wise Distribution between Study and Control Group

P-value=0.887

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.

Group	NEC	Percentage	p-value
Test	2	2	0.017
Control	10	10	
Total	12	6	

Table 3. Incidence of NEC in both Test and Control Groups

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.

Staging	Groups		Total	p-value
	Test	Control		
No NEC	98 (98%)	90 (90%)	188 (94.5%)	0.023
Stage I	2 (2%)	3 (3%)	5 (2.5%)	
Stage II	0 (0%)	5 (5%)	5 (2.5%)	
Stage III	0(0%)	2(2%)	2(1%)	

Table 4. Showing Stages of NEC in Test and Control Groups

In our study, out of the 12 babies developed NEC, 5 babies developed stage I NEC (2.5%), 5 babies (2.5%) with stage II NEC and 2 babies with stage III NEC. More severe NEC i.e. stage 2 and stage 3 were seen in control group (3.5%) NEC was less severe in the probiotic group. There is significant difference between the test and control group in different stages of NEC ($p<0.05$).

DISCUSSION

Probiotics may offer potential benefits for premature infants. We are still in the early stages of understanding the numerous interactions that occur between the intestinal microflora and probiotics, and their interaction with the intestinal micro- environment over time. Nevertheless, probiotic treatment provides a promising strategy to prevent NEC in premature neonates. In our opinion, probiotics have three advantages, compared to other strategies proposed for the prevention of NEC; first, probiotics represent a simple, non-invasive attempt to recreate a natural normal flora rather than a disruption of nature; secondly, it appears to be effective in preventing major source of morbidity in low birth weight infants, and thirdly, its safety record renders it an attractive alternative to many of the more aggressive therapeutic options.

Necrotizing Enterocolitis (NEC) is the most commonly acquired neonatal intra-abdominal emergency and causes significant mortality and morbidity in preterm neonates with mortality approaching 30%. Approximately 25% of survivors experience long term sequelae. The causes of this intestinal catastrophe is complex, but common factors associated with this disease are prematurity, immaturity of intestinal tract, intestinal ischaemia, microbial colonization with pathogenic organisms and enteral feeding.[10]

A proposed strategy for the prevention of NEC is the administration of oral probiotics. 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 and alleviating intestinal inflammation. Functions such as promotion of fermentation to produce organic acids and production of antimicrobial bacteriocins and fatty acids add 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.[10]

Most probiotics are lactic acid producing bacteria. Among them, Bifidobacterium, Lactobacillus and Streptococcus are some of the most common probiotics found in the intestine of healthy infants.

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 environment 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]

Recent prospective randomized trials have shown that enterally fed probiotics are beneficial in the prevention of NEC.

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.

Choice of Probiotics

Probiotics are live microbial supplements that colonise the gut and provide benefit to the host. Many different species of bacteria and fungi have been used as probiotics. Probiotic organisms generally consist of strains of Lactobacillus, Bifidobacterium, Streptococcus and Saccharomyces. The selection of optimal probiotic mixture is not clear. It seems that double or triple probiotic strains provide the greatest protection.

The studies done by different randomized controlled trials had used different strains of probiotic organisms.

Sl. No.	Study	Probiotics Used
1.	Hoyos et al. (1999)[12]	Bifidobacterium infantis, Lactobacillus acidophilus
2.	Dani et al. (2002)[13]	Lactobacillus rhamnosus GG
3.	Costalos et al. (2003)[14]	Saccharomyces boulardii
4.	Lin et al. (2005)[15]	Lactobacillus acidophilus, Bifidobacterium infantis
5.	Bin Nun et al. (2005)[16]	Bifidobacterium infantis, Streptococcus thermophiles, Bifidobacterium bifidum
6.	Manzoni et al. (2006)[17]	Lactobacillus casei subspecies rhamnosus
7.	Lin et al. (2008)[18]	Lactobacillus acidophilus, Bifidobacterium bifidum
8.	Present study	Bifidobacterium longum, Lactobacillus rhamanosus, Lactobacillus acidophilus, Streptococcus thermophiles, Saccharomyces boulardii

Table 5. Probiotics Used in Different Studies

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 neonates 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%; $p=0.04$).[15]

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%; $p=0.031$).[16]

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.[13]

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).[14]

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).[17]

Our study showed that the test group has a lower incidence of NEC.

NEC and Bell Staging

In our study, out the 12 babies developed NEC, 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. 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).[15,16]

Similar observations were found in the study done by Bin Nun et al and Manzoni et al.[14,16]

NEC and Severity

In the present study, more severe 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. They reported 6 cases of severe NEC >/= 2 in the control group versus none in the probiotic group (p=0.003).[15]

Bin Nun et al reported similar observations in terms of severe NEC >/= 2 (1% vs. 14%; p=0.013).[16]

According to the study done by Dani et al. a lower incidence of NEC >/= 2 were seen in the probiotic group (1.4% vs. 2.8%) but this did not reach statistical significance. But in this study, patients were not stratified by severity.[13]

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).[17]

Summary

Two hundred preterm neonates <34 weeks of gestation admitted to NICU of Anil Neerukonda hospital, Visakhapatnam were studied over a period of 1½ years. They were assigned randomly to test and control group.

- Test group received probiotic along with breast milk and control group only breast milk without probiotics.
- The test and control groups were compared for demographic and clinical variables and did not differ significantly.
- The incidence of NEC in the test group is 2% and in the control groups 10% (p<0.05).
- 2.5% babies developed stage I NEC, 2.5% babies stage II NEC and 1% babies stage III NEC.
- More severe NEC is stage 2 and stage 3 were seen in control group (3.5%) (p<0.05).

CONCLUSION

Necrotizing Enterocolitis is a worldwide problem in very low birth weight infants (VLBW). It causes 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.

However, more research is required involving larger sample size to support the use of probiotics in preterm neonates.

REFERENCES

[1] Clonerty JP, Eichenwald EC, Stark AR. Manual of neonatal care. 6th edn. Philadelphia: Lippincott Williams and Wilkins 2008:608-615.

[2] Hunter CJ, Upperman JS, Ford HR, et al. Understanding the susceptibility of the premature infant to necrotizing enterocolitis (NEC). Pediatr Res 2008;63(2):117-123.

[3] Thompson AM, Bizzarro MJ. Necrotizing enterocolitis in newborns: pathogenesis, prevention and management. Drugs 2008;68(9):1227-1238.

[4] Sharma R, Hudak ML. A clinical perspective of necrotizing enterocolitis: past, present, and future. Clin Perinatol 2013;40(1):27-51.

[5] Yee WH, Soraisham AS, Shah VS, et al. Incidence and timing of presentation of necrotizing enterocolitis in preterm infants. Pediatrics 2012;129(2):e298-e304.

[6] Singh M. Care of the newborn. Chap- 25. 7th edn. New Delhi: Sagar Publications 2010: p.407.

[7] Sharma R, Hudak ML, Tepas JJ, et al. Impact of gestational age on the clinical presentations and surgical outcome of necrotizing enterocolitis. J Perinatol 2006;26(6):342-347.

[8] Walsh MC, Kleigman RM. Necrotizing Enterocolitis: treatment based on staging criteria. Pediatr Clin North Am 1986;33(1):179-201.

[9] Millar M, Wilkis M, Costeloe K, et al. Probiotics for preterm infants? Arch Dis Child Fetal Neonatal Ed 2003;88(5):F354-F358.

[10] Scaler RJ. Probiotics and necrotising enterocolitis in premature infants. Arch Dis Child Neonatal Ed 2006;91(6):F395-F397.

[11] Deshpande G, Rao S, Patole S, et al. Updated meta-analysis of probiotics for preventing necrotizing enterocolitis in preterm neonates. Pediatrics 2010;125(5):921-930.

[12] Hoyos AB. Reduced incidence of necrotizing enterocolitis associated with enteral administration of lactobacillus acidophilus and bifidobacterium infants to neonates in an intensive care unit. Int J Infection Dis 1999;3(4):197-202.

[13] Dani C, Baidaioli R, Bertini G, et al. Probiotics feeding in prevention of urinary tract infection, bacterial sepsis and necrotizing enterocolitis in preterm neonates. A prospective double-blind study 2002;82(2):103-108.

[14] Costalos C, Skouteri V, Gounaris AD, et al. Enteral feeding of premature infants with Saccharomyces boulardii. Early Hum Dev 2003;74(2):89-96.

[15] Lin HC, Su BH, Chen AC. Oval Probiotics reduce the incidence and severity of necrotizing enterocolitis in very low birth weight neonates infants. Pediatrics 2005;115(1):1-4.
[16] Bin-Nun A, Bromiker R, Wilschanski M, et al. Oral probiotics prevent Necrotizing Enterocolitis in very low birth weight neonates. J Pediatr 2005;147(2):192-196.
[17] Manzoni P, Mostert M, Leonessa ML, et al. Oral supplementation with lactobacillus casei subspecies rhamnosus prevents enteric colonization by candida species in preterm neonates: a randomized study. Clin Infec Dis 2006;42(12):1735-1742.
[18] Lin HC, Hus CH, Chen HL, et al. Oral probiotics prevent necrotizing enterocolitis in very low birth weight preterm infants: a multicenter randomized controlled trial. Pediatrics 2008;122(4):693-700.