ORIGINAL ARTICLE

Role of Probiotics in Prevention of Necrotising Enterocolitis in Preterm Neonates

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ABSTRACT

Background: Necrotizing enterocolitis (NEC) is among common cause of mortality and morbidity in neonates particularly in preterm babies. In preterm neonates, the NEC has been reduced with the use of various probiotics. This study examined the impact of routine use of a probiotics (Ecotec sachet 2.0g) in preterm neonates for developing NEC.

Objective: To compare the frequency of necrotizing enterocolitis (NEC) in preterm newborns with and without probiotics treatment.

Materials and Methods: This randomized controlled trial study was carried out on neonates admitted during 21-4-2014 to 21-10-2014 at Neonatal intensive care unit of Fatima Memorial Hospital Lahore. A total of 140 neonates meeting the inclusion criteria were selected. Cases were registered for the study and demographic information of the patients (name, gestational age, sex and address) was documented. Study population was divided into two equal groups. Group A received probiotics (Ecotec sachet 2.0g) once daily. Probiotics were started on starting of feeding mixed in milk of newborn and continued administration until hospital discharge. Group B received the placebo. Cases were assessed on daily basis regarding the clinical signs of NEC.

Results: Total 140 preterm neonates were included in this study, 70 in probiotic group and 70 in control group. The frequency of NEC was significantly low in the preterm neonates who received probiotics (3 of 70 neonates [4.3%] versus 6 of 70 untreated preterm neonates [8.6%]).

Conclusion: Prophylactic use of the probiotics result in prevention of necrotizing enterocolitis with statistically significant benefit. However, the optimum type of probiotic supplementation and their long-term effects need further study.

Keywords: Necrotizing enterocolitis(NEC), Probiotics, Preterms babies.

INTRODUCTION

Necrotizing enterocolitis one of the common and lethal disease in neonates. Moreover, it is troublesome to eradicate[1] and therefore has become the priority for diagnosis.[2] Conditions that closely resemble NEC were delineated before the 1960s, however the entity was not well known till once the appearance in a neonate[1]. Since then, the frequency of NEC and its morbidity and mortality have remained unchanged in premature neonates. In some instances, the number of cases have truly increased. The estimated death related to NEC is between 20-30%, and it is highest rate among those infants who require surgery.[3,4]

The inflammatory changes that start within the extremely immunoreactive intestine extend the reaction of the disease systemically, touching distant organs like the brain and put the affected infant at a high risk for neuro-developmental delay.[5] Indeed, associated degree of illness from NEC might have a 25% likelihood of abnormality and high neuro-developmental delays.[6] In many centers early enteral feeding is avoided to prevent the NEC and this results in increased duration of parenteral nutrition. This strategy put the infants in danger of infections and septicemia and therefore the length of hospital stay is increased.[7]

The cost of treatment of NEC is high; the entire annual calculable value of the management affected infants within the US is between $500 million and $1 billion. In one study, the length of hospital stay in infants with NEC was 60 days longer than unaffected preterm infants, in whom surgery was needed. The requirement for gut surgical procedure is to avoid the severe complications of NEC and that is the major explanation for the short bowel syndrome in these patients. The average cost of care for a baby with

the short bowel syndrome has been calculable to be nearly $1.5 million over five years period.

Probiotics are defined as the live microorganisms, that confer health benefits on people with specific illnesses when administered in adequate amount. Probiotics have been reported effective in terms of NEC incidences in preterms. However, studies in local settings reporting the influence of probiotics are very limited. Therefore, objective of this study was to compare the frequency of necrotizing enterocolitis (NEC) in preterm newborns with and without probiotics treatment.

MATERIALS AND METHODS

We carried out a prospective and interventional study over six month period (from 21-4-14 to 21-10-14) in neonatal intensive care unit of Fatima Memorial Hospital, Lahore. The study was approved by ethical committee of our institute. Following inclusion and exclusion criteria was followed:

Inclusion Criteria:

1. Premature infants delivered before 37 weeks of gestation
2. Infants of both gender
3. Infants within 72 hours of birth

Exclusion criteria:

1. Critically ill babies on ventilator were excluded.
2. Any other medical problem like infection, perinatal asphyxia, fits and jaundice diagnosed on clinical assessment and lab investigations.
3. Any other surgical/congenital anomalies.
4. Any baby having dysmorphic features.

We included in our study a total of 140 cases of prematurity meeting the inclusion criteria. A baby born less than 37 weeks of gestation, as calculated from the first day of the last menstrual period of mother was defined as preterm infant. Informed consent from parents was taken. Protocol of the study was approved by the Ethical Committee of our institute. Cases were registered for this study and all the demographic information of the patients (name, age, sex, address) was obtained. Of a total 170, 70 were randomly placed in group A (treated with Probiotic) and rest of the 70 were placed in group B (termed as control). Group A received once daily 2.0g of probiotics. Probiotics containing L.acidophilus, Bifidobacterium, S.thermophilus and L.delbrueckii cells were started on starting of feeding mixed in milk of newborn and continued administration until hospital discharge or 40 week post conceptional age. Group B received the placebo in same manner as group A. Cases were assessed on daily basis regarding presence of NEC. NEC for this study was defined as: clinical findings including lethargy, vomiting, abdominal distention and bloody stools; Lab investigations including thrombocytopenia(platelets <50,000) and deranged coagulation profile (PT >18); Radiological findings consisting of intramural gas in gut, gas in portal vein and gas under diaphragm. All this information was collected and recorded on a predefined proforma.

Statistical analyses

The descriptive statistical analysis included examinations of means, standard deviations, ranges, frequencies and the percentages. The statistical packages SPSS (Version 20) and MS Excel (MS Office 2010) were used. Chi square test was used to compare NEC in group A and B. Gestational age and birth weight were taken as effect modifiers. Chi-square test was also applied post-stratification with P-value ≤0.05 considered as significant.

RESULTS

In present study, male to female ratio in both groups was comparable. In group A, 39 (55.72%) neonates were males and 31 (44.28%) were the females with male to female ratio of 1.2:1 (Table 1). Similarly in group B, 38 (54.28%) were males and 32 (45.72%) were the females with male to female ratio of 1.3:1 (Table 1). Out of a total of 140 newborn infants who fulfilled the inclusion and exclusion criteria, 70 babies were allocated to the probiotics group and 70 babies to the control group. The basic characteristics of newborns were remained same in both groups.

Table 1: Gender distribution of infants in study groups.

Gender	Group A (Probiotic) (N=70)	Group B (Control) (N=70)
Male	39	38
Female	31	32
Total	70	70
Male to Female Ratio	1.2:1	1.3:1

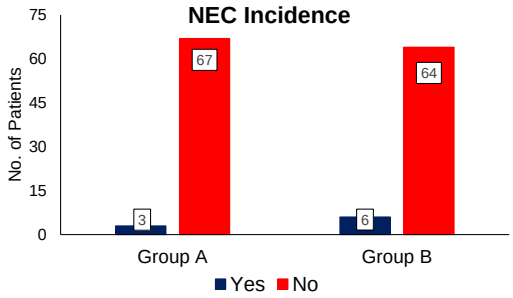

Figure 1. Incidence of NEC in two groups i.e. Group A (treated with Probiotica) and Group B (Control).

The risk of NEC was decreased significantly in the preterm infants who were supplemented with the probiotics as compared to the placebo group. Among the 70 preterm neonates of probiotic group, 3 (4.3%) confirmed cases of NEC were observed while in 70 preterm neonates of control group, 6 (8.6%) confirmed cases of NEC were observed. So the frequency of NEC was high in placebo group as compared to probiotic group. (Figure 1). In group A, overall mortality was 3 (4.3%) while in group B, overall mortality was 5 (7.1%). Although there was no difference between the groups in relation to initiation of enteral feeding and increasing volume of enteral feeding. But the infants who were in the probiotics group they achieved full enteral feeding faster than those in the control group.

Stratification of gestational age was done to see the frequency of NEC in both treatment groups. It was observed that in Group A, there were 2 neonates who had NEC and their gestational ages were 28-30 weeks while in the gestational ages 31-34 weeks only 1 neonate had NEC. On the other hand in the placebo group, 6 neonates had NEC and gestational ages of all these neonates were 28-30 weeks.

Table 2: Grading according to gestational age in relation to Incidence of Necrotizing Enterocolitis (NEC)

	Group A				Group B		
	Yes	**No**	**Total**		**Yes**	**No**	**Total**
28-30 weeks	2	11	13		6	8	14
31-34 weeks	1	25	26		0	25	25
35-36^{+6} weeks	0	31	31		0	31	31
Total	3	67	70		6	64	70
p-value	0.070				0.000		

However in placebo group neonates whose gestational ages were in between 31-34 weeks and 35-36+6 weeks, none of the neonates had NEC. As per p-value no statistically significant association was seen between NEC and gestational ages of neonates in treatment group however in placebo group, a statistically significant association (p-value=0.001) was seen for NEC and gestational ages (Table No.2).

In treatment group, there were 3 neonates who had NEC. Among these neonates 1 neonate had weight <1000g, 1 neonate weight was in between 1000-1500 g and 1 neonate weight was 1500-2500g. On the other hand in placebo group, 3 neonates whose weight was <1000g and 3 neonates whose weight was 1000-1500g had NEC. In treatment group, no statistically significant association was observed for NEC and birth weights of neonates while in placebo group, a statistically significant association was observed between NEC and birth weights of neonates (Table No.3). This study also showed that maximum number neonates presented to the department during their first 24 hours of life in both groups (data not shown).

Table 3: Grading according to weight in relation to Incidence of Necrotizing Enterocolitis (NEC)

	Group A (NEC)				Group B (NEC)		
	Yes	**No**	**Total**		**Yes**	**No**	**Total**
<1000g	1	3	4		3	2	5
1000-1500g	1	19	20		3	15	18
1500-2500g	1	45	46		0	47	47
Total	3	67	70		6	64	70
p-value	0.094				0.000		

DISCUSSION

Although NEC is always a major challenge in neonatology. Much information has been obtained regarding its pathogenesis, allowing a better study of its prevention and management. Special attention has been given to supplement the preterm infants with probiotics, especially those with very low birth weight, in an attempt to decrease the burden of this disease. Probiotics are the living microorganisms offered as nutritional supplements that act by regulating the local bacterial flora in the intestine of the host organism. They act by increasing permeability and improving the resistance of the mucosa against bacterial penetration in the intestine. They also increase the resistance of the intestinal barrier against the passage of bacterial toxins; modify the host response to the microbial products; increase the mucosal response to IgA; produce bactericidal substances and competitively exclude potential pathogens.

The present study was aimed to determine the role of probiotics in the prevention of NEC, to decrease its mortality and morbidity and also to provide guidelines for the better management of preterm neonates with NEC. A total of 140 preterm neonates who presented within 72 hours of life and fulfilling the inclusion criteria were included as study. The study population was divided into two equal groups, Group A and Group B. Group A received once daily 2.0g of commercially made Ecotec sachet containing >8 billion CFU of freeze dried L.acidophilus, Bifidobacterium, S.thermophilus and L.delbrueckii cells. In this group, probiotics were started on beginning of feeding mixed in milk of newborn and continued administration until hospital discharge or 40 week post conceptional age, while Group B received the placebo.

The results show that with supplementation of probiotics, NEC was found to be decreased significantly in preterm infants as compared to the placebo group. Among the 70 preterm neonates of probiotic group, 3 (4.3%) confirmed cases of NEC were observed while in 70 preterm neonates of control group, 6 (8.6%) confirmed cases of NEC were observed. Similarly, this study also show that in the probiotics group, the incidence of NEC stage ≥ 2 was 3.2% versus 7.2% in controls.[8] One of the study done by Mihatsch et al. (2010) showed that in the probiotics group, the incidence of NEC was 2.2% versus 4.5% in controls.[9]

We found that the supplementation of probiotics was associated with decreased risk of mortality significantly in preterm VLBW infants. In our study, mortality in group A was 3(4.3%) while in group B, mortality was 5(7.1%). Recent study published in 2012 showed the mortality with probiotics group was 4.3% while the mortality in the control group was 8.5%.[10] Similarly another study conducted by Monzani (2009) confirmed that the death in preterm VLBW neonates was reduced to much extent with the use of probiotics. In his study, the overall mortality in probiotics group was 4.0% versus 7.1% in control group.[11]

Incidence of NEC is inversely proportional to the gestational age, with increasing gestational age, incidence of NEC decreases. In present study, the gestational age analysis of group 1 patients showed that 13 (18.6%) neonates were 28-30 weeks of age, 26 (18.3%) neonates were 31-34 weeks and 31(20%) neonates were 35-36^{+6} weeks while the gestational age analysis of group 2 patients showed that 14 (40%) neonates were 28-30 weeks of age, 25 (18.3%) neonates were 31-34 weeks and 31(20%) neonates were 35-36^{+6} weeks. Gestational age analysis of the patients in both groups showed no statistical difference. A study conducted by Ren B in 2010 determined the effect of probiotics in preterm with weight <1800 grams which is consistent to the majority of our study population.[12]

Analysis of birth weight was done in both groups. In **group A**, there were 4 preterm babies with birth weight <1000 grams, 20 neonates with birth weight 1000-1500 grams and 46 neonates with birth weight 1500-2500 grams. While in **group B**, there were 5 preterm babies with birth weight <1000 grams, 18 neonates with birth weight 1000-1500 grams and 47 neonates with birth weight 1500-2500 grams. A study conducted by Ren (2010) determined the effect of probiotics in preterm up to 33 weeks gestation which is consistent to the majority of our study population.[12]

Nonetheless, the results of our study confirmed that the supplementation of probiotics can reduce risk of NEC and also mortality in preterm VLBW infants and further identify their safety. Further studies are needed to evaluate the supplementation of probiotics their safety and long term effect on the health of the infants.

CONCLUSION

Prophylactic use of probiotics in preterm neonates resulted in statistically significant reduction in

frequency of NEC (4.3% in preterm newborns treated with probiotics as compared to 8.6% in preterm newborns treated without probiotics). The benefits were mainly focused on the medical NEC and death related to NEC in infants born ≤ 1500 grams. These results suggest a significant benefit of prophylactic use of probiotics in these high risk premature infants.

The set of results showed, with consistent data, that enteral administration of probiotics reduced the frequency of severe cases of NEC. Based on these results, it can be concluded that the probiotics are another useful tool in pediatric clinical practice. However, more studies are needed to assess different type of probiotics, their doses, duration, safety and as well as best preparation methods for use in neonates.

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