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Research Article

# Effect Of Adding Probiotics Sachet In Standard Formula Feed On Prevention Of Necrotizing Enterocolitis In Preterm Babies

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## ABSTRACT

**Background:** Annually 15 million babies are born prematurely throughout the world and of which 1 million die due to complications related to prematurity; necrotizing enerocolitis (NEC) being one of them. Objective of our study was to use probiotics in feed to reduce incidence of NEC in preterm babies ⩽34 weeks and its effect on secondary outcomes such as mortality, time to reach full feed and weight gain.

**Methods:** This was an observational cohort study that was conducted in combined military hospital Quetta. 50 premature babies ⩽34 weeks were selected and probiotics were given to them.

**Results:** The incidence of NEC and other complications in babies taking formula feed with probiotics was very low, 78% babies had no complications and they were discharged healthy. Mean days to reach full feed were 5.2 with standard deviation of 2.329. Daily weight gain was observed with the p value of <0.01 that is statistically significant value.

**Conclusion:** Preterm, Formula feed with probiotics, NEC (necrotizing enterocolitis), days to reach full feed.

**Keywords:** Quality of Life,

## INTRODUCTION

An estimated 15 million babies are born preterm and approximately 1 million children die each year due to complications of prematurity[1]. Sixty percent of preterm births (PTBs) occur in South Asia and Sub Saharan Africa[2]. Pakistan has 748,100 PTB annually and is ranked fourth after India, China and Nigeria[3]. Prematurity is associated with number of complications such as Respiratory Distress Syndrome, Bronchopulmonary Dysplasia, Retinopathy of Prematurity, Pneumonia, Sepsis, Intraventricular Hemorrhage, Necrotising eterocolitis, Apnea, Bradycardia etc.

Necrotizing enterocolitis (NEC) is a serious condition that occurs in premature babies with significant mortality and morbidity rate. 90% babies are preterm and 10% are full term babies4. Studies show that 12% of infants born weighing less than 1500 grams will develop NEC; of those, about 30% will not survive[4,5].

As compared to mother's milk which is rich in prebiotic oligosaccharides and also contains some probiotics, a standard infant formula contains none of both. Unfortunately, In some premature deliveries EBM is not available due to early delivery. Lactogenesis (milk production) occurs under the influence of hormones, such as estrogen, insulin, cortisol, progesterone, prolactin, and human placental lactogen[6]. Preterm birth may alter the normal sequence of lactogenesis. A delay in secretory activation can be associated with a negative impact on successful lactation[7]. Mothers of preterm infants can have problems in lactogenesis as a result of their preterm delivery, coupled with antenatal corticosteroids, stress, maternal illness and operative delivery[8,9].

Parental nutrition is another option to promote growth and neurodevelopment but it is associated with many complications including nosocomial infections[10]. So we decided to add commercially available probiotics in formula feed.

Delayed enteral feeding, frequent use of antibiotic therapy, and changes of normal digestive microflora(intestinal dysbiosis) are considered to be contributing factors for the increased risk of necrotizing enterocolitis (NEC) in preterm infants[11,12] and is the rationale for probiotic supplements.

Probiotics are oral supplements that contain a sufficient number of viable microorganisms to alter the microflora of the host and has the potential for beneficial health effects[13]. A Cochrane review in 2008 concluded that enteral probiotic supplementation reduced the incidence of NEC and mortality[14]. Another Cochrane review concluded that oral supplementation of probiotics prevents severe NEC and reduces mortality in preterm infants but more studies are needed to assess efficacy of probiotics in LBW infants and its role in reducing incidence of complications[15].

Our study was primarily focused on evaluating role of probiotics in reducing incidence and severity of necrotizing enterocolitis in preterm neonates ⩽34 weeks alongwith its role on other outcomes like mortality, time to reach full feeds.

## METHODS

This study was an observational study and was conducted in neonatal intensive care unit from September 2018 to June 2019 at Combined Military Hospital Quetta. 50 preterm babies fulfilling the inclusion criteria were given formula feed with probiotics and outcome was measured in the form of daily weight gain, incidence of NEC and other complications and mortality rate.

**Inclusion criteria**

- Preterm babies ≤34 weeks gestational age
- Hemodynamically stable enough to start oral feeds (stable vital signs, normal bowel sounds without abdominal distension and no abnormal gastric aspirates.
- Those whose mothers were not providing EBM at the time of commencement of feeds inspite of persuading and frequent support.

**Exclusion Criteria**

- Gestational age >34 wks.
- Severe cardiorespiratory compromise.
- Those with surgical abdominal disorders with strict NPO orders from Surgical team.
- Babies of mothers who were willing to adequately provide EBM/directly breast feed.
- Those having obvious syndromic features.

Gestational age was calculated according to LMP and first trimester antenatal scans. Birth weight on admission and initiation of feeds were recorded. Feeding was started when the infant had stable vital signs, normal bowel sounds without abdominal distension and no abnormal gastric aspirates. Formula feed was started at 10-60 ml/kg/day according to weight and gestational age. The amount of feeding was advanced slowly if tolerated with no more than a 20-30ml/kg increment per day upto 150-180ml/kg/day.

Probiotics were added in formula feed of all preterm babies. Feeding was stopped if there was any sign of feeding intolerance such as the presence of gastric aspirates in the amount that was more than half of previous feeding, or with abdominal distension or blood in stool and apnea episodes, abdominal ultrasound was advised if needed.

Probiotic sachets were used in this study, each sachet of 1g containing Lactobacillus acidophilus, lactobacillus bulgaricus and Bifidobacterium longum.

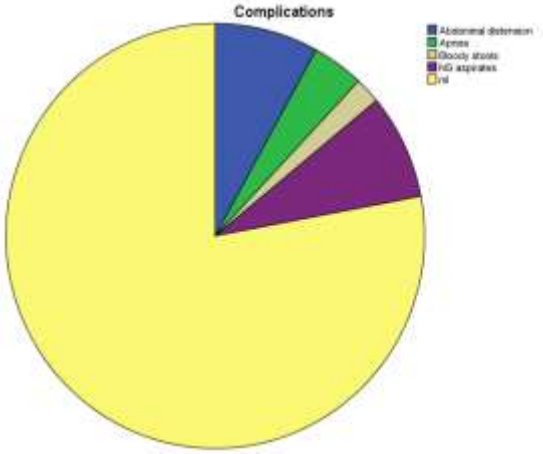
## RESULTS

In our study 50 patients of ⩽34 weeks of gestational age were selected according to inclusion and exclusion criteria. They were given formula feed with probiotics.

**Table 1: Demographic characteristics**

| | Frequency | Percentage |
|---|---|---|
| **Gender** | | |
| Male | 32 | 64% |
| Female | 18 | 36% |
| **Gestational age** | | |
| 28-31 weeks | 20 | 40% |
| 32-34 weeks | 30 | 60% |
| **Birth weight** | | |
| <1500 grams | 17 | 34% |
| >1500 grams | 33 | 66% |
| **Mode of delivery** | | |
| Vaginal delivery | 7 | 14% |
| Caesarean section | 43 | 86% |
| **Antenatal steroids** | | |
| Yes | 37 | 74% |
| No | 13 | 26% |
| **Antenatal risk factors** | | |
| Yes | 45 | 90% |
| No | 5 | 10% |

Out of 50 patients 32(64%) were male babies and 18(36%) were females. 20 babies (40%) had gestational age gestational age 28-31 weeks and 30 babies (60%) had gestational age 32-34 weeks (Table 1). Mean gestational age was 32.128 with standard deviation of 1.4022. Mothers of 45 babies (90%) had antenatal risk factors such as PPROM, GDM, PIH, Oligohydramnios, absent diastolic flow in umbilical artery, placenta previa and Eclampsia etc. and Five mothers (10%) had no such antenatal risk factor. To reduce the




onset of complications such as RDS, 37 mothers (74%) received 2 doses of antenatal steroids and 13 mothers (26%) delivered in emergency, thereby did not receive antenatal steroids.

Out of 50 patients 43(86%) were delivered by LSCS and 7(14%) were delivered by SVD. These preterm babies had birth weight of minimum 985 grams and maximum weight of 2215 grams, their mean birth weight was

1670.32 grams with standard deviation of 286.66. 17 babies(34%) had birth weight <1500grams and 33 babies(66%) had birth weight >1500grams(Table 1).

Formula feed with probiotics was started on 1st or 2nd day of life. Mean days to reach full feed were 5.20 with standard deviation of 2.329(Table 2).

**Table 2: Days to reach full feed:**

| Total number of patients | Mean of days | Standard deviation |
|---|---|---|
| 50 | 5.20 | 2.329 |

Feed was slowly increased not more than 30ml/kg/day. Most of babies 39(78%) had no complications, only 11 babies (22%) had complications. Out of these babies 4(8%) had abdominal distension, 4(8%) had NG aspirates, 2(4%) developed apnea episodes and only 1 baby (2%) had bloody stools (Table 3).

**Table 3: Complications**

| Complications | Frequency | Percentage |
|---|---|---|
| Abdominal distension | 4 | 8% |
| Apnea | 2 | 4% |
| Bloody stool | 1 | 2% |
| NG Aspirates | 4 | 8% |
| Nil | 39 | 78% |
| Total | 50 | 100% |

Onset of complications in 11 x babies was also compared with many other factors such as MOD: Out of 43 babies which were delivered by LSCS 10 babies (90.9%) had complications and out of 7 babies (9.09%) which were delivered by SVD only one baby had complication (Table 4).

**Table 4: Comparison of MOD and complications:**

| MOD | Frequency of complications | Percentage of complications |
|---|---|---|
| SVD | 1 | 9.09% |
| Caesarean section | 10 | 90.9% |

Most of babies with complication had low birth weight. 7 babies (63.6%) had birth weight <1500 grams and 4 babies (36.3%) had birth weight >1500 grams (Table 5).

**Table 5: Comparison of birth weight and complications:**

| Birth weight | Frequency of complications | Percentage of complications |
|---|---|---|
| <1500grams | 7 | 63.6% |
| >1500grams | 4 | 36.3% |

Most of babies with complications of NEC were below 31 completed weeks of gestational age, 8 babies (72.7%) were below 31 weeks and 3 babies (27.2%) were above 31 weeks of gestational age.

## DISCUSSION

In our study incidence of NEC and other complications is very low. 78% preterm babies receiving probiotics in feed had no complications. Similar observation was seen in a study of Bin et al. which showed lower incidence of NEC in the probiotics group (4% versus 16.6%; p=0.031)16.

The incidence of NEC with the use of probiotics was also evaluated in a study held in Taiwan by Lin et al. wherein, a single-center, randomized, masked, controlled trial was conducted in 367 preterm infants. The incidence of NEC was 5% in the study group compared with 12.8% in the control group (P = 0.009). Death occurred in 3.9% of the study group and 10.7% of the control group (P = 0.009)17.

Probiotics reduce not only incidence of necrotizing enterocolotis but also decrease occurrence of gut associated sepsis and mortality in preterm infants18. A Cochrane review proved that probiotics supplementation in preterm babies reduced 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)19.

Another research performed in Iran by Amini et al. showed that the incidence of NEC and C-reactive protein(CRP) was high in control group as compared to study group with probiotics(P=0.02). Incidence of NEC grade 1 was 16.7% in probiotics group and 26.7% in control group. Incidence of NEC grade 2 was 0% in probiotic group and 20% in control group20.

Similar results were found in study in India that incidence of NEC was significantly lower in babies taking feed with probiotics compared with control group (1 of 75 neonates vs 12 of 75 neonates; p=0.001). Severity of NEC, nosocomial sepsis and mean duration of hospital stay was significantly lower in the test group21.

Another study was conducted in Israel by Bin-Nun et al. to evaluate the effect of prophylactic probiotic supplementation on the incidence and severity of NEC in preterm infants. The incidence of NEC was 4% in the study group compared with 16.4% in the control group (P = 0.03). A 75% relative risk reduction for the development of NEC was found with the use of probiotics compared with the control, with an absolute risk reduction of 12% with the use of probiotics22.

Other factors were also observed during our research. There is significant effect of antenatal steroids in mother to reduce occurrence of postnatal complications such as intraventricular hemorrhage and necrotizing enterocolitis in babies23. It is also suggested that mode of delivery also affects on outcome of baby, a cesarean section is associated with change of microflora of intestine of baby which leads to NEC24, in our study most of babies with complications were delivered by same mode of delivery (90.9%).

In present study mean days to reach full feed were 5.2 with standard deviation of 2.329. Daily weight gain was significant with p value of <0.01 that is statistically significant value. Similarly a study conducted on infants treated with probiotics which showed improved daily weight gain(20.8±6.6 vs 22.2±5.2,p<0.001)25. Another research observed better weight gain in newborns receiving synbiotics (14.61±9.6 grams per day vs 2.97±3.81 grams per day, p=0.0000001)26.

Seven of 12 randomised controlled trials retrieved (n=1393) were eligible for inclusion in the analysis. Meta-analysis using a fixed effects model estimated a lower risk of necrotising enterocolitis (relative risk 0.36, 95% CI 0.20-0.65) in the probiotic group than in controls, risk of death was reduced in the probiotic group (0.47, 0.30-0.73). The time to full feeds was significantly shorter in the probiotic group (weighted mean difference -2.74 days, 95% CI -4.98 to -0.51) than in controls27.

In another study 274 preterm VLBV babies were admitted in NICU, 186 babies were randomized, of them 91 babies were given probiotics and 95 were not. The number of days required to reach full enteral feeding (13.76±2.28 vs 19.2±2.02; p<0.001) were significantly low in babies who received probiotics. Feeding tolerance was better in the probiotic-exposed group. The incidence of NEC was significantly low in the probiotic-exposed group when compared with non-exposed group (5 of 92 [5.5%] vs. 15 of 95 [15.8%], respectively; P = 0.042)28.

In our study incidence of NEC was high in babies with low birth weight <1500grmas, out of 11 babies who had complications 7 babies (63.6%) had low birth weight and 4 babies (36.3%) had birth weight >1500 grams. 1167 patients from 95 NICUs in mainland China with necrotizing enterocolitis were included in a study in 2011, incidence was 2.50% in LBW(<2500 grams) babies and 4.53% in VLBW(birth weight <1500 grams).29

Similarly chances of NEC are high in babies with gestational age <32 weeks. Most of

babies with complications of NEC were below 31 completed weeks of GA that were 8 babies (72.7%). A study in Sweden also proved that chances of necrotizing enterocolitis is more in babies <32weeks and with weight <1500grams30.

## CONCLUSION

At the end of our study it is concluded that in the preterm babies who cannot be provided EBM, we can give formula milk to them with probiotics. Incidence of complications is lower with the usage of probiotics.

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