



Clinical and Safety Profile of Probiotics in Preterm Infants

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Abstract

Breastfeeding helps in the development of healthy microflora in neonates. When babies are born preterm, breastfeeding is delayed, resulting in the development of an unnatural variety of gut microflora. This adversely affects the absorption of nutrition, mucosal barrier and systemic inflammatory response. Probiotics in preterm babies can help develop a healthy gut flora and avoid complications.

In our analysis, none of the babies had any immediate complications associated with introducing probiotics, and they have tolerated feeds well at the expected rate. We have noted a reduction in sepsis and NEC rates.

Keywords: Probiotics; Preterm Nutrition; NEC/Necrotising Enterocolitis; LOS/Late-Onset Sepsis

Introduction

The most common cause of mortality and morbidity is neonatal sepsis. In India, sepsis can be attributed to 25% to 65% of neonatal deaths [1]. Recent research has provided ample evidence for using various strategies to reduce the incidence of sepsis. Probiotics are one of these strategies that have helped reduce the necrotising enterocolitis (NEC) rate and late-onset sepsis (LOS) in preterm infants [2].

What do we know so far

NEC has been associated with premature babies having an immature gut and transmigration of bacteria from the gut into the bloodstream. This intestinal dysbiosis has been associated with NEC, a type of severe neonatal sepsis. Dietary supplementation of probiotics has proven primarily effective in reducing NEC and LOS in preterm infants by modulating intestinal bacteria to provide resistance to invasive species and promote the mucosal barrier [3-5].

UK Practice - Probiotics most popularly used have been lactobacillus and bifidobacteria among the bacteria [6]. The dose used is 1 billion CFU of either or both bacteria. Probiotics are started after the introduction of feeds, and it has been confirmed that this initial amount has been tolerated in most neonatal units in the UK. Probiotics are started in most neonatal units in preterm babies under 32 weeks and continued till 34 weeks, and feeds have been tolerated for at least two weeks [7,8].

Following the introduction of probiotics containing the above two agents, we aimed to look at the effect of this practice on our NEC and LOS rates in the unit.

Methods

A retrospective cohort analysis of 50 preterm infants born less than 32 weeks or less than 1500 grams in the neonatal unit and started on probiotics was done. The probiotics started after start-

ing feeds on day one, and it has been confirmed that the feeds are being tolerated as defined as tolerating 1ml every 2 hours for 24 hours.

We reviewed the journey of the babies in the neonatal unit till discharge and noted.

Primary outcomes

- Number of cases of NEC and LOS.
- Mortality rate.

Secondary outcomes

- Feed tolerance.
- Growth rate.

Results

- The median gestation age for the infants receiving probiotics was 29 weeks (range - 25 weeks to 31 weeks), and the median birth weight was 1350 grams (range - 685 to 1840 grams). The male-to-female ratio was 1:1.
- The NEC rate was 8%, and the LOS rate was 4% after the introduction of probiotics in the overall cohort analysed. There was no mortality associated with sepsis in the cohort.
- Feed intolerance was seen in 2% and 92% showed optimal growth rates following the centiles on the growth charts when the babies were on probiotics in the neonatal unit. The effect on feed tolerance and growth stayed with the infant receiving probiotics till discharge.

Discussion

The retrospective analysis helped us assess our practice and examine the benefits of starting probiotics in our neonatal unit. In a survey conducted in the UK, 62% of the neonatal units are using probiotics. This number has risen, especially after multiple RCTs and the Cochrane review highlighting the benefits of starting probiotics. In our study, we found a relative risk reduction of 64% (RR 0.35; 95% CI 0.13 to 0.95) and a number needed to treat of 7 (95% CI 3.7 to 47.3) for NEC and 63% (RR 0.36; 95% CI 0.1 to 1.5) and 15 respectively for LOS. A Cochrane review by Sharif, *et al.* found a risk reduction of 46% and a number needed to treat of 33.4. The study also showed a decrease in mortality (RR 0.76, 95% CI 0.65 to 0.89) and the number needed to treat 50 (95% CI 50 to 100).

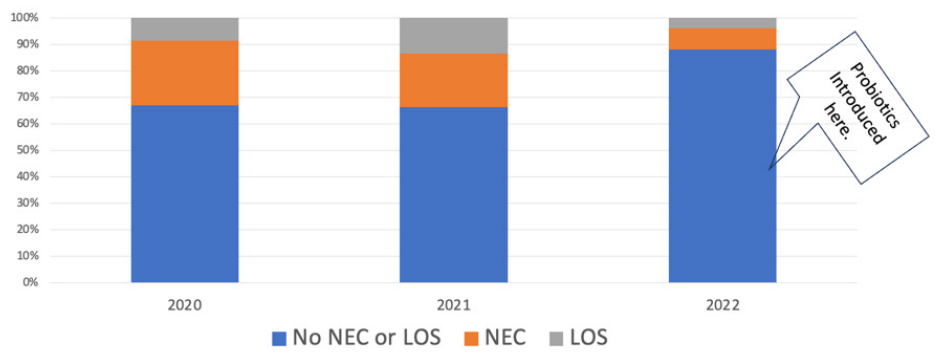
We used lactobacillus and bifidobacteria in our analysis. A systematic review by Morgan, *et al.* found this to be the most helpful combination in reducing overall mortality (OR, 0.56; 95% CI 0.39-0.80) and NEC (OR, 0.35 [95% CI, 0.20–0.59]).

The reduction in the NEC and LOS rates has helped reduce expenses towards treatment, improving the cost-benefit ratio after introducing probiotics. Probiotic safety has always been something that has hindered clinician confidence in using the product in the most fragile lives. A regular check of practice will help alleviate concerns and convince managers to continue funding the project to help reduce neonatal morbidity and mortality.

In our analysis, none of the infants showed any adverse effects after starting probiotics. There was no feed intolerance or sepsis increase attributed to the bacteria used in the probiotics. This has been consistently evidenced in systematic reviews and meta-analyses [5,7,9]. In our study, we had a feed intolerance rate of only 2%. In feed intolerance, we looked at developing food allergy and reflux with symptoms like vomiting, desaturation with or without bradycardia, etc., while or after feeding. Charlotte L Weeks, *et al.* in a 2021 meta-analysis, demonstrated that the prevalence of Feed Intolerance in preterm babies varied from 15 to 30% with an overall prevalence of 27% (95% CI 23% to 31%) [10].

All babies had a consistent growth rate while on probiotics, which followed the growth chart for their gestational age. I could not find consistent literature to support this and could suggest an incidental finding rather than assuming that probiotics could have influenced better absorption of nutrients. We could infer that the reduction in sepsis rates has helped maintain consistent nutrition and kept the baby's growth rate in the unit. Consistent nutrition could help reduce rates of bronchopulmonary dysplasia and retinopathy of prematurity, as per available literature.

The limitations would be that we are looking at a retrospective cohort analysis of this population and a small sample size. Further studies on neurological outcomes and the incidence of allergies and asthma could be potential research interests.



Graph 1: Rates of LOS, NEC and well babies in two years preceding and the last one after introduction of probiotics.

Conclusion

In keeping with current literature, there has been an improvement in NEC and LOS rates after using probiotics for preterm infants in our neonatal unit.

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