NEONATAL OUTCOMES FOLLOWING INTRODUCTION OF ROUTINE PROBIOTIC SUPPLEMENTATION TO VERY PRETERM INFANTS

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INTRODUCTION

Meta-analyses of probiotic supplementation have demonstrated a reduction in risk of all-cause mortality and necrotising enterocolitis (NEC). Administration of exogenous probiotics influences the structure of the preterm microbiome. It has been demonstrated that infants in receipt of Bifidobacterium/Lactobacillus probiotics are more likely to progress to have a microbiome dominated by Bifidobacterium compared to those not supplemented. Importantly, development of NEC appears to be less frequent in these infants. Retrospective studies across time periods before and after introduction for routine probiotic supplementation have demonstrated mixed results.

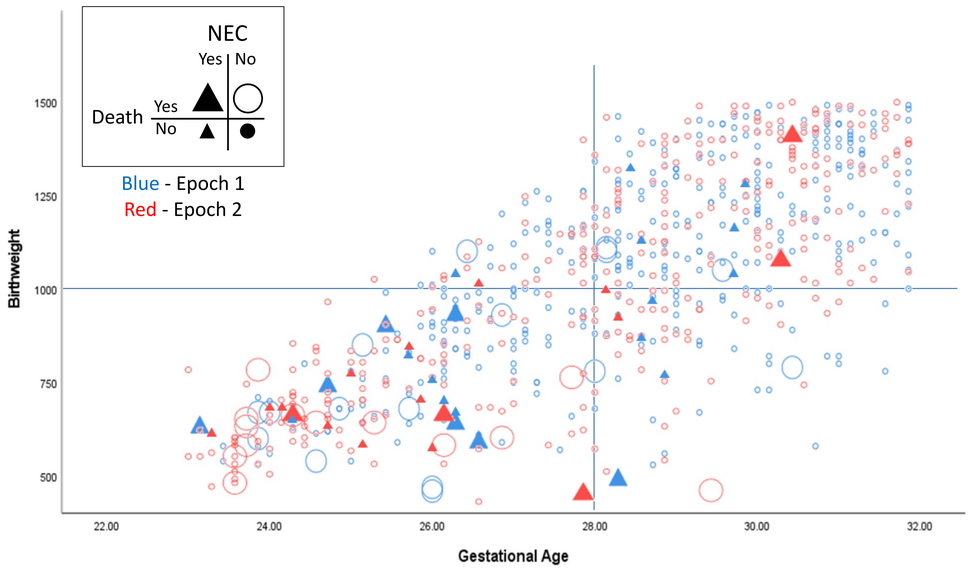
The aim of this study was to investigate if the introduction of a Bifidobacterium bifidum and Lactobacillus acidophilus probiotic was associated with a reduction in mortality and/or NEC Stage ≥2a in very preterm infants by comparing data over a 12-year period at our institution (6 years before its introduction and 6 years after).

METHODS

A retrospective study of infants <32 weeks gestation and <1500g surviving beyond 72 hours of life was performed. Two 6-year epochs; pre-probiotics (Epoch 1: 2008-2013) and with probiotics (Epoch 2: 2015-2020), were evaluated. Infants born in the year of policy introduction (2014) were excluded to account for inconsistencies in practice with the introduction of a new policy. Infants were excluded if they died or were transferred to another hospital within 72 hours of birth. The primary outcome was defined as death after 72 hours or NEC Bell stage 2a or greater. Data were extracted from the Vermont Oxford Network database. Infants documented as having NEC or focal intestinal perforation had their health record reviewed individually to confirm diagnosis and Bell Staging.

RESULTS

Seven-hundred-and-forty-four infants were included (Epoch 1: n=391, Epoch 2: n=353), of which 301 were less than 28 weeks gestation at birth (Epoch 1: n=142, Epoch 2: n=159). Infants in Epoch 1 had significantly higher gestational age and birthweight and were less likely to have antenatal steroids, antenatal magnesium sulphate and postnatal steroids or mothers with antenatal hypertension. Binary logistic regression analysis was performed to adjust for confounding and potential confounding variables. Differences between epochs did not depend on gestational age group (< 28 weeks; ≥ 28 weeks). The figure illustrates the distribution of mortality and NEC by birthweight and gestational age. The table shows results of the unadjusted and adjusted analysis.



	Epoch 1 *(n=391)*	Epoch 2 *(n=353)*	Unadjusted analysis			Adjusted analysis		
Model 1 [1]	%(n)	%(n)	OR	(95% CI)	P-value	OR	(95% CI)	P-value
Combined outcome	9.5(37)	8.5(30)	0.89	(0.54-1.47)	.646	0.53	(0.29-0.97)	.038
Mortality	5.9(23)	5.1(18)	0.86	(0.46-1.62)	.64	0.51	(0.24-1.08)	.08
Necrotising enterocolitis	5.4(21)	4.8(17)	0.89	(0.46-1.72)	.731	0.63	(0.30-1.31)	.216
Late-onset sepsis	31(121)	18.1(64)	0.49	(0.35-0.70)	<.001	0.35	(0.24-0.52)	<.001

	Adjusted analysis		
Model 2 [2]	OR	(95% CI)	P-value
Combined outcome	0.45	(0.24-0.85)	.013

[1] adjusted for birthweight and postnatal steroid use

[2] adjusted for birthweight, postnatal steroid use, sex, small for gestational age, early-onset sepsis, and non-steroidal anti-inflammatory treatment of patent ductus arteriosus

DISCUSSION

In unadjusted analysis, probiotic supplementation in this single-centre retrospective study was not associated with a reduction in the combined outcome of severe grade NEC or death or its individual components in infants who survived longer than 72 hours from birth. However, after adjustment for differences in birthweight and use of postnatal steroids, a significant reduction in the primary outcome association with probiotic use ((OR(95% CI): 0.53 (0.29 to 0.97) p=.038) was demonstrated. This was primarily driven by reduced mortality across all gestational ages and fewer cases of NEC in infants ⍰28 weeks, however these differences were not significant. The secondary outcomes of death and NEC alone were not significantly different between time periods before or after adjustment. A significant reduction in the incidence of late-onset sepsis in the probiotic era was also seen. Notably, there was a marked and sustained reduction in late-onset sepsis incidence between 2009 and 2011 (Figure 1), particularly in infants greater than 28 weeks. This was concurrent with introduction of a targeted quality improvement initiative to reduce sepsis rates in our neonatal unit and therefore quantification of the effect of probiotics on late-onset sepsis was not possible.

CONCLUSIONS

There was an associated reduction of the composite outcome of severe grade NEC and/or death, after adjustment for confounding variables, with introduction of routine administration of a B. bifidum and L. acidophilus probiotic at our institution.

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