The availability of probiotics and donor human milk is associated with improved survival in very preterm infants

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Abstract

Background To determine whether the introduction of pasteurized donor human milk and probiotics for infants born < 32 weeks gestational age or < 1500 g birthweight is associated with a reduction in mortality and the incidence of necrotising enterocolitis (NEC) and sepsis.

Methods We performed a retrospective analysis of two cohorts: before and after the introduction of probiotics and pasteurised donor human milk. Univariate analysis of primary and secondary outcomes was performed; variables impacting outcomes were assessed using multivariate logistic regression.

Results There were 1791 infants: 1334 in the pre-donor milk/probiotic cohort and 457 in the post-donor milk/probiotic cohort. On univariate analysis, mortality (7.6 vs. 2.4%, $P < 0.001$) and incidence of sepsis (6.2 vs. 3.5%, $P = 0.028$) were statistically significantly lower in the post-donor milk/probiotic group. NEC (2.8 vs. 1.5%, $P = 0.14$) and non-NEC associated gastrointestinal perforation (1.6 vs. 0.4%, $P = 0.052$) were lower in the post-donor milk/probiotics cohort, but these were not statistically significant. The difference in mortality remained statistically significant on multivariate analysis in the post-donor milk/probiotic cohort compared to those in the pre-donor milk/probiotic cohort (odds ratio 0.31, 95% confidence interval 0.16–0.61). The decrease in the incidence of NEC was consistent with previous observational studies but the difference was not statistically significant.

Conclusion The availability of probiotics and pasteurised donor human milk is associated with a reduction in mortality in very preterm infants.

Keywords Enterocolitis, necrotizing · Infant, newborn · Milk, human · Milk banks · Probiotics

Introduction

Despite decreased mortality and morbidity in very preterm and very low birth weight infants, some of them still die; and necrotising enterocolitis (NEC) and infection continue to be ongoing causes of death and chronic illness in this vulnerable group [1].

The use of probiotic supplementation for very low birth weight infants has been shown to reduce the rate of NEC and all-cause mortality [2–6]; possibly due to improved intestinal maturation, down-regulation of intestinal inflammation and direct competition for host binding-sites and nutrients [7, 8]. Some trials have also shown a decreased time to full enteral feeds in infants given probiotics [4, 8]. Importantly, no increased risk of sepsis due to probiotic bacterial species has been documented in any trials [2–6]. One retrospective cohort study did show an increase in NEC [9].

It is well established that breast milk from the infant's own mother is protective against both NEC and death in preterm infants, due to the presence of active enzymes which promote gastrointestinal mucosal maturation [10, 11], and immunomodulating and anti-microbial factors [12]. Provision of pasteurized human donor milk to infants whose mothers are unable to supply sufficient breastmilk reduces the risk of NEC compared with feeding with formula [13–15].

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Multiple randomized controlled trials and cohort analyses have been performed investigating the effects of probiotics and pasteurized donor human milk provision individually in preterm infants [3–7, 9, 12–22]; however, currently no data exists on the benefits of combined probiotic use and donor breast milk supplementation. Subgroup analysis in the systematic review by Aceti et al. did find that probiotics only prevented late-onset sepsis in infants fed human milk [20].

Our nursery introduced prophylactic probiotics, in the form of *Lactobacillus acidophilus* and *Bifidobacterium bifidum* (Infloran® capsules—*L. acidophilus* LA37 and *B. bifidum* BB07—Laboratorio Farmaceutico, Mede, Italy), for all infants less than 32 weeks gestation, and pasteurized donor human milk for infants less than 34 weeks gestation or less than 1500 g birthweight, in September and October 2012, respectively. We hypothesized that the joint introduction of pasteurized donor human milk and probiotics would result in a reduction in overall mortality and the incidence of NEC and sepsis, as well as improved short term outcomes including reduced time to establishment of full enteral feeds and central venous catheter use.

Methods

We performed a retrospective analysis of two cohorts: before and after the introduction of probiotics and pasteurised donor human milk supplementation. The infants studied were admitted to the Grantley Stable Neonatal Unit with a gestational age of <32 weeks or a birthweight of <1500 g. The pre-donor milk/probiotic cohort included babies born in the 5 years from 1 July 2007 to 30 June 2012. The post-donor milk/probiotic cohort included babies born in the 2 years from 1 January 2013 to 31 December 2014. Probiotics were given to infants <32 weeks, after informed parental consent, for a total of 42 days. Probiotics were withheld if enteral feeds were withheld, or ceased on treating clinician discretion, or if the infant was back-transferred out of the neonatal unit. Pasteurized donor human milk was provided to infants <34 weeks gestational age or <1500 g birthweight after informed parental consent, and only given if mother's own milk was not available. Infants with major congenital abnormalities, and infants who were transferred to GSNU after receiving the majority of their neonatal intensive care at another unit were excluded.

Infants meeting the inclusion criteria were identified from the neonatal unit database. All infants were included on an intention to treat basis, regardless of whether donor milk and/or probiotics were actually received. Data for all variables listed in Table 1 were recorded (including major risk factors for, and associations with, mortality, infection and NEC). Sepsis was defined as a positive blood culture at the time of a clinical deterioration, which was treated with a course of intravenous antibiotics appropriate for that

organism [23]. NEC was diagnosed in babies with at least stage 2 disease on the Modified Bell Criteria [24]. Mortality was defined as death prior to discharge home.

Primary outcomes investigated were mortality, and the incidence of NEC and sepsis. Secondary outcomes included the postnatal age at full enteral feeds (defined as 150 mL/kg/day), duration of ventilation, total duration of respiratory support (including any mechanical ventilation, continuous positive airway pressure or high-flow nasal cannula use), duration of peripherally inserted central venous line (CVL) use, and the incidence of NEC associated gastrointestinal perforations and non-NEC associated gastrointestinal perforations.

Sample size

For univariate analysis a sample size calculation (<http://clincalc.com>) using pre-intervention data for mortality in our unit (8%) showed that 388 in the intervention group (post-donor milk/probiotics) and 1175 in the control group (pre-donor milk/probiotics) would give 80% power to detect a 50% decrease in mortality ($\alpha=0.05$). Slightly smaller numbers (347 and 1043) would be adequate to show a 60% decrease in sepsis (pre-intervention sepsis in our unit 6%); and much larger numbers (1082 and 3250) would be adequate to show a 50% decrease in NEC (pre-intervention NEC in our unit 3%). Cohorts of 5 years in the pre-donor milk/probiotics group and 2 years in the post-donor milk/probiotics group would give approximately adequate numbers (for mortality and sepsis, but not NEC) with a pre/post-ratio of about 3:1.

Statistical analysis

The demographics are summarised by counts and percentages for categorical variables and means and standard deviations for normally distributed continuous variables; medians and interquartile range were used otherwise. Associations between categorical variables were assessed using Pearson's Chi-squared test of association. Differences between means were compared using Student's *t* test. Differences between medians were compared using the Mann–Whitney test.

Variables impacting outcomes were assessed using multivariate logistic regression, allowing estimation of odds ratios (OR) and 95% confidence intervals (CI). For the logistic regression: Apgar score at 5 minutes was categorised into two groups, Apgar scores >7 and ≤7; duration of ventilation was categorised into three groups (0, 1–168, and >168 hours); duration of CVL use was also categorised into three groups (0, 1–14, and >14 days); umbilical artery catheter inserted or not; postnatal age at reaching full enteral feeds was categorised into two groups (4–14 and >14 days). For the outcomes of sepsis and NEC, babies that died <7 days after birth were excluded from the analyses ($n=50$). Pre- or post-donor milk/probiotic cohort, gestation, sex, CVL duration (as classed

Table 1 Data collected for infants per cohort (including major risk factors for, and associated with, mortality, infection and necrotising enterocolitis) and outcomes

All infants	Pre-donor milk/probiotics (<i>n</i> = 1334)	Post-donor milk/probiotics (<i>n</i> = 457)	<i>P</i> value
Birthweight (g), mean (SD)	1236.8 (387.2)	1255.2 (364.9)	0.374
Gestational age (wk), mean (SD)	29.1 (2.4)	29.4 (2.3)	0.020
Apgar 5 min ≤ 7 , <i>n</i> (%)	491 (36.9)	156 (34.7)	0.391
Died before discharge, <i>n</i> (%)	101 (7.6)	11 (2.4)	<0.001
Sepsis, <i>n</i> (%)	83 (6.2)	16 (3.5)	0.028
Necrotising enterocolitis (NEC), <i>n</i> (%)	37 (2.8)	7 (1.5)	0.139
NEC associated gastrointestinal perforation, <i>n</i> (%)	19 (1.4)	6 (1.3)	0.861
Non-NEC associated gastrointestinal perforation, <i>n</i> (%)	22 (1.6)	2 (0.4)	0.052
Patent ductus arteriosus, <i>n</i> (%)	350 (26.2)	132 (28.9)	0.271
Umbilical arterial catheter, <i>n</i> (%)	802 (60.1)	234 (52.2)	0.003
Infants who survived to discharge	Pre-donor milk/probiotics (<i>n</i> = 1233)	Post-donor milk/probiotics (<i>n</i> = 446)	<i>P</i> value
Age at full enteral feeds (d), median (IQR)	13 (11)	11 (9)	<0.001
Age at full enteral feeds by category (d), <i>n</i> (%)			
≤ 14	600 (59.2)	328 (74.4)	<0.001
> 14	413 (40.8)	113 (25.6)	
Duration of CVL days (d), median (IQR)	9 (15)	7 (12)	<0.001
Duration of CVL by category (d), <i>n</i> (%)			
0	502 (39.2)	191 (42.0)	<0.001
1–14	454 (35.4)	201 (44.2)	
> 14	326 (24.4)	63 (13.8)	
Duration of ventilation, median (IQR)	23 (95)	13 (50)	<0.001
Duration of ventilation by category (h), <i>n</i> (%)			
0	470 (36.5)	199 (44.6)	0.002
1–168	541 (42.1)	180 (40.4)	
> 168	275 (21.4)	67 (15)	
Total duration of respiratory support (h), median (IQR)	158 (867)	90 (578)	0.001

CVL central venous line, SD standard deviation, IQR interquartile range

above), ventilation duration (as classed above), no vs. presence of any umbilical artery catheter, and age at full enteral feeds (as defined above) were assessed for impact.

To investigate, post hoc, for improvements over time, the pre-donor milk/probiotic cohort was divided into two equal groups of 2.5 years and logistic regression predicting mortality was repeated comparing each cohort with the post-donor milk/probiotic cohort.

Ethics approval was granted by the Royal Brisbane and Women's Hospital Human Research Ethics Committee.

Results

There were 1791 infants included in the analysis: 1334 in the pre-donor milk/probiotic cohort and 457 post-donor milk/probiotic cohort. Demographics of the two groups are displayed in Table 1.

The comparison between groups on univariate analysis are shown in Table 1. Mortality and the incidence of sepsis, NEC, and non-NEC associated gastrointestinal perforation were lower in the post-donor milk/probiotics cohort, but the differences in NEC and non-NEC associated gastrointestinal perforation were not statistically significant. The decrease in the incidence of NEC was consistent with previous observational studies [21]; but the difference was not statistically significant due to the sample size.

There were also differences between the cohorts for postnatal age at reaching full enteral feeds, the duration of ventilation, total duration of ventilator support and the duration of peripherally inserted CVL use and whether a UAC was inserted or not.

In the 457 babies in the post-donor milk/probiotic cohort, 309 (68%) received donor human milk, 370 (81%) received probiotics, 264 (58%) received both and 42 (9%) received neither.

Table 2 Logistic regression predicting neonatal mortality from sex, pre- or post-donor milk/probiotic cohort and gestational age

Variables	<i>P</i> value	OR	95% CI for OR	
			Lower	Upper
Gender				
Female	Reference	1.000		
Male	0.056	1.535 ^a	0.989	2.381
Cohort				
Pre-donor milk/probiotic	Reference	1.000		
Post-donor milk/probiotic	0.001	0.313	0.160	0.612
Gestational age (wk)	<0.001	0.501 ^b	0.449	0.560

OR odds ratio, CI confidence interval. ^aThe odds of death were 1.5 times higher for male compared to female infants (not statistically significant). ^bThe odds of death were halved for each additional week of gestation

The difference in mortality remained statistically significant when adjusting for gestational age and gender on logistic regression (Table 2). The odds of mortality were reduced by 69% for infants after introduction of donor milk and probiotics in the post-donor milk/probiotic cohort compared to those in the pre-donor milk/probiotic cohort (OR 0.31, 95% CI 0.16–0.61). There was no statistically significant difference in mortality rates for infants born in the first 2.5 years of the pre-donor milk/probiotics cohort, compared with infants born in the second half of this period (OR 1.06, 95% CI 0.67–1.68).

After logistic regression of infants who survived at least 7 days the difference in incidence of sepsis was no longer statistically significant (OR 0.79, 95% CI 0.44–1.42) when adjusting for associated variables (Table 3).

After logistic regression of infants who survived at least 7 days the difference in incidence of NEC was still not statistically significant (OR 0.92, 95% CI 0.32–2.62) when adjusting for associated variables (Table 4).

Discussion

Following the combined introduction of probiotics and pasteurized donor human milk we have seen a significant decrease in mortality in very preterm and very low birth-weight infants. We have also seen these babies achieve full enteral feeds earlier, with reduced duration of CVL use. They spent less time on mechanical ventilation and respiratory support. There may also be clinically important reductions in the incidence of sepsis and NEC but the differences seen were not statistically significant. The reduced mortality may be explained by numerous properties of human breast milk and probiotics. Donor human milk has natural antioxidants and immunomodulating factors which persist despite the pasteurization process [12, 25, 26]. These may provide a protective effect, compared to preterm formula, against

Table 3 Logistic regression predicting sepsis from gestational age, CVL, ventilation and cohort

Variables	<i>P</i> value	OR	95% CI for OR	
			Lower	Upper
Gestational age (wk)	<0.001	0.766 ^a	0.669	0.877
CVL (d)	0.003			
> 14	Reference	1.000		
1–14		0.430 ^b	0.259	0.712
0		0.500 ^b	0.222	1.128
Ventilation (h)	0.002			
0	Reference	1.000		
1–168		3.548 ^c	1.362	9.245
> 168		6.762 ^c	2.331	19.615
Cohort	0.434			
Pre-donor milk/probiotic	Reference	1.000		
Post-donor milk/probiotic		0.793	0.443	1.419

OR odds ratio, CI confidence interval, CVL central venous line. ^aThe odds of sepsis were reduced by 23% for each additional week of gestation. ^bThe odds of sepsis are reduced by 57% for infants who had a CVL ≤ 14 d, compared to infants who had a CVL for > 14 d. ^cThe odds of sepsis were increased for increasing duration of ventilation compared with no ventilation: babies ventilated for ≤ 168 and > 168 h were 3.5 and 6.8 times more likely, respectively, to develop sepsis

Table 4 Logistic regression predicting necrotising enterocolitis from gestational, CVL, age at full enteral feeds, cohort and ventilation

Variables	<i>P</i> value	OR	95% CI for OR	
			Lower	Upper
Gestational age (wk)	0.036	0.780 ^a	0.618	0.983
CVL (d)	<0.001			
> 14	Reference	1.000		
1–14		0.044 ^b	0.012	0.170
0		0.034 ^b	0.003	0.339
Age at full enteral feeds (d)	0.003			
≤ 14	Reference	1.000		
> 14		0.246 ^c	0.097	0.624
Cohort	0.875			
Pre-donor milk/probiotic	Reference	1.000		
Post-donor milk/probiotic		0.919	0.322	2.624
Ventilation (h)	0.543			
0	Reference	1.000		
1–168		0.768	0.177	3.336
> 168		1.385	0.306	6.268

OR odds ratio, CI confidence interval, CVL central venous line, NEC necrotising enterocolitis. ^aThe odds of NEC are reduced by 22% for each additional week of gestation. ^bThe odds of NEC are reduced by 97% in infants with no CVL compared to infants who had a CVL for > 14 d duration. ^cThe odds of NEC are reduced by 75% for those infants who took > 14 d to reach full enteral feeds compared with infants who reached full enteral feeds at < 14 d

conditions caused (in part at least) by oxygen free radical processes [17, 27]: for example neonatal chronic lung disease (arguably reflected by the reduction in duration of ventilation) that could result in death prior to discharge. Although some bioactive milk molecules are inactivated by pasteurization, some immunomodulating biological compounds found in breastmilk, such as oligosaccharides, immunoglobulins and long chain fatty acids, persist after heating [12, 23, 25], and these as well as the competitive bacterial colonization afforded by probiotics [7], may also provide protection against bacterial and viral infection. It is important to note that as both interventions were introduced at the same time that the effects of each intervention cannot be separated.

The combination of donor human milk and probiotics failed to demonstrate a statistically significant reduction in the incidence of NEC and sepsis. However, we speculate that they may have decreased the severity in these conditions when they did occur, allowing more infants to survive. Although there were still episodes of NEC, the provision of probiotics and donor milk may have placed the infant in an improved condition to limit the invasiveness, extent and ultimately, the severity of the enterocolitis. The interventions will have allowed a comparatively more mature and functional gastrointestinal tract [12, 13], with a higher level of competitive colonization by commensal organisms [7, 19] and modulation of the pro-inflammatory responses [7, 8], limiting the virulence and colonic extent of the pathogenic bacteria to invade, and thus a less severe infection, with fewer episodes becoming fulminant.

The near halving of the incidence of NEC, although not statistically significant, is clinically important and is consistent with previous observational studies [21]. This suggests that the availability of donor milk and probiotics is still worthwhile in neonatal units with a low baseline incidence of NEC.

Not only are more preterm infants surviving, but the infants surviving have overall shorter durations of ventilation and central venous line use in the post-donor human milk/probiotics cohort. Shorter durations of ventilation and central venous line use are associated with improved outcomes [28–31]. This suggests that infants are surviving in improved condition requiring reduced amount of prolonged critical care interventions. This will likely convert into less comorbidities and reduced length of hospital stay. These were not assessed as part of our study; however, further research in these areas would be warranted.

Time to development of full enteral feeds, along with reduced duration of central venous line use, are markers of feed tolerance. Our study demonstrated that the use of probiotics and donor human milk improved feed tolerance in preterm infants. This is likely through mechanisms including improved maturation of the gut lining due to enzymes and oligosaccharides found in donor breast milk [12, 25], improved gastric motility, and protection of the gut from pathogenic bacterial colonization with the use of probiotics

[7, 8, 18]. Improved feed tolerance is a well known benefit of breast milk [12, 13, 15] and probiotics [4] in preterm infants, and our study reflected these findings.

The differences seen could be due to factors other than the introduction of probiotics and pasteurized donor human milk. There may be unknown differences between the two cohorts. Nevertheless, the results are consistent with previous meta-analyses [2–6, 8]. Changes in management strategies (e.g., ventilation techniques) and technology between the two study periods have occurred, however, these have been minor. Our criteria for extubation were similar between cohorts, and protocols for enteral feed advancement and central venous line placement or removal were no different. Demographic data showed birthweight was comparable between the cohorts; however, infants in the post-donor human milk/probiotics cohort were slightly more mature, however, this is unlikely to have had clinical significance. The lack of a statistically significant difference in mortality rates when dividing the pre-donor human milk cohort into two epochs further demonstrates little improvement with time, until the introduction of donor human milk and probiotics.

There are no other retrospective cohort studies published comparing the joint introduction of these two managements, however, there was a recent meta-analysis by Olsen et al., which analysed 12 cohort studies investigating outcomes of the introduction of probiotics [21]. This showed a significantly reduced incidence of NEC with a RR of 0.55, and significantly reduced incidence of mortality with a risk reduction of 0.72. Sepsis incidence was not significantly reduced. This meta-analysis shows similar results to ours, when comparing the significant mortality reduction and trend towards NEC reduction. This meta-analysis included studies with infants < 35 weeks and < 2500 g, and the studies used multiple different formulations of probiotics so gives a degree of similarity, however, not a direct comparison.

Similar to that analysis, our results also reflect meta-analyses of RCTs investigating both pasteurised donor human milk compared with preterm formula [13–15], and probiotics [2–6, 8], which show reduced mortality and NEC, demonstrating that clinical results from RCTs and observational analyses around the world can be reproduced in a tertiary level neonatal intensive care unit in Australia.

Given that this study has shown that the availability of probiotics and pasteurised donor human milk is associated with a reduction in mortality in very preterm infants, the continued use of probiotics and pasteurized donor human milk is supported in our neonatal intensive care unit.

In conclusion, our cohort study demonstrates significantly reduced mortality, with improved feed tolerance and reduced duration of ventilation and central venous line use, following the introduction of probiotics and pasteurized donor human milk in very preterm and very low birth weight infants. The ongoing use of probiotics and pasteurised donor human milk is supported.

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Compliance with ethical standards

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