Bovine-based breast milk fortifier and neonatal outcomes in premature infants <32 weeks' gestational age

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Study protocol

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Abstract

Purpose: To examine if the use of bovine-based breast milk fortifier (BMF) in preterm infants plays a role in the development of necrotising enterocolitis (NEC), or an increase in all-cause mortality.

Methods: Retrospective audit of 952 preterm infants, born <32 weeks gestational age (GA) between January 2010 and September 2020 at a tertiary surgical level 3 Neonatal Intensive Care Unit (NICU) (St George's Hospital, London, United Kingdom). Odds ratios (OR), risk ratios (RR), and number needed to treat (NNT) were calculated for the total cohort, and in subgroup analyses by GA.

Results: Use of BMF increased significantly across the ten-year study timeframe, from 10.5% of infants in 2010 to 45.8% in 2020. Conversely, NEC rates have been stable across this timeframe (6.3% from 2010 – 2014 and 5.8% from 2015 – 2019). BMF was not associated with an increased risk of developing NEC in preterm infants <32 weeks GA (RR 0.63), including within subgroup analyses. BMF was not associated with an increased risk of all-cause mortality within the cohort (RR 0.31). In the most clinically vulnerable subgroup, GA <26 weeks, BMF use was associated with a decreased risk of developing NEC (RR 0.36, *P*=0.019, NNT 4.80 – 30.3) and decreased all-cause mortality (RR 0.30, *P*=.0033, NNT 3.91 – 15.65).

Conclusion: Use of bovine BMF was not associated with adverse outcomes in this study. BMF use was associated with a decreased rate of adverse outcomes in the most clinically vulnerable infants.

What Is Known

- Breast milk (maternal or donor) is gold standard nutrition for preterm infant. Breast milk fortifier (BMF) provides supplementary nutrition to avoid high growth failure rates in preterm infants. Conflicting reports have implicated BMF, especially bovine-based products, in the development of necrotising enterocolitis (NEC).
- Persistent safety concerns regarding BMF have lead to variability in use across the UK and internationally.

What is new

- This study demonstrates that breast milk fortification with bovine-based products was not linked to an increase risk of developing necrotising enterocolitis in pre-term neonates <32 weeks gestational age across our 10-year study. Pre-term infants on bovine-based breast milk fortification did not have an increased risk of all-cause mortality.
- Encouraging results from this study can affect the practice of using BMF in preterm infants in neonatal intensive care settings.

Introduction

Adequate nutrition and growth in hospitalised preterm infants is fundamental to their long-term physical and neurodevelopmental outcomes [1].

Breast milk is gold standard nutrition for preterm infants due to it multiplicative protective features including a reduced risk of developing necrotising enterocolitis (NEC) [2-3]. However, preterm infants receiving breast milk have high postnatal growth failure rates [4]. Supplementation with breast milk fortifier (BMF) has been shown to support growth and development in preterm and very low birthweight infants [5].

In practice, BMF use is variable due to persistent safety concerns and conflicting reports implicating bovine-based BMF with the development NEC [6-8].

Within our tertiary surgical neonatal intensive care unit (NICU), bovine BMF is routinely used as a supplement to human breast milk (maternal or donor). We undertook a 10-year retrospective audit of premature infants <32 weeks' gestational age (GA) to explore the possible relationship between BMF use and neonatal outcomes.

Materials And Methods

Design

Retrospective, single-centre audit conducted in the tertiary surgical NICU of St George's Hospital (SGH), an NHS hospital in London, United Kingdom.

Subjects

Pre-term infants, <32 weeks' GA, born at SGH between January 2010 and September 2020, whose treatment was complete when data collection and analysis were performed.

Total cohort included N = 952 infants. Analyses included total cohort and subgroups by GA: GA 23^{+0} – $25^{+6)}$ (N = 221), GA 26^{+0} – 28^{+6} (N = 325), GA 29^{+0} – 31^{+6} (N = 406).

Data collection

Demographic and clinical variables were obtained from patients' notes on BadgerNet, UK, the national electronic neonatal database containing all clinical notes.

NEC

Bell Stage II NEC diagnosis was confirmed from clinical notes and defined as any infant who had clinical features consistent with NEC (abdominal distension, abdominal pain, bloody stools, radiographic evidence consistent with NEC) and received either medical treatment ≥ 5 days or had surgical treatment or surgical review confirming NEC. Infants who received medical treatment for <5 days or had surgery for spontaneous intestinal rupture not associated with NEC were excluded.

NEC cases were further sub-grouped as having surgical/severe (SS) NEC if they met the criteria for Bell Stage IIIB NEC (requiring surgery) or died with a cause of death directly due to/contributed to by NEC.

Mortality Data

All-cause mortality was defined as neonatal death during any episode onsite at the NICU. NEC causing or contributing to death was defined as infants who had NEC listed on their death certificate and/or those who died during treatment for NEC.

Analysis

Association between BMF use and the outcomes of interest was examined by calculating odds ratios, risk ratios, and number needed to treat. Significance was defined by P values and corresponding confidence intervals. Only NEC cases that developed after the introduction of BMF were included in relationship analyses.

Results

BMF use over time

Use of BMF increased in our NICU from 2010 to 2020 in all subgroups analysed (Fig 1a, 1b). In 2010, 10.5% of the cohort received BMF, compared to 45.8% of the 2020 cohort.

NEC rates over time

During audit timeframe, 5.9% of the total cohort developed NEC (N = 56 infants) (Supplementary Table 1). Among NEC cases, 53.6% (N = 30) developed surgical/severe NEC (3.2% of the total cohort).

The majority of the infants who developed NEC (51.8%) were GA < 26 weeks (N = 29, 13.1% of admissions in that subgroup); 10.4% were GA 26-28 weeks (5.2% of admissions within that subgroup); and 17.9% were GA 29-31 weeks (2.5% of admissions within that subgroup) (Fig 1c).

Rates of developing NEC did not change significantly over time: from 2010 – 2014 6.3% of the cohort developed NEC; from 2015 onwards, 5.8% of the cohort developed NEC (Fig 1c).

BMF use and the development of NEC

BMF use did not increase the odds or risk of developing NEC within the total cohort (OR 0.62, CI 0.30 to 1.29, *P* = .20; RR 0.64, CI 0.32 to 1.28, *P* = .21), nor within any subgroups analysed by GA (Supplementary Table 2). Extremely premature infants, GA <26 weeks, were at less risk of developing NEC if they received BMF (OR 0.31, CI 0.12 to 0.76, *P* =.01; RR 0.36, CI 0.16 to 0.90, *P*= .01; NNT for benefit 4.80 – 30.32).

BMF use was associated with a decreased risk of developing surgical/severe NEC in our total cohort (OR 0.23, CI 0.06 to 0.98, *P* = .05; RR 0.24, CI 0.06 to 0.99, *P* = .05; NNT 18.04 – 344.95), and for infants in the

GA <26 weeks subgroup (OR 0.16, CI 0.03 to 0.71, *P* = .02; RR 0.17, CI 0.04 to 0.75, *P* = .02; NNT 6.36 – 37.66) (Supplementary Table 2).

BMF can be introduced at any postnatal age, and introducing BMF early in postnatal development (between days 8 – 13) was not associated with an increase in developing NEC (OR 1.73, CI 0.36 to 8.39, *P* =.89; RR 1.66, CI 0.40 to 7.95, *P* =.89) (Supplementary Table 2).

Mortality

NEC was a cause of death for N = 17 infants across the study timeframe, representing 56.7% of the infants who had develop surgical/severe NEC (Supplementary Figure 1).

BMF use was associated with a decreased risk of all-cause mortality in preterm infants <32 weeks' GA (OR 0.28, CI 0.12 to 0.59, *P* =.001; RR 0.31, CI 0.15 to 0.63, *P* =.001; NNT for benefit 7.95 – 27.42) (Supplementary Table 2). Within subgroup analysis, there was no increased risk of all-cause mortality associated with BMF use (Supplementary Table 2). Extremely premature infants <26 weeks' GA, were at less risk of all-cause mortality if on BMF; this was true for all infants in this subgroup, and those who survived >10 days postnatally (OR 0.25, CI 0.10 to 0.61, *P*=.003; RR 0.30, CI 0.13 to 0.67, *P*=.003; NNT 3.91 – 15.65) (Supplementary Table 2).

Discussion

Rates of BMF use increased over time, while NEC rates remained stable

BMF use increased significantly over time on our NICU (Fig 1a, 1d), consistent with results of a recent UK-wide survey of neonatal dieticians reporting BMF use in all responding units [9].

Notably, increase in BMF use on our unit corresponds to the implementation of a standardised local protocol for introducing BMF in 2016, rather than an increase in overall use of breast milk in the NICU (as demonstrated by a stable rate of breast feeding on discharge across the audit timeframe Supplementary Figure 2). Nationally, 77% of UK neonatal units employ standardised BMF guidelines, with variation between them in criteria for starting BMF [9].

Contrasting with increasing BMF use, incidence of NEC on our NICU did not increase over time (Fig. 1d). In our cohort there was a 3.2% rate for severe NEC, which corresponds with a whole population surveillance study carried out in England between 2012-2013 [10] showing a national rate of severe NEC of 3.15%. For the current study, the criteria for defining NEC were intentionally broad, so as not to underestimate NEC incidence.

Use of BMF did not increase risk of negative outcomes

Reassuringly, use of BMF was not associated with either an increased risk of NEC or all-cause mortality.

Internationally, variability in BMF use is unsurprising given the persistent belief that an exclusively human milk derived diet is best for NEC prevention. However, a Cochrane review found insufficient evidence to support this conclusion: there was low certainty evidence from one study which showed no change in risk of NEC between infants given human milk derived versus bovine derived fortifier [11]. A recent meta-analysis suggesting NEC rates were increased with bovine vs human BMF had only weak quality evidence and included significantly fewer infants than our study [8]. Our work, which is a large single study analysis over a long time period, provides reassurance as to the safety of bovine derived fortifier for preterm infants. This is especially important considering the great cost burden of providing human milk fortifier, and the remaining ethical controversies in the processes required to produce human milk fortifier.

As our unit's BMF protocol has no minimum postnatal age, we were reassured by results that early BMF introduction (postnatal days 8 -13) was not associated with an increased risk of NEC or all-cause mortality.

Furthermore, stable rates of breastfeeding at discharge over time also reflect no negative impact of BMF on the establishment of breastfeeding, which supports findings of a UK-wide audit published in 2017 [12].

Protective role of BMF

BMF use was associated with a decreased risk of developing NEC, surgical/severe NEC, and all cause-mortality in extremely clinically vulnerable infants <26 weeks' GA. A Cochrane review of trials of multi-nutrient fortification found a slightly improved in-hospital rate of growth associated with BMF use [7]. Our work may suggest that extremely clinically vulnerable infants are those in whom adequate nutrition, as provided by BMF, has the strongest protective benefit. Further investigation is needed to corroborate this finding.

Abbreviations

BMF: breast milk fortifier

NEC: necrotising enterocolitis

NICU: neonatal intensive care unit

SGH: St George's Hospital, London

SS NEC: surgical/severe necrotising enterocoloitis

Declarations

Competing Interests: The authors have no competing interests to disclose.

Data collection was authorised as part of a registered audit.

Contributors: AK and LDR conceived the study and developed the methodology. KJ performed data collection, analysis and prepared the first draft of the study manuscript. All authors developed the final manuscript. This publication is the work of the authors and AK will serve as the guarantor for the contents of this paper.

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Ethics: This study was conducted as a registered audit.

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Figures

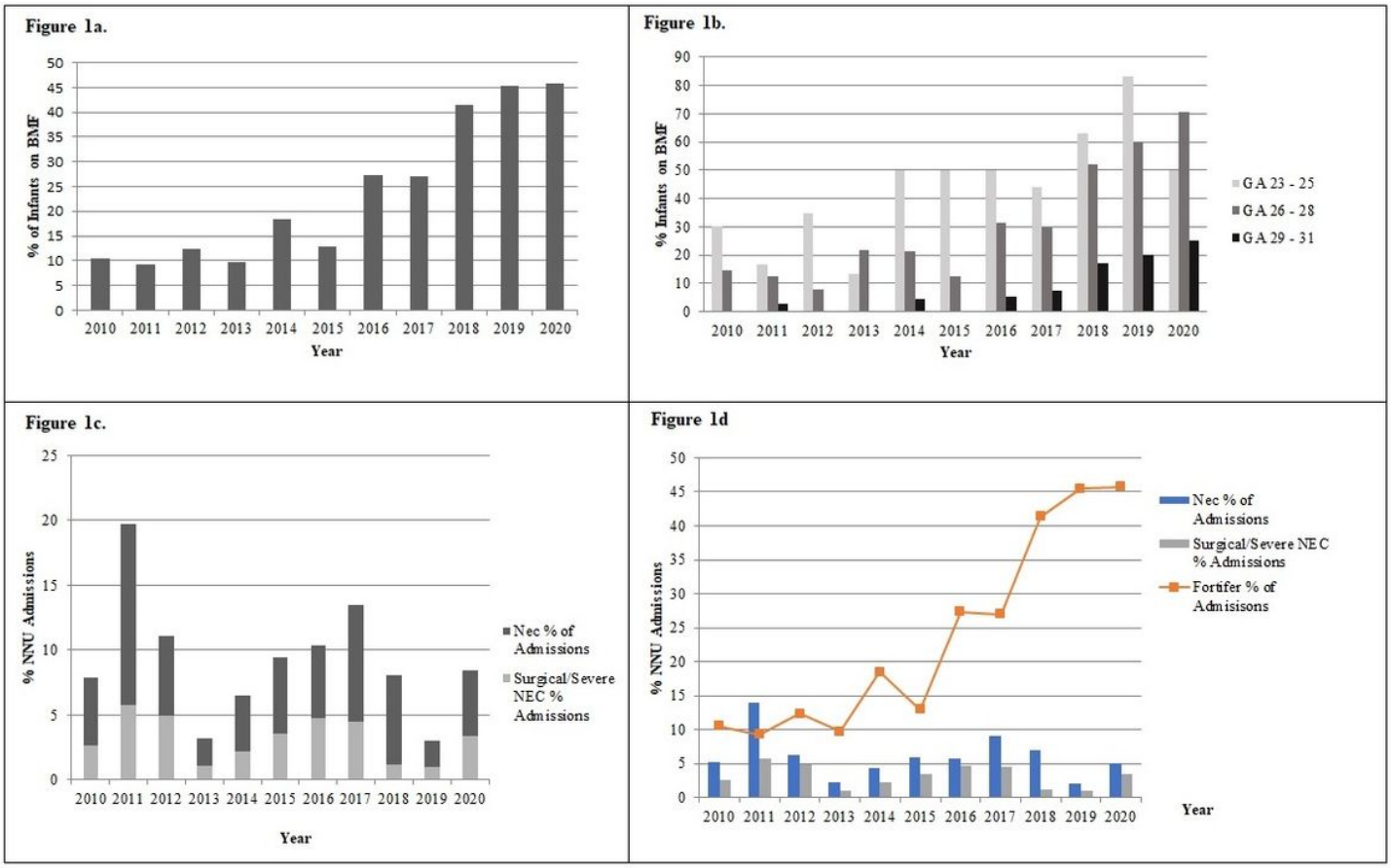

Figure 1

Bovine-based breast milk fortifier (BMF) use and the development of necrotising enterocolitis (NEC) on the neonatal unit (NICU) of St George's University Hospital (SGH) from 2010 – 2020. Fig 1a BMF use in full cohort of preterm infants <GA 32 weeks at the SGH NICU 2010 – 2020. **Fig 1b.** Subgroup analysis of BMF use in the SGH NICU from 2010 – 2020 by GA. **Fig 1c** NEC rates, Bell Stage II and surgical/severe NEC, at the SGH NICU in babies GA<32 weeks from 2010 – 2020. **Fig 1d.** BMF use overlayed with rates of Bell Stage II NEC and surgical/severe NEC at the SGH NNU 2010 – 2020.

Supplementary Files

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