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CRC Research Presentation

Determining whether breastmilk intake is associated with lower risk of NEC (Necrotizing Enterocolitis) in term and late-preterm infants born with congenital heart disease

BACKGROUND

The benefits of human breast milk (mother's own or donor breast milk) in reducing the risk of NEC (necrotizing enterocolitis) amongst premature infants has been demonstrated in numerous studies, including randomized control trials. NEC can affect term infants as well, particularly neonates born with congenital heart disease (CHD). Overman et al conducted a retrospective study which demonstrated that out of 170 infants diagnosed with Modified Bell stage 2 or greater NEC, 17% (28) were full-term infants. Amongst these full-term infants, 64% had congenital heart defects requiring surgical intervention [1]. Several studies have suggested that NEC in infants with CHD may be a different disease process than in pre-term infants. In premature infants, multiple factors contribute to the development of NEC including excessive inflammatory response by an immature immune system, immature intestinal barrier, and bacterial dysbiosis [3][4]. NEC in CHD infants is likely driven by systemic inflammation and impaired intestinal perfusion, the latter of which can occur pre-operatively due to poor circulation/oxygenation and intra-/post-operatively due to cardiopulmonary bypass [5]. This calls into question whether breastmilk is as protective against NEC in late pre-term and term infants born with CHD as in premature populations.

OBJECTIVE:

The objective of this study is to determine whether breastmilk is associated with decreased risk of NEC in late pre-term and term infants born with CHD.

SUBJECTS

Infants born with CHD at gestational age >33 weeks and birthweight >1.5 kg who were admitted to the CUMC NICU from ***2009-2019*** will be included in the study. CHD is defined as any structural cardiac anomaly, excluding PFO (patent foramen ovale) [6]. Only infants >1.5 kg in birthweight will be included in the study since these infants are not eligible for donor human milk in CUMC. Similarly, although late pre-term is defined as birth at or above 34 weeks gestational age, we will include infants born at or above 33 weeks since these neonates are not eligible for donor human milk. Exclusion criteria include no enteral feeds/incomplete feeding data during first 6 days of life and supplementation with arginine, lactoferrin, and probiotics.

DATA COLLECTION

The primary variable of interest is breastmilk intake. Studies on the relationship between breastmilk intake and NEC risk have used variable endpoints for data collection on enteral feeds.

Sisk et al conducted a retrospective study of 551 infants </= 32 weeks gestation looking at maternal milk, donor human milk, and preterm formula intake associated with NEC. Feeding data was collected on each patient from birth to NEC diagnosis or 34 weeks PMA (post menstrual age) [7]. This may be based on evidence that rate of NEC declines after 32 weeks PMA [10].
Corpeleijn et al conducted a retrospective study on infants with birth weight <1500 g in which they compared percent of mother's milk intake over first 10 days of life to development of NEC in first 60 days of life [9]

Meinzen-Derr et al arbitrarily chose to study breastmilk intake in first 14 days of life amongst infants weighing 401-1000g at birth to determine if there was an association with risk of NEC. [9]

In order to determine the time frame over which we will collect feeding data in this study, it is important to realize that time to NEC after birth is earlier in term infants compared to pre-term infants. Gonzalez-Rivera et al conducted a study on 84 infants with NEC to determine the relationship between gestational age and age of NEC onset. The 25th percentile, median, and 75th percentile of day of NEC diagnosis in neonates with gestational age >33 weeks is 2,6 and 7 days, respectively. The mode of this distribution is 6 days. For our study, we will collect data on enteral feeds during the first 6 days of life to define breastmilk intake in neonates who did not develop NEC. In neonates who developed NEC, enteral feeding data will be collected for each day prior to NEC diagnosis. Feeding data will be expressed as (1) the proportion of human breastmilk of total enteral feeds and (2) volume per weight per day (mL/kg/day) of breast milk.

Other key variables of interest include established risk factors for NEC such as gestational age, birth weight, gender, small for gestational age, empiric antibiotics, umbilical catheter, vasopressor use, mechanical ventilation, 5 minutes Apgar scores, day of life of first enteral feed, and HLHS (hypoplastic left heart syndrome) diagnosis.

OUTCOMES
Outcomes of interest include NEC Stage >/= 2 and surgical NEC. NEC stage >/= 2 will be defined according to the Bell's Criteria and confirmed with radiographic evidence of pneumatosis intestinalis, portal venous gas, or pneumoperitoneum [8] [11]. Surgical NEC is defined as requiring peritoneal drain or laparotomy.

STUDY DESIGN
All the patients enrolled in the study will be divided into two cohorts: NEC vs no-NEC. Groups will be compared to determine if there is a significant difference in proportion of human breastmilk intake of total enteral feeds and volume of breastmilk intake.

STATISTICAL ANALYSIS
Based on the distribution of the enteral feed data, either Student T-test or Wilcoxon Rank Sum will be used to determine if the proportion of human breastmilk intake and volume of breastmilk (mL/kg/day) intake is significantly different between the NEC and no-NEC group. Multivariate logistic regression analysis will be used to determine significant predictors for NEC when potential confounders are controlled.

POWER ANALYSIS
According to the power analysis for unpaired t-test, presuming that the NEC group has approximately 20% breast milk intake of total enteral feeds and that the non-NEC group has approximately 40% breast milk intake of total enteral feeds with a standard deviation of 20%, we will need 17 subjects in the NEC and non-NEC group to reach statistical significance

CONFIDENTIALITY OF STUDY DATA
All data will be de-identified and stored on a password protected, encrypted device.

POTENTIAL RISKS

There are no potential risks to the study subjects given that this is a retrospective study. Standard precautions will be taken to secure PHI.

POTENTIAL BENEFITS

There are no potential benefits for subjects enrolled in the study. If the result demonstrates that breastmilk is beneficial, it may provide the impetus to expand donor human milk eligibility to late-preterm and term infants born with congenital heart disease.

CITATIONS

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