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Randomized Clinical Trial of Pre-operative Feeding to Evaluate Intestinal Barrier Function in Neonates Requiring Cardiac Surgery

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Abstract

Objective—To evaluate intestinal barrier function in neonates undergoing cardiac surgery using lactulose/mannitol (L/M) ratio measurements and to determine correlations with early breast milk feeding.

Study design—This was a single-center, prospective, randomized pilot study of 27 term neonates (< 37 weeks gestation) requiring cardiac surgery who were randomized to one of two pre-operative feeding groups: 1) nil per os (NPO) vs. 2) trophic (10 cc/kg/day) breast milk feeds. At three time points (pre-op, post-op day 7, and post-op day 14), subjects were administered an oral lactulose/mannitol solution and subsequent L/M ratios were measured using gas chromatography, with higher ratios indicative of increased intestinal permeability. Trends over time in the mean urine L/M ratios for each group were estimated using a general linear mixed model.

Results—There were no adverse events related to pre-operative trophic feeding. In the NPO group (n=13), the mean urine L/M ratios at pre-op, post-op day 7, and post-op day 14 were 0.06, 0.12, and 0.17, respectively. In the trophic breast milk feeds group (n=14), the mean urine L/M ratios at pre-op, post-op day 7, and post-op day 14 were 0.09, 0.19, and 0.15, respectively. Both groups had significantly higher L/M ratios at post-op day 7 and 14 compared with pre-op (p<0.05).

Conclusions—Neonates have increased intestinal permeability after cardiac surgery extending to at least post-op day 14. This pilot study was not powered to detect differences in benefit or

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adverse events comparing NPO with breast milk feeds. Further studies to identify mechanisms of intestinal injury and therapeutic interventions are warranted.

Trial registration—Registered with [ClinicalTrials.gov](https://clinicaltrials.gov): NCT01475357.

Keywords

Nutrition; growth failure; congenital heart disease

Gastrointestinal morbidity and growth failure continue to be widespread health problems amongst infants with congenital heart disease, specifically those who require heart surgery as a neonate.(1–5) Most infants who require cardiac surgery in the neonatal period are appropriate weight-for-gestational-age at birth; yet, they struggle with gastrointestinal morbidities and growth failure during the post-operative period and through the first 4–8 weeks after birth.(6, 7) Gastrointestinal morbidities and growth failure are increasingly important modifiable factors given their negative impacts on outcomes such as poor wound healing, infections, prolonged hospitalizations, and longterm neurodevelopmental disability with worse school performance.(8, 9)

The etiologies of gastrointestinal morbidity and growth failure are likely multifactorial and include the increased metabolic stress of cardiac surgery, inadequate caloric delivery, mechanical feeding difficulties, altered splanchnic perfusion, and gastrointestinal complications e.g., malabsorption and severe reflux.(3, 5, 10–12) Despite the high incidence of gastrointestinal morbidity and growth failure in the cardiac infant population, there is a paucity of knowledge regarding the specific intestinal mucosal and barrier insults incurred during neonatal cardiac surgery.

Urine lactulose/mannitol (L/M) ratios have been safely used as a marker of small intestinal maturation in premature infants and healthy term infants.(13, 14) Following the ingestion of lactulose and mannitol, there is systemic absorption of the markers as measured by increased serum and urine concentrations. The markers pass across the gut wall via different routes: lactulose by a paracellular pathway between the tight junctions of gut epithelial cells and mannitol via a transcellular pathway.(15) With advancing postnatal age, intestinal permeability should decrease as evidenced by closer tight junctions, less lactulose absorption, lower concentration in urine, and smaller urinary L/M ratios. In healthy control subjects, the L/M ratio is typically low (<0.09) because permeability to the larger molecule lactulose is much lower than permeability to the smaller molecule mannitol.(14, 16) We sought to determine perioperative intestinal barrier permeability using L/M ratio measurements and identify correlations with early breast milk feeding in neonates requiring cardiac surgery. We hypothesized that infants who received trophic breast milk feeding during the pre-operative period would have decreased intestinal permeability post-operatively.

Methods

The Institutional Review Board of the Medical University of South Carolina (MUSC) approved this study. This was a single-center, prospective, randomized pilot study of term

neonates with structural heart disease requiring cardiac surgery. Written informed consent was obtained from the parents or legal guardians of the children who served as subjects of the investigation. All study subjects were consented and enrolled by the principal investigator (S.C.Z.). Inclusion criteria included: (1) term neonates ≥ 37 weeks gestation; (2) admission to the MUSC pediatric cardiac intensive care unit (PCICU) or neonatal intensive care unit (NICU); (3) a diagnosis of structural heart disease; and (4) required cardiac surgery with cardiopulmonary bypass prior to hospital discharge. Exclusion criteria included: (1) infants who were admitted after 72 hours of age; (2) discharge to home prior to PCICU or NICU admission; (3) hemodynamic instability requiring preoperative inotropic support and/or mechanical circulatory support; and (4) major congenital gastrointestinal malformations. There were no significant changes to the study protocol after trial commencement. The study was discontinued when target enrollment was achieved.

Enrolled subjects were randomized to one of two pre-operative feeding groups: 1) NPO vs. 2) trophic breast milk feeds every three hours for a total daily volume of 10 mL/kg/day via nasogastric tube. Study subjects were randomized by the biostatistician (P.J.N.) in a 1:1 ratio using a permuted block design. Because the cardiac diagnoses hypoplastic left heart syndrome and truncus arteriosus may pose increased risk for necrotizing enterocolitis (11), randomization of infants with either diagnosis was stratified to ensure balance of the randomization groups with respect to cardiac diagnosis. With the exception of the biostatistician, all study personnel were blinded to treatment group assignment until after the subjects consented to randomization. For those randomized to trophic breast milk feeding, the feeding was discontinued at midnight prior to the scheduled surgery per routine pre-operative clinical practice. After cardiac surgery, standard PCICU post-operative feeding guidelines were applied to both randomization groups. Both randomization groups received parenteral nutrition pre-operatively and postoperatively as per standard PCICU clinical practice guidelines until full enteral feeds were achieved.

At three time points (pre-op, post-op day 7, and post-op day 14), subjects were administered an enteral 2 mL/kg lactulose/mannitol solution (dose of 100 mg of lactulose/kg and 40 mg of mannitol/kg) for two doses separated by three hours. Starting at the time of the second lactulose/mannitol dose, urine was collected for a continuous 6-hour period by urine bag or Foley catheter. The urine samples were stored at -80°C until analysis. In analysis, lactulose and mannitol were measured by enzymatic assay and gas chromatography by previous published techniques (Genova Diagnostics, Asheville, NC). (17, 18) Subsequent urine L/M ratios were calculated, with higher ratios indicative of increased intestinal permeability.

Clinical data including birth and perinatal history, cardiac diagnosis and surgery, intraoperative course, perioperative antibiotics, post-operative ICU course, nutrition delivery, post-operative enteral feeding data, and gastrointestinal complications were collected on all study subjects using bedside hospital charts and electronic medical records. Clinical data were collected until the day of hospital discharge.

Post-operative enteral feeding was initiated via nasogastric (NG) tube once hemodynamic stability had been achieved for at least 24 hours as defined by decreasing inotropic support and normalization of serum lactate levels. Breast milk or infant formula was started at low

continuous volumes (20 mL/kg/day) via NG tube and then increased by 1 mL/kg/hr every six hours. After goal volume intake had been achieved, the breast milk or formula was fortified to 24 kcal/oz to achieve a daily caloric intake of 120 kcal/kg/day. Once the daily caloric intake was achieved, enteral feeds were compressed from continuous to bolus feeds in incremental fashion. Once feeds were compressed to one hour and tolerated, oral feeding was attempted. During the study period, prior to introducing oral feeds, it was institutional practice to perform vocal cord evaluation with flexible bedside laryngoscopy and swallowing assessment with modified barium swallow studies in all patients who underwent a Norwood operation, Hybrid procedure, or aortic arch reconstruction.

Statistical analyses

Between-group comparisons at baseline and hospital discharge were conducted using Fisher's exact tests or Wilcoxon rank sum tests, as appropriate. Trends over time in the mean urine L/M ratios for each group were estimated using a general linear mixed model. In this model, the dependent variable was the log (base 10) of the L/M ratio, with the transformation being necessary to ensure that normality assumptions were achieved.

Independent variables included group (NPO vs. trophic), time point (treated as a categorical variable), and interaction between group and time. A random subject effect was included to account for the fact that repeated measurements were correlated within subjects over time. The model results were back-transformed to estimate the mean L/M ratios by group at each time point. Because this was a pilot study, it was not powered to detect significant between-group differences; instead, the primary purpose of the analyses was to assess study feasibility and estimate the between-group differences and withingroup trends over time. Having $n=27$ subjects in our sample allowed us to estimate relatively precise measures of feasibility (i.e. within ± 19 percentage points). Descriptive statistics including medians and interquartile ranges were calculated for relevant study subgroups such as single vs. 2-ventricle repair, Norwood and non-Norwood infants, and prostaglandin and non-prostaglandin dependent lesions. Hypothesis testing was not performed between study subgroups due to insufficient sample sizes.

Results

Twenty-seven neonates were enrolled with 14 randomized to trophic breast milk feeding during the pre-operative period, and 13 randomized to NPO between September 2011 and December 2013 (the trial was registered shortly after the onset of patient enrollment). All subjects were included in the analysis for the primary outcome. There were no adverse events associated with trophic feeding during the pre-operative period. There were no adverse events associated with the administration of the L/M solution. Two neonates (7%) died after the post-op day 14 time point but before hospital discharge. Both neonates who died had been randomized to trophic breast milk feeding during the preoperative period and both required ECMO on the day of cardiac surgery. There were no significant differences in clinical characteristics between groups (Tables I and II; Table II available at www.jpeds.com). L/M were not successfully measured from every subject at all three time points secondary to clinical contraindications to enteral use or inadequate urine volume

obtained. At the pre-op time point, 18 subjects (67%) had successful urine sample collection. At the post-op day 7 time point, 25 subjects (93%) had successful urine sample collection. At the post-op day 14 time point, 17 subjects (63%) had successful urine sample collection.

As illustrated in Figure 1, both groups had a significantly higher L/M at post-op day 7 and 14 compared with pre-op ($p < 0.05$). Results of the general linear mixed model indicated that in the NPO group, the mean urine L/M at pre-op, post-op day 7, and post-op day 14 were 0.06, 0.12, and 0.17, respectively. Similarly, in the trophic breast milk feeds group, the mean urine L/M at pre-op, post-op day 7, and post-op day 14 were 0.09, 0.19, and 0.15, respectively. In the trophic breast milk feeds group, there was a trend for the L/M to increase from pre-op to post-op day 7 followed by a slight decline. There was no significant association between pre-operative trophic breast milk feeding and lower L/M. Group differences over time were not statistically significant (Figure 1). When compared by cardiac subgroups, in the 2-ventricle group, there was a trend for the L/M to increase from pre-op to post-op day 7 followed by a slight decline. In the single ventricle palliation group, there was a trend for the L/M to increase from pre-op to post-op day 7 and then remain persistently elevated through post-op day 14.

The incidence of gastrointestinal morbidity was high in both groups (Table IV). Three subjects were diagnosed with NEC (Modified Bell's Stage II or worse), 2 in the preoperative trophic feeding group and 1 in the NPO group. All 3 subjects developed NEC in the post-operative period, more than 7 days after the initiation of enteral feeding and after achieving goal enteral feeds. Subject 1 had a cardiac diagnosis of right ventricular dominant atrioventricular septal defect with truncus arteriosus and was diagnosed with NEC on postoperative day 22. Subject 2 had a cardiac diagnosis of hypoplastic left heart syndrome and was diagnosed with NEC on post-operative day 21. Subject 3 had a diagnosis of truncus arteriosus and was diagnosed with NEC on post-operative day 22. None of the NEC subjects required surgical intervention, and all were treated medically with bowel rest and intravenous antibiotics.

Discussion

In this cohort of term neonates who underwent cardiac surgery, intestinal permeability continued to increase through post-operative day 14, suggesting prolonged dysfunction of the intestinal tight junctions and barrier function despite advancing postnatal age. These findings are relevant given that gastrointestinal morbidity is a widespread problem in the cardiac population.(5, 11, 19) In this pilot study, there were no adverse events related to early enteral trophic feeding in the pre-operative period. At the very least, trophic breast milk feeding during the pre-operative period was not injurious. We were unable to demonstrate any significant benefits, however.

Maturation of the gastrointestinal tract is a dynamic process that continues after birth and requires a complex interaction between the development of the intestinal mucosal barrier, establishment of a stable and commensal microflora, and enhancement of the local immune response. Multiple environmental factors including postnatal age, maternal microflora, mode

of delivery, antibiotic use, and early breast milk feedings affect this interaction.(14, 20, 21) The small intestine functions as both a physiologic barrier and an important modulator of immune function with selective permeability to macromolecules. In the immediate postnatal period, increased intestinal permeability is a normal finding, potentially to allow for the uptake of larger nutritional molecules. With advancing postnatal age and intestinal maturation, however, intestinal barrier rapidly changes with decreasing permeability over the first month of life.(13, 14) Failure to develop adequate intestinal barrier function may result in less restricted antigen transport, increased susceptibility to infectious agents, inflammation, and systemic hypersensitivity.(14)

The specific biologic mechanisms of intestinal injury in cardiac infants are poorly understood. The perioperative nutrition literature for cardiac infants focuses primarily on delivery of calories and standardized feeding algorithms.(3, 22, 23) Although adequate caloric delivery is critical, the current paradigm fails to identify perioperative measures that protect intestinal barrier and mucosal and immune function in this fragile infant population.

Given the bioactive role of human milk in early postnatal gut maturation and function, early low-volume enteral feeding with human milk may have a protective effect in perioperative cardiac infants. Even in small volumes, human milk has been demonstrated to protect the gastrointestinal epithelium, promote commensal bacteria, and decrease intestinal permeability.(24–28) Even though the study failed to demonstrate improvements in intestinal barrier function or decreased incidence of feeding intolerance, this study design was not powered to detect these between-group differences. Additionally, this lack of benefit may be explained by an inadequate duration or volume of trophic feeding before surgery. The perfusion and inflammatory insults of cardiac surgery and the effects of broad-spectrum perioperative antibiotics may also simply overwhelm any protective effects of human milk.

Our study has several limitations. The study population was small and limited to a single institution; thus the statistical power to detect group differences was limited. The L/M ratios may be biased toward a healthier population because the sickest subjects (e.g., subjects who required ECMO) were unable to receive the L/M solution secondary to a relative clinical contraindication to enteral use. Patients exhibiting any clinical evidence of hemodynamic instability or acidosis during the pre-operative period were excluded; therefore, safety of trophic feeding is not translatable to all pre-operative congenital cardiac populations. The L/M ratio patterns could not be characterized in the subjects who developed NEC due to inadequate urine samples and clinical contraindications to enteral use resulting in incomplete L/M measurements for all three time points.

More definitive study on preoperative and perioperative enteral feeding is indicated. Further studies to identify mechanisms of perioperative intestinal injury and therapeutic intervention in the cardiac infant population are also warranted.

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Abbreviations

ASD	Atrial septal defect
AVSD	Atrioventricular septal defect
DILV	Double inlet left ventricle
DORV	Double outlet right ventricle
d-TGA	d-Transposition of the great arteries
ECMO	Extracorporeal membrane oxygenation
HLHS	Hypoplastic left heart syndrome
L/M	Lactulose/mannitol
LV	Left ventricle
MUSC	Medical University of South Carolina
NEC	Necrotizing enterocolitis
NG	Nasogastric
NICU	Neonatal intensive care unit
NPO	Nil per os
PCICU	Pediatric cardiac intensive care unit
PGE	Prostaglandin
RV	Right ventricle
VSD	Ventricular septal defect

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Figure 1. Box plots of urine lactulose/mannitol ratios by randomization group. The boxes reflect the median (horizontal bars within the boxes) and interquartile ranges. Circles indicate mean values, and squares represent outliers.

Figure 2.
CONSORT diagram.

Table 1

Patient clinical characteristics

	NPO (n=13)	Trophic (n=14)	P value
Birth weight (kg)	3.38 (2.66–4.08)	3.25 (2.54–4.0)	0.4
Gestational age of 39–40 weeks, n (%)	10 (77%)	7 (50%)	0.2
Male, n (%)	6 (46%)	6 (43%)	0.9
PGE dependent, n (%)	9 (69%)	12 (86%)	0.4
Age at time of surgery (days)	7 (4–8)	6 (4–9)	0.8
Single ventricle diagnosis, n (%)	8 (61%)	8 (57%)	0.9
Norwood operation, n (%)	5 (38%)	7 (50%)	0.7
Delayed sternal closure, n (%)	10 (77%)	10 (71%)	1.0
Post-operative ECMO, n (%)	0 (0%)	3 (21%)	0.2
Duration in PCICU (days)	24 (10–86)	19 (13–69)	0.4
Duration in hospital (days)	54 (21–111)	44 (18–86)	0.2
Survival to hospital discharge, n (%)	13 (100%)	12 (86%)	0.9

* Continuous variables represented with mean values (ranges).

Table 2

Cardiac diagnosis by randomization group

NPO	n (%)	Trophic Feeds	n (%)
HLHS	6 (46)	HLHS	6 (43)
Truncus arteriosus	1 (8)	Truncus arteriosus	1 (7)
d-TGA	2 (15)	d-TGA	3 (21)
Other		Other	
LV dominant AVSD	1 (8)	d-TGA, pulmonary atresia	1 (7)
RV dominant AVSD	1 (8)	DILV, pulmonary atresia	1 (7)
DORV, Taussig Bing	1 (8)	DILV, d-TGA, hypoplastic aorta	1 (7)
DORV, d-TGA, VSD, straddling mitral valve	1 (8)	Coarctation of aorta, VSD, ASD	1 (7)

Table 3

Lactulose/mannitol ratios by cardiac subgroup and time point

	Time 1: Median [IQR]	Time 2: Median [IQR]	Time 3: Median [IQR]
2-ventricle repair	0.07 [0.05, 0.07] (n=6)	0.14 [0.09, 0.46] (n=8)	0.09 [0.08, 0.13] (n=5)
Single ventricle palliation	0.08 [0.07, 0.11,] (n=13)	0.15 [0.06, 0.22] (n=17)	0.15 [0.10, 0.25] (n=12)
Norwood	0.11 [0.08, 0.14] (n=8)	0.09 [0.03, 0.20] (n=11)	0.18 [0.12, 0.30] (n=10)
Non-Norwood	0.08 [0.05, 0.08] (n=5)	0.21 [0.15, 0.36] (n=6)	0.09 [0.07, 0.10] (n=2)
Prostaglandin dependent lesion	0.08 [0.05, 0.11] (n=15)	0.15 [0.07, 0.36] (n=21)	0.12 [0.08, 0.19] (n=15)
Non-prostaglandin dependent lesion	0.07 [0.06, 0.20] (n=4)	0.12 [0.07, 0.51] (n=4)	1.14 [0.09, 2.19] (n=2)

IQR: interquartile range

Table 4

Gastrointestinal morbidity characteristics

	NPO (n=13)	Trophic (n=14)	p
Weight at hospital discharge (kg)	4.1 (2.9–5.0)	3.7 (2.9–4.6)	0.1
NEC – Bell Stage II or worse, n (%)	1 (8%)	2 (14%)	0.9
Formula change for feeding intolerance, n (%)	6 (46%)	9 (64%)	0.7
G-tube dependence at hospital discharge, n (%)	7 (54%)	8 (57%)	0.9
Gastroesophageal reflux medications at discharge, n (%)	9 (69%)	12 (86%)	0.4
Exclusive breast milk feeds at hospital discharge, n (%)	4 (31%)	4 (29%)	0.9