Randomized Clinical Trial of Preoperative Feeding to Evaluate Intestinal Barrier Function in Neonates Requiring Cardiac Surgery

Sinai C. Zyblewski, MD, MSCR[1], Paul J. Nietert, PhD[2], Eric M. Graham, MD[1], Sarah N. Taylor, MD, MSCR[3], Andrew M. Atz, MD[1], and Carol L. Wagner, MD[3]

Objectives 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-born neonates (≥37 weeks gestation) requiring cardiac surgery who were randomized to 1 of 2 preoperative feeding groups: nil per os (NPO) or trophic (10 mL/kg/day) breast milk feeds. At 3 time points (preoperative [preop], postoperative [postop] day 7, and postop day 14), subjects were administered an oral L/M solution, after which urine 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 preoperative trophic feeding. In the NPO group (n = 13), the mean urine L/M ratio was 0.06 at preop, 0.12 at postop day 7, and 0.17 at postop day 14. In the trophic breast milk feeds group (n = 14), the mean urine L/M ratio was 0.09 at preop, 0.19 at postop day 7, and 0.15 at postop day 14. In both groups, L/M ratios were significantly higher at postop day 7 and postop day 14 compared with preop ($P < .05$).

Conclusion Neonates have increased intestinal permeability after cardiac surgery extending to at least postop day 14. This pilot study was not powered to detect differences in benefit or adverse events comparing the NPO and trophic breast milk feeds groups. Further studies to identify mechanisms of intestinal injury and therapeutic interventions are warranted. *(J Pediatr 2015;167:47-51).*

Trial registration Registered with ClinicalTrials.gov: NCT01475357.

Gastrointestinal morbidity and growth failure continue to be widespread health problems among infants with congenital heart disease, specifically those needing 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 struggle with gastrointestinal morbidities and growth failure during the postoperative period and throughout the first 4-8 weeks after birth.[6,7] Gastrointestinal morbidities and growth failure are increasingly important modifiable factors given their negative impacts on such outcomes as poor wound healing, infections, prolonged hospitalizations, and long-term neurodevelopmental disability with poor 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 (eg, malabsorption, severe reflux).[3,5,10-12] Despite the high incidence of gastrointestinal morbidity and growth failure in infants with congenital heart disease, there is a paucity of knowledge regarding the specific intestinal mucosal and barrier insults incurred during neonatal cardiac surgery.

Urine lactulose/mannitol (L/M) ratio has been safely used as a marker of small intestinal maturation in both preterm and healthy term infants.[13,14] Following the ingestion of lactulose and mannitol, systemic absorption of the markers occurs, 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, decreased lactulose absorption, lower urine concentrations, 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]

In the present study, we sought to determine perioperative intestinal barrier permeability using L/M ratio measurements and to identify correlations with early breast milk feeding in neonates requiring cardiac surgery. We hypothesized

L/M	Lactulose/mannitol
NEC	Necrotizing enterocolitis
NPO	Nil per os
PCICU	Pediatric cardiac intensive care unit

From the [1]Division of Pediatric Cardiology, Department of Pediatrics, [2]Department of Public Health Sciences, and [3]Division of Neonatology, Department of Pediatrics, Medical University of South Carolina, Charleston, SC

Supported by the National Center for Advancing Translational Sciences (UL1TR000062). The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Center for Advancing Translational Sciences or the National Institutes of Health. The authors declare no conflicts of interest.

Portions of the study were presented as a poster at Translational Science, Washington, DC, April 9-11, 2014.

0022-3476/$ - see front matter. Copyright © 2015 Elsevier Inc. All rights reserved.

http://dx.doi.org/10.1016/j.jpeds.2015.04.035

that infants who received trophic breast milk feeding during the preoperative period would have decreased intestinal permeability postoperatively.

Methods

This was a single-center, prospective, randomized pilot study of term neonates with structural heart disease requiring cardiac surgery. The Institutional Review Board of the Medical University of South Carolina approved the study. 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.Z.). Inclusion criteria included: (1) term birth at ≥37 weeks gestation; (2) admission to the Medical University of South Carolina's pediatric cardiac intensive care unit (PCICU) or neonatal intensive care unit; (3) diagnosis of structural heart disease; and (4) need for cardiac surgery with cardiopulmonary bypass before hospital discharge. Exclusion criteria included: (1) admission after 72 hours of age; (2) discharge to home before PCICU or neonatal intensive care unit admission; (3) hemodynamic instability requiring preoperative inotropic support and/or mechanical circulatory support; and (4) a major congenital gastrointestinal malformation. 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 1 of 2 preoperative feeding groups, nil per os (NPO) or trophic breast milk feeds every 3 hours, for a total daily volume of 10 mL/kg/day via nasogastric tube. Study subjects were randomized by the biostatistician (P.N.) 1:1 using a permuted block design. Because the cardiac diagnoses of hypoplastic left heart syndrome and truncus arteriosus may pose an increased risk for necrotizing enterocolitis (NEC),[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 before the scheduled surgery in accordance with routine preoperative clinical practice. After cardiac surgery, standard PCICU postoperative feeding guidelines were applied to both randomization groups. Both randomization groups received parenteral nutrition preoperatively and postoperatively in accordance with standard PCICU clinical practice guidelines until full enteral feeds were achieved.

At 3 time points (preoperative [preop], postoperative [postop] day 7, and postop day 14), subjects were administered an enteral 2 mL/kg L/M solution (100 mg of lactulose/kg and 40 mg of mannitol/kg) in 2 doses separated by 3 hours. Starting at the time of the second L/M dose, urine was collected over a continuous 6-hour period by a urine bag or Foley catheter. The urine samples were stored at −80°C until analysis. In analysis, lactulose and mannitol levels were measured by enzymatic assay and gas chromatography using previous published techniques (Genova Diagnostics, Asheville, North Carolina).[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, postoperative intensive care unit course, nutrition delivery, postoperative 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.

Postoperative enteral feeding was initiated via nasogastric 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 a low continuous volume (20 mL/kg/day) via nasogastric tube and then increased by 1 mL/kg/hour every 6 hours. After the target volume intake was 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 1 hour and tolerated, oral feeding was attempted. During the study period, before the introduction of oral feeds, it was institutional practice to perform vocal cord evaluation with flexible bedside laryngoscopy and swallowing assessment with a modified barium swallow study 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 the Fisher exact test or Wilcoxon rank-sum test, 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 necessary to ensure that normality assumptions were achieved.

Independent variables included group (NPO vs trophic), time point (treated as a categorical variable), and group–time interaction. 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 ratio 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 within-group trends over time. Having 27 subjects in our sample allowed us to estimate relatively precise measures of feasibility (within ±19 percentage points). Descriptive statistics,

Download English Version:

https://daneshyari.com/en/article/6220262

Download Persian Version:

https://daneshyari.com/article/6220262

Daneshyari.com