Randomized Controlled Trial of Early Enteral Fat Supplement and Fish Oil to Promote Intestinal Adaptation in Premature Infants with an Enterostomy

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Objective To test the hypothesis that early enteral supplementing fat and fish oil decreases the duration of parenteral nutrition (PN) and increases enteral nutrition (EN) before bowel reanastomosis in premature infants with an enterostomy.

Study design Premature infants (<2 months old) who had an enterostomy and tolerated enteral feeding at 20 mL/kg/day were randomized to usual care (control = 18) or early supplementing enteral fat supplement and fish oil (treatment = 18). Intravenous lipid was decreased as enteral fat intake was increased. Daily weight, clinical and nutrition data, and weekly length and head circumference were recorded. The primary outcomes were the duration of PN and volume of EN intake, and the secondary outcomes were weight gain (g/day), ostomy output (mL/kg/d), and serum conjugated bilirubin level (mg/dL) from initiating feeding to reanastomosis. Data were analyzed by Student *t* test or Wilcoxon rank sum test.

Results There were no differences in the duration of PN, ostomy output, and weight gain between the 2 groups before reanastomosis. However, supplemented infants received less intravenous lipid, had greater EN intake, and lower conjugated bilirubin before reanastomosis, and they also received greater total calorie, had fewer sepsis evaluations and less exposure to antibiotics and central venous catheters before reanastomosis, and had greater weight and length gain after reanastomosis (all $P < .05$).

Conclusion Early enteral feeding of a fat supplement and fish oil was associated with decreased exposure to intravenous lipid, increased EN intake, and reduced conjugated bilirubin before reanastomosis and improved weight and length gain after reanastomosis in premature infants with an enterostomy. *(J Pediatr 2014;165:274-9)*.

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Intestinal perforation, caused by necrotizing enterocolitis or spontaneous intestinal perforation, typically is treated with resection of necrotic or perforated bowel and the creation of an enterostomy (hereafter referred to as an ostomy).[1] In the interval between this surgical procedure and bowel reanastomosis, which can be weeks to months, many infants with an ostomy do not absorb enteral feedings adequately. Thus, provision of nutrition sufficient to support normal growth for infants with an ostomy is challenging and usually requires a combination of enteral nutrition (EN) and parenteral nutrition (PN) including intravenous lipid. However, prolonged PN often can cause cholestasis (defined as serum conjugated bilirubin level >2 mg/dL), which is associated with high mortality and morbidity in infants.[2,3] Soy-based intravenous lipid is associated with cholestasis,[3] and a decrease in intravenous lipid administration leads to improved cholestasis,[4] suggesting that intravenous lipid infusion is one of the risk factors for PN-associated cholestasis and that infants with an ostomy might benefit from an intervention that reduces exposure to PN and intravenous lipid.

After bowel resection in animal studies, a low-fat diet impairs and high-fat diet,[5] especially the long-chain polyunsaturated fatty acids (PUFAs),[6-8] promotes intestinal adaptation and increases dietary fat absorption.[9] However, there is scant information regarding the translation of these research findings into clinical practice. The parenteral fish oil emulsion Omegaven (Fresenius Kabi, Bad Homburg, Germany) has been used as the sole source of lipid to treat infants with short bowel syndrome (SBS) and PN-associated cholestasis,[10] but it is neither readily available in the US nor approved by the Food and Drug Administration. Infants with SBS have been supplemented with enteral fat and/or fish oil to prevent or treat PN-associated cholestasis.[4,11,12] The objective of this randomized controlled trial was to test the hypothesis that in premature infants with an ostomy, early enteral fat supplementation with Microlipid (fat supplement; Nestle Nutrition, Florham Park, New Jersey) and fish oil decreases the number of days of PN and increases the EN intake before bowel reanastomosis.

DHA	Docosahexaenoic acid
EN	Enteral nutrition
PN	Parenteral nutrition
PUFA	Polyunsaturated fatty acid
SBS	Short bowel syndrome

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Methods

The study protocol was approved by Wake Forest University Health Science Institutional Review Board (WF IRB00011501) and implemented in the neonatal intensive care unit of Brenner Children's Hospital at Wake Forest Baptist Medical Center. Eligibility criteria were the presence of a jejunostomy or ileostomy, preterm birth (birth prior to 37 completed weeks of gestation), and age less than 2 months. We excluded the infants who had a colostomy, congenital anomaly, or metabolic disease and those who had received enteral feedings for more than 4 days or were unable to initiate enteral feedings within 28 days after ostomy placement. Written informed consent was obtained from the parent. We used blocked randomization with a block size of 8. Sealed envelopes were used to conceal the randomization assignments.

Infants in the control group received usual nutritional care. Infants in the treatment group received usual nutritional care plus enteral fat supplement and fish oil once they tolerated enteral feedings at 20 mL/kg/d. Enteral fat supplement (Microlipid) was started at 1 g/kg/day and then increased by 0.5 g/kg/d up to 2.5 g/kg/d as Intralipid (intravenous lipid; Baxter Healthcare, Deerfield, Illinois) was decreased by 0.5 g/kg/d. The amount of fish oil provided was initially 0.2 g every 12 hours for infants with body weight <1000 g and 0.25 g every 12 hours for infants with body weight >1000 g. As an infant's weight increased, the dose of fish oil was increased, up to a maximum of 0.5 g every 6 hours. The initial dose of fish oil was based on the rate of uterine accretion of docosahexaenoic acid (DHA; 50 mg/d),[13] and the maximal dose of fish oil was based on the assumption that DHA ≤315 mg/d appears to be safe in infants 1-6 months of age.[14] To obtain the growth-stimulating effect from both n-3 and n-6 PUFA,[15] we provided a ratio of fat supplement (n-6 PUFA) to fish oil (n-3 PUFA) at 3.75 to 5.1. During the trial, our hospital purchased 2 brands of fish oil, Major Fish Oil 500 (Major Pharmaceuticals, Livonia, Michigan) and then Rugby Sea Omega 50 (Rugby Laboratories, Inc, Corona, California). Both are US Pharmacopeia-certified. The enteral fat supplement and fish oil were mixed with human milk or infant formula and administered through a naso- or orogastric feeding tube or fed by bottle.

All infants randomized to enteral fat supplementation received this intervention during the feeding period before reanastomosis. After reanastomosis, this intervention was used only under 2 circumstances. Infants who did not have SBS but had a serum conjugated bilirubin ≥2 mg/dL were given fish oil when enteral feedings were started, and fish oil was continued until the infant was no longer receiving PN and had a serum conjugated bilirubin <2 mg/dL. If the surgeon assigned a diagnosis of SBS, the infant was fed both the enteral fat supplement and fish oil until the infant was discharged from hospital.

Upon recovery of gastrointestinal function postoperatively, infants were fed their own mother's milk when available or infant formula. As enteral feeds were increased, PN and intravenous lipid were adjusted to achieve a normal growth rate of 15 g/kg/d. Intravenous lipid was usually started at 0.5-1.0 g/kg/d and then gradually increased to 3 g/kg/d. PN was usually discontinued when EN reached 120 mL/kg/d. The targeted total fluid intake and total caloric intake for premature infants were 150 mL/kg/d and 120-130 kcal/kg/d, respectively. Enteral fat supplement, up to 10-15 cal/kg/d, usually was given to infants with poor growth while on full enteral feedings with high calorie formula. Bowel reanastomosis typically was performed once infants attained a weight of 2 kg.

For infants with a central venous catheter, a sepsis evaluation included a culture from both central line and a peripheral vein and an initiation of antibiotics treatment. Clinical signs for prompting a sepsis evaluation included hypo- or hyperthermia, new onset of apnea or a significant increase in the frequency of apnea, lethargy, irritability, abdominal distention with radiographic signs indicative of ileus, hypo- or hyperglycemia, and a significant increase in level of respiratory support. In general, if both cultures were positive for the same organism, the infant was diagnosed with sepsis. When only the central line culture was positive, the cause usually was presumed to be a colonization of the catheter. If these cultures were negative, the central line typically was not removed until it was no longer required for PN. If the daily cultures were positive, the central line was removed.

The data were collected during 2 feeding periods: the first feeding period, defined as the interval between ostomy placement and reanastomosis, and the second feeding period, defined as the interval between bowel reanastomosis and the tolerance of full feedings (150 mL/kg/d). Daily weight, clinical and nutritional data, and weekly length and head circumference were recorded. Clinical data included the level of serum conjugated bilirubin, the number of sepsis evaluations, the number of days for antibiotics treatment, and the duration of central venous catheter use during the first feeding period. Central venous catheters included a peripherally inserted central catheter and a surgically placed Broviac catheter (Bard Access Systems, Salt Lake City, Utah). The duration of central venous catheter use was defined as the percent of feeding days when PN and intravenous lipid were infused through the catheter. We excluded days when the central venous catheter was not used to administer PN during the first feeding period. We relied on bedside nurses' notes for information about feeding intolerance or adverse gastrointestinal reactions, such as increasing gastric residuals and abdominal distension.

Statistical Analyses

All results are reported as mean ± SD. When the distribution of continuous variables did not depart substantially from normal, we used the Student *t* test to compare group means; otherwise, we used the Wilcoxon rank sum test. We performed overall group comparisons as well as comparisons in 2 subgroups: (1) infants with a high ostomy (defined as jejuno- to proximal ileostomy); and (2) infants with a low