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The effect of lipid restriction on the prevention of parenteral nutrition-associated cholestasis in surgical infants☆

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Abstract

Purpose: Surgical infants requiring long-term parenteral nutrition (PN) are at risk for parenteral nutrition-associated liver disease (PNALD). The purpose of this study was to determine the effect of a lipid restricted PN regimen in preventing the development of PNALD in surgical infants.

Methods: In 2009, we implemented a lipid restricted strategy in surgical infants expected to be on long-term PN using a soy-based lipid emulsion at a goal provision of 1 g/kg/day throughout a patient's entire PN course. An experimental cohort of surgical infants treated with lipid restriction from 2009 to 2011 (n=82) was retrospectively compared to a control cohort of infants from 2005 to 2008 receiving standard intravenous lipid dosing (n=132). A multivariable relative risk regression model was constructed analyzing the association between lipid restriction and PNALD.

Results: Patients admitted during the lipid restriction era had reduced daily lipid provisions compared to the control group ($p<0.001$). There were no significant differences in demographic or measured clinical characteristics between the two groups. A significant reduction in the incidence of PNALD was demonstrated in the lipid restricted group compared to the control group (22% vs. 43%, $p=0.002$). On multivariable relative risk regression, patients treated with standard lipid provisions were 1.77 times more likely to develop PNALD than patients who were lipid restricted (95% CI: 1.2–2.7; $p=0.007$).

Conclusion: Restriction of intravenous soy-based lipid in PN-fed surgical infants is associated with a reduction in the incidence of liver disease. Early lipid restriction should be considered in all surgical infants who require PN as a preventative measure against PNALD.

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Parenteral nutrition-associated liver disease (PNALD) is a frequent complication of intravenous nutrition and accounts for a substantial proportion of the morbidity in parenterally-fed surgical infants [1,2]. PNALD can lead to cholestasis, portal hypertension, progressive liver failure, and even death, and it has been shown to hinder the process of intestinal adaptation [3].

Along with prematurity, duration of parenteral nutrition (PN), and sepsis, intravenous lipids likely play a key role in the development of PNALD [4-7]. It has been shown in multiple studies that switching from soy-based to fish oil-based intravenous lipid emulsion can reverse the biochemical changes associated with PNALD [8-10]. There are also more recent data supporting the use of lipid restriction to treat PNALD [5,11]. In this fashion, lipid dosages are reduced once PNALD has developed with the goal of normalizing conjugated hyperbilirubinemia. However, there is limited evidence that the histologic damage already sustained by the liver improves with either approach. Thus, prevention of PNALD is important to preserve normal liver function in surgical infants on long-term parenteral nutrition.

At present, there is only anecdotal evidence supporting the use of lipid restriction for the prevention of PNALD in surgical infants. Based on the recent associations between intravenous lipid infusions and the treatment of PNALD, we hypothesized that a lipid restricted PN regimen in surgical infants would be associated with a decreased risk of developing PNALD.

1. Methods

1.1. PN Regimen

Beginning in January of 2009, a lipid restriction strategy was implemented at our institution for all general surgical infants expected to receive long-term PN ($\geq$ 2 weeks). This strategy consisted of a goal lipid provision of 1 g/kg/day using a soy-based lipid emulsion throughout the patient's entire PN course or until the lipid component of PN was weaned off. Prior to the implementation of this strategy, surgical infants had received standard intravenous lipid dosing with a goal lipid provision of 2–3 g/kg/day while on PN.

Our institutional protocol for PN utilized estimated energy requirements of 90–120 kcal/kg/day for preterm infants and 85–105 kcal/kg/day for term infants. Macronutrient goals for full PN support for patients in the control group included a dextrose infusion rate of 10–14 mg/kg/min, protein allotment of 2–4 g/kg/day, and lipid provision of 2.5–3 g/kg/day. In patients treated with lipid restriction, the dextrose allotment was increased to maintain adequate caloric provision although the dextrose infusion rate did not generally exceed 16 mg/kg/min. There was no alteration in the goal protein provision for lipid restricted patients.

Initiation and advancement of enteral nutrition were encouraged but the ultimate enteral nutrition regimen was provider dependent.

1.2. Study population

To determine whether lipid restriction affected the incidence of PN-associated cholestatic liver disease, we performed a retrospective review of surgical infants at Seattle Children's Hospital (SCH) from June, 2005 to June, 2011 (IRB approval #13654). We included infants with the primary diagnoses of gastroschisis, necrotizing enterocolitis (NEC), and jejuno-ileal atresia since the majority of these children are expected to receive PN for at least 2 weeks after their initial diagnosis. Additionally, previous data from our group demonstrated that these diagnoses are associated with the highest incidence of PN-associated cholestasis [12]. The analysis was designed to compare the incidence of PNALD in infants admitted from 2005 to 2008 and treated with standard intravenous lipid allotments (the control cohort) with the more recent group of infants admitted from 2009 to 2011 and treated with lipid restriction (the experimental cohort).

For the purposes of this study, PNALD was defined as a serum direct bilirubin $\geq$ 2 mg/dL for a minimum of two weeks and for at least two consecutive measurements. Serum liver function tests were performed weekly per institutional protocol for all patients on PN. Ursodiol (30 mg/kg/day divided in three doses) was administered to patients who met the definition for cholestasis. We collected data for each patient throughout the duration of their index admission to SCH. Additional data variables included gestational age in weeks, duration of PN in days, and weight parameters. The absolute number of days of positive blood cultures during each patient's entire index admission was used as a proxy for sepsis.

1.3. Statistical analysis

Descriptive statistics were used to describe the experimental and control cohorts based on their date of admission (2009–2011 and 2005–2008, respectively). Chi-square tests and t-tests assuming unequal variance were used to compare categorical and continuous variables between the two groups. Relative risk regression was used to model the probability of PNALD between children receiving a standard PN lipid regimen and children receiving a lipid restricted PN regimen. Our implementation of relative risk regression modeled the probability of PNALD as a function of covariates using a generalized linear model with a log link and Poisson error distribution. Robust standard error estimates were used for generating confidence intervals and calculating p-values. Relative risk regression was used rather than logistic regression because the incidence of PNALD in this study population was not rare (>20% for participants in each cohort), and thus the odds ratio is an overestimate of the