Randomized Controlled Trial of Early Parenteral Nutrition Cycling to Prevent Cholestasis in Very Low Birth Weight Infants

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Objectives To compare the incidence of cholestasis in very low birth weight infants receiving cycled versus continuous parenteral nutrition, and to determine factors that predispose to parenteral nutrition–associated cholestasis (PNAC).

Study design Preterm infants weighing ≤1250 g (n = 70) at birth were randomly assigned within the first 5 postnatal days to either cycle (n = 34) or continuous (n = 36) parenteral nutrition. Liver function tests were obtained at baseline, and sequentially thereafter. Cholestasis was defined as direct bilirubin >2 mg/dL. Infants with major congenital anomalies, congenital hepatic disease, clinically apparent congenital viral infection, and those who required major abdominal surgery were excluded.

Results The incidence of PNAC was similar in the 2 groups (cycle 32% vs continuous 31%; $P = 1.0$). Bilirubin and transaminases were similar in both groups by repeated measures of ANOVA. Gestational age, birth weight, and Apgar scores were significantly lower, and Clinical Risk Index for Babies II scores were significantly higher in infants who developed PNAC. Using backward selection logistic regression, bronchopulmonary dysplasia, duration of parenteral nutrition, and days to full enteral nutrition emerged as factors independently associated with PNAC.

Conclusions Early prophylactic parenteral nutrition cycling in very low birth weight infants in this study did not reduce cholestasis. Time to full feedings is a significant predictor for PNAC in very low birth weight infants. Preterm infants with bronchopulmonary dysplasia are more likely to have PNAC as a comorbidity. The Clinical Risk Index for Babies II score may help identify those preterm infants who might benefit from future prospective prevention trials. *(J Pediatr 2012;161:229-33)*.

Prolonged parenteral nutrition is the most common cause of direct hyperbilirubinemia in preterm infants. The rate of parenteral nutrition–associated cholestasis (PNAC) varies between 10% and 50%, with the highest incidence in very low birth weight (VLBW) infants.[1,2]

Typically PNAC is diagnosed when the conjugated bilirubin is >2 mg/dL with parenteral nutrition use for at least 2 weeks.[1,3] Even though the mechanism of hepatic dysfunction related to parenteral nutrition is not fully understood, there are several risk factors that have been implicated such as sepsis, necrotizing enterocolitis (NEC), major bowel surgery, delayed or lack of enteral alimentation, duration of parenteral nutrition, and degree of prematurity.[3-7]

Parenteral nutrition cycling is the technique of infusing a daily volume of solution in less than a 24-hour period. Meehan and Georgeson[8] retrospectively evaluated 47 children with short bowel syndrome using parenteral nutrition cycling, initially 20 hours on and 4 hours off, as part of an intensive program aimed at preventing PNAC. Jensen et al[9] reported the retrospective but nonrandomized use of parenteral nutrition cycling in 36 infants with gastroschisis, but they used no standard amount of time for cycling off parenteral nutrition. Early use of parenteral nutrition cycling in VLBW infants is tempered by concerns for metabolic abnormalities, such as hypoglycemia, as well as potential infectious complications from multiple entries into lines to change solutions.

To date, there are no data on the efficacy of early parenteral nutrition cycling to prevent cholestasis in preterm infants and no published prospective randomized trials on the efficacy of parenteral nutrition cycling. We hypothesized that early cycling

BPD	Bronchopulmonary dysplasia
CRIB II	Clinical Risk Index for Babies II
ELBW	Extremely low birth weight
GGT	Gamma-glutaryl transferase
LFT	Liver function test
NEC	Necrotizing enterocolitis
NICU	Neonatal intensive care unit
NPO	Nothing per orem
PDA	Patent ductus arteriosus
PNAC	Parenteral nutrition–associated cholestasis
VLBW	Very low birth weight

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of parenteral nutrition in VLBW infants may prevent or delay the onset of cholestasis associated with prolonged parenteral nutrition. Our objectives were to compare the incidence of cholestasis in VLBW infants receiving cycled parenteral nutrition and those receiving continuous parenteral nutrition, and to identify factors that predispose these infants to PNAC.

Methods

This prospective randomized controlled trial was conducted in a level 3 neonatal intensive care unit (NICU) with all inborn patients from an inner city population. The study was approved by the hospital's Institutional Review Board. Inclusion criteria were birth weight ≤1250 g and enrollment within the first 5 days after birth. Infants with major congenital anomalies, congenital hepatic disease, and clinically apparent congenital viral infection were excluded.

Informed consent was obtained before study entry within the first 5 days after birth. Enrolled patients were randomly divided into a cycle parenteral nutrition group and a continuous parenteral nutrition group. Randomization was done using sealed envelopes stratified into 3 birth weight categories (≤750 g, 751-1000 g, and 1001-1250 g) to ensure an equal chance of enrollment of extremely low birth weight (ELBW) and VLBW infants.

Antenatal steroid use and history of chorioamnionitis were abstracted from maternal records. Patient demographic data collected included gestational age, birth weight, sex, Apgar score, temperature at admission, and base excess within the first 12 hours. Clinical Risk Index for Babies II (CRIB II) score was the risk adjustment instrument used to define severity of illness on admission.[10] Morbidities, including respiratory distress syndrome, patent ductus arteriosus (PDA), NEC, bronchopulmonary dysplasia (BPD), and early- and late-onset sepsis, were abstracted from the chart. The diagnosis of respiratory distress syndrome was based on chest X-ray, and diagnosis of PDA was based on echocardiogram. Patients with a hemodynamically significant PDA were treated either medically or surgically. NEC was defined as Bell's stage 2 or greater. Only infants with medically treated NEC were included in the final analysis, because infants who required surgery were dropped from the study due to transfer to a children's hospital. BPD was defined as oxygen requirement at 36 weeks postmenstrual age. Sepsis diagnosed more than 3 days after birth was considered late-onset sepsis. Proven sepsis required growth of an organism from the blood. Presumed sepsis was diagnosed if the patient was judged clinically unstable by the NICU team, with laboratory evidence of infection and antimicrobial therapy for at least 7 days without a positive culture. A history of fluconazole prophylaxis was recorded because of its documented association with cholestasis in preterm infants.[11]

Nutritional history included the number of days that the patient was kept on nothing per orem (NPO) status and was receiving parenteral nutrition, the postnatal day of initiation of trophic feeding, and the postnatal days when 30%, 60%, and full enteral nutrition were achieved. The initiation of trophic feeding was left to the discretion of the NICU team. Infants were kept NPO if clinically unstable on high ventilator support, on vasopressor therapy, or receiving medical treatment for a hemodynamically significant PDA.

The infants in the continuous parenteral nutrition group received amino acid solution (TrophAmine; B. Braun Medical, Irvine, California) over a 24-hour period. Intralipid 20% (Fresenius Kabi, Homburg, Germany) was infused over 18 hours in accordance with NICU protocol, and dextrose was given over 24 hours. The infants in the cycle parenteral nutrition group received TrophAmine over 20 hours, Intralipid over 18 hours, and dextrose over 24 hours. Parenteral solution was infused using di(2-ethylhexyl)phthalate–free polyvinylchloride infusion systems.[12]

Total and direct bilirubin levels were obtained at baseline and then weekly thereafter. Liver function tests (LFTs) and gamma-glutaryl transferase (GGT) levels were obtained at baseline and then biweekly. These tests were performed while the infant was receiving parenteral nutrition. No further studies were obtained after 2 normal bilirubin and LFT levels were detected after discontinuation of parenteral nutrition. Cholestasis was defined as a direct bilirubin level >2 mg/dL. For those infants who developed PNAC, bilirubin, LFT, and GGT testing was continued until cholestasis resolved. Analyses were performed with a Siemens Dimension RxL chemistry analyzer (Siemens Healthcare Diagnostics, Tarrytown, New York). The workup and management of infants with PNAC was at the discretion of the NICU team. Glucose monitoring was performed in accordance with NICU protocol.

Statistical Analysis

The cycle and continuous parenteral nutrition groups, as well as infants with and without PNAC, were compared using the Student t test and χ^2 test, as appropriate. Factors associated with PNAC in univariate analyses at a P value ≤.10 were included in a multivariate analysis, performed using backward selection logistic regression.

Results

A total of 83 patients were enrolled in the study between November 2007 and July 2010; 70 patients (34 in the cycle parenteral nutrition group and 36 in the continuous parenteral nutrition group) completed the study protocol. Thirteen patients were excluded from the final analysis because of transfer to a children's hospital for various reasons (**Figure**; available at www.jpeds.com).

Gestational age (22-30 weeks), birth weight (420-1250 g), sex, Apgar score, and CRIB II score were similar in the cycle and continuous groups (**Table I**). In addition, there was no difference in antenatal steroid use and clinical or histological chorioamnionitis between the 2 groups (data not shown).

Combined presumed and proven late-onset sepsis was higher in the cycle group, but the incidence of proven late-onset sepsis was similar in the 2 groups (**Table II**).