High Rates of Resolution of Cholestasis in Parenteral Nutrition-Associated Liver Disease with Fish Oil-Based Lipid Emulsion Monotherapy

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Objective To determine factors leading to resolution of cholestasis in patients with parenteral nutrition-associated liver disease treated with fish oil-based lipid emulsion (FOLE).

Study design Prospective observational study of 57 infants <6 months of age with parenteral nutrition-associated liver disease who received parenteral FOLE as monotherapy.

Results Median gestational age of subjects at birth was 28 weeks (range 22.7-39.5). Median conjugated bilirubin level at initiation of therapy with FOLE was 7.5 mg/dL (range 2.1-25). Resolution of hyperbilirubinemia (conjugated bilirubin <2.0 mg/dL) and survival to hospital discharge occurred in 47 (82.5%) infants. Median number of days to resolution of cholestasis was 35 (range 7-129). Ten infants (17.5%) died. Non-survivors showed a trend towards being more premature than survivors at birth (25.9 vs 29.1 weeks, $P = .056$). Infants with higher conjugated bilirubin at initiation of therapy (>10.0 compared with <5.0 mg/dL) had longer times to resolution (98 vs 56 days, $P < .005$). Time to resolution correlated inversely with gestational age at birth ($r^2 = 0.14$, $P = .02$) and directly with time to receive 100% calories enterally ($r^2 = 0.12$, $P = .03$).

Conclusions Younger gestational age infants demonstrated higher degree of cholestasis, longer time to resolution of cholestasis, and increased mortality. Higher levels of cholestasis were associated with longer time to resolution. FOLE monotherapy led to resolution of cholestasis in all surviving infants. *(J Pediatr 2013;162:793-8)*.

Parenteral nutrition-associated liver disease (PNALD) is a common problem in the neonatal intensive care unit.[1-3] Although total parenteral nutrition (TPN) has been crucial in providing nutrition and preventing essential fatty acid deficiency (EFAD),[4] its prolonged use often results in PNALD, especially in premature infants.[1] Severe PNALD results in irreversible liver failure and is associated with high mortality and morbidity, including need for liver transplantation.[5] Mortality rates as high as 38%-51% have been described in subjects with PNALD.[6,7] Dependence on TPN secondary to short bowel syndrome has been reported to have a mortality of 30%.[8]

Though the etiology of PNALD remains unclear, it is certainly multifactorial.[1,6,9] Several factors are known to play a role in the causation of this disease, including prematurity, sepsis, and high-risk states such as necrotizing enterocolitis, spontaneous ileal perforation, and multiple gastrointestinal surgical procedures.[1,8] Resolution of PNALD often requires resumption of enteral feeds and discontinuation of TPN, which may be difficult to achieve. Several strategies to minimize the hepatic damage in PNALD, including cycling of TPN, decreased doses of lipid infusions,[10] and antibiotic therapies to counter bacterial overgrowth, have met with limited success. None of these individual treatment modalities have matched the success observed with the use of fish oil-based lipid emulsions (FOLE).[10] Recent laboratory and clinical data have implicated the use of soy-based lipid emulsions in the etiology of PNALD, while highlighting the beneficial role of FOLE in the treatment of PNALD.[11-13]

The benefits of FOLE over soy-based emulsions have been attributed to the anti-inflammatory properties of omega-3 polyunsaturated fatty acids in the former and the pro-inflammatory, hepatotoxic, cholestatic properties of the predominant omega-6 polyunsaturated fatty acids and phytosterols in the latter.[14-19] Several reports describing the salutary effects of FOLE therapy in PNALD have been published.[12,13,20-27]

In the US, Intralipid (100% soybean oil) (Baxter/Fresenius Kabi, Deerfield, Illinois) and Liposyn II (50% soybean oil, 50% safflower oil) (Hospira Inc, Lake Forest, Illinois) are the only Food and Drug Administration-approved lipid emulsions. FOLE formulations are not yet approved for intravenous administration in the US. In most of Europe and Asia, FOLE, such as SMOFlipid (30% soybean oil, 30% medium-chain triglycerides, 25% olive oil and 15% fish oil) (Fresenius Kabi AG, Bad Homburg, Germany) and Omegaven (100% fish oil) (Fresenius Kabi AG,

EFAD	Essential fatty acid deficiency
FOLE	Fish oil-based lipid emulsion
PMA	Post-menstrual age
PNALD	Parenteral nutrition-associated liver disease
PN	Parenteral nutrition
TPN	Total parenteral nutrition

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Bad Homburg, Germany) are approved for use. In the US, Omegaven is currently being used only on an investigational basis with an Investigational New Drug permit. We describe a large, single-center experience of the use of FOLE rich in omega-3 fatty acids (Omegaven) as compassionate use monotherapy in the treatment of PNALD. We delineate the clinical correlates that are associated with the resolution of cholestasis treated with FOLE monotherapy.

Methods

The research protocol was approved by the Institutional Review Board of Baylor College of Medicine and Affiliated Hospitals (registered with ClinicalTrials.gov: NCT00738101). An informed consent was obtained from the parent or legal guardian of the infant. Between September 2007 and July 2011, 57 infants with PNALD younger than 6 months of age were enrolled in a compassionate use protocol to receive 1 g/kg/d intravenous infusion of Omegaven at Texas Children's Hospital, Houston, Texas. Infants older than 2 weeks and younger than 6 months of age were eligible for enrollment if the serum conjugated bilirubin was ≥4 mg/dL in the absence of prior gastrointestinal surgical procedure, or ≥2 mg/dL with a history of gastrointestinal surgical intervention or severe feeding intolerance. These infants were expected to receive parenteral nutrition (PN) for at least 28 days. Upon enrollment, the soy-based lipid emulsion, Intralipid, was discontinued and substituted with FOLE Omegaven, at 1 g/kg/d infused over 24 hours. Subjects having a congenital diagnosis with lethal prognosis, clinically severe coagulopathy unresponsive to standard therapy, or cholestasis secondary to primary hepatic disease were excluded from the study. Weekly measurements of conjugated bilirubin and triglycerides were performed until resolution of cholestasis (conjugated bilirubin was <2 mg/dL) or death. Other liver function tests were monitored as clinically considered appropriate. Evidence for coagulopathy, EFAD, and sepsis were monitored clinically and appropriate confirmatory tests were performed when these were suspected.

Statistical Analyses

Descriptive statistics were performed using SigmaPlot v. 11.0 (Systat Software, San Jose, California). The comparison of parameters between the survivors and non-survivors were assessed using a Mann–Whitney test. Statistical comparison of baseline characteristics and time to resolution were assessed using t test when reporting means, Mann–Whitney test when reporting medians, χ^2 test when reporting proportions, and one way ANOVA when more than 2 groups were compared. $P < .05$ was considered statistically significant; all analyses were 2-sided.

Results

Fifty-seven infants received FOLE for a diagnosis of PNALD. The male-to-female ratio of patients was 1.8:1. The median gestational age at birth was 28 weeks (range 22.7-39.5). The median post-menstrual age (PMA) at the initiation of FOLE therapy was 39.3 weeks (range 26.8-62). The median conjugated bilirubin level at the initiation of FOLE therapy was 7.5 mg/dL (range 2.1-25). Forty-seven (82.5%) infants survived with resolution of conjugated hyperbilirubinemia over a median period of 35 days (range 7-129). Ten infants died (17.5%); 9 among them had persistent cholestasis.

The baseline characteristics of the 47 survivors and the 10 non-survivors are shown in Table I. In order to further delineate the factors that determined the resolution of cholestasis and the overall survival, the data were further analyzed by categorizing the survivors into 3 groups based on the severity of cholestasis at initiation of FOLE therapy. Those with bilirubin levels between 2.1 and 5.0 mg/dL were categorized as Group A, whereas those with levels 5.1-10.0 mg/dL and >10.0 mg/dL as Groups B and C, respectively (Table II). The median gestational age at birth in Group A (34.2 weeks) was significantly higher ($P = .003$) compared with the non-survivors (25.9 weeks) (Figure 1). Similarly, the median PMA at the initiation of FOLE was significantly higher in Group A (42 weeks) compared with that of the non-survivors (33.7 weeks, $P = .008$)(Figure 2; available at www.jpeds.com). Gestational age at birth inversely correlated with the time to resolution of cholestasis ($r^2 = 0.08$, $P = .02$) and severity of cholestasis at the initiation of FOLE therapy ($r^2 = 0.12$, $P = .01$).

The patterns of resolution of conjugated hyperbilirubinemia following the initiation of FOLE are shown in Figure 3. The median time for resolution of cholestasis (conjugated bilirubin <2.0 mg/dL) was not significantly different between the groups (data not shown). However, the median time for complete resolution of cholestasis (conjugated bilirubin of <0.2 mg/dL) in Group C (98 days) was significantly longer compared with that in Group A (56 days, $P < .005$) as shown in Figure 4.

The conjugated bilirubin increased during the first week of therapy with FOLE in all groups followed by a gradual decline. The resolution of cholestasis coincided with an improvement but not complete normalization of the hepatocellular indices as assessed by aspartate aminotransferase, alanine aminotransferase, and gamma-glutamyl transferase (Figure 5). Thirty-nine infants in the survivor group were transitioned to full oral feeds, whereas the remaining 8 infants were discharged home on FOLE therapy.

All survivors demonstrated resolution of cholestasis, whereas only one out of the ten non-survivors demonstrated

Table I. Baseline characteristics of infants who received FOLE monotherapy for conjugated hyperbilirubinemia

	Survivors	Non-survivors	*P* value
Number	47	10	
M:F number (%)	32:15 (68:32)	5:5 (50:50)	.29
Gestational age at birth in wk (range)	29.1 (23.8-38.3)	25.9 (22.7-39.5)	.056
PMA at start of FOLE in wk (range)	39.5 (27.3-39.5)	33.7 (26.8-47.3)	.088
Bilirubin in mg/dL (range)	5 (2.1-2.5)	10.7 (3.6-14.3)	.03

M:F, male:female.