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A comparison of lipid minimization strategies in children with intestinal failure

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ABSTRACT

Purpose: The purpose of this study was to compare outcomes of lipid minimization with either Intralipid (IL) or Omegaven® in children with intestinal failure (IF) who developed intestinal failure-associated liver disease (IFALD) while receiving parenteral nutrition (PN).
Methods: A retrospective review of children with IF requiring PN who developed IFALD (direct bilirubin >2 mg/dL) while receiving IL (2009–2016) was performed. Clinical characteristics, nutritional, and laboratory values were compared between children treated with reduced IL or Omegaven®.
Results: 16 children were reviewed (8 treated with IL and 8 treated with Omegaven® at a median dose of 1g/kg/d). Both groups had similar demographics, small bowel length, and parenteral nutritional intake during the study (82.9 ± 27.1 kcal/kg/d vs. 75.9 ± 16.5 kcal/kg/d, p = 0.54). The mean direct bilirubin (DBili) prior to initiating treatment was 7.8 ± 4.3 mg/dL and 7.5 ± 3.5 mg/dL (p = 0.87) in the IL and Omegaven® groups, respectively. The IL group took a median of 113 days to achieve a DBili <0.5 mg/dL compared to 124 days in the Omegaven® group (p = 0.49). There were no differences in markers of liver function or growth trajectories among groups.
Conclusions: Lipid minimization with either IL or Omegaven® has similar success in achieving a normal DBili in children with IF and IFALD without major differences in nutritional status or growth.
Type of study: Treatment Study
Level of evidence: III.

Parenteral nutrition (PN) is critical for providing essential fluids and macronutrients to children with intestinal failure (IF). It has revolutionized the long-term survival of these children, and provides an opportunity for intestinal adaptation to occur after significant small bowel loss. Unfortunately, it is not without considerable morbidity. As many as 60% of children with IF on long-term PN develop intestinal failure-associated liver disease (IFALD) and approximately 10% of those will progress to cirrhosis and hepatic failure [1–9]. Once IFALD occurs, it is unclear whether hepatic inflammation can be reversed, and if there is progression to cirrhosis, there are limited options other than transplant for these children. Therefore, utilizing strategies to minimize and prevent IFALD is of utmost importance [10].

Although there are many factors that contribute to IFALD including prematurity and sepsis [11–15], intravenous lipid emulsions are thought to be a significant cause of hepatic inflammation. Specifically, Intralipid (IL), the most commonly used form of intravenous lipid emulsion in the United States, which is predominantly composed of omega-6 fatty acids, can contribute to progressive cholestasis. Thus, alternative lipid strategies have been explored to minimize liver damage. This includes replacing IL with a fish oil-based lipid, Omegaven®, containing omega-3 fatty acids, which are thought to have anti-inflammatory properties [10,16,17]. However, most studies using Omegaven® administer it at a decreased dose of 1 g/kg/d. This has made it difficult to discern whether the benefits from Omegaven® are partly owing to lipid minimization, which has also been studied as a potential means of halting the progression of hepatic inflammation and cholestasis [18]. In fact, lipid minimization with IL has been used effectively, and without evidence of major fatty acid deficiencies [18], in children with IFALD. This retrospective study sought to compare the outcomes of children with IF and IFALD, treated with either IL or Omegaven® as the sole source of intravenous lipid emulsion, at a concentration less than 1.5 g/kg/day.

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1. Methods

1.1. Study population

After approval was obtained from the University of Texas Southwestern Medical Center Institutional Review Board (CR00012827/STU122012–010), a retrospective review of infants treated by the Center for Intestinal Rehabilitation at Children's Health from January 2009 through June 2016 was conducted. Only children with IF who were receiving PN for more than 6 weeks, developed IFALD, and were treated with lipid minimization with either IL or Omegaven® were included. IFALD was defined as a direct bilirubin >2 mg/dL for at least 2 weeks in a child with intestinal failure who was receiving PN. Lipid minimization was defined as treatment with either IL or Omegaven® at a concentration less than 1.5 g/kg/d. Prior to 2014, Omegaven® was not available at the study institution and, therefore, lipid minimization with IL was used for children with progressive cholestasis. After 2014, a compassionate use protocol was approved for the use of Omegaven® at a dose less than or equal to 1 g/kg/d, allowing comparison of both strategies.

1.2. Data collection

The electronic medical record was queried to identify eligible patients. Data were collected by a single reviewer, starting 1 month prior to initiation of lipid minimization. Demographic data, intestinal anatomy (remaining small bowel length and presence or absence of the ileocecal valve), laboratory values, and timing of initiation and termination of PN (if applicable) were collected. The percentage of remaining small bowel based on gestational age was calculated using a published algorithm [19]. Nutrition notes were used to obtain the data regarding parental and enteral calories, nutrient adjustments, and growth anthropometrics. The primary data points for analysis were obtained at the initiation of lipid minimization and at the time of normalization of direct bilirubin.

1.3. Statistical analysis

Differences between groups were examined through Student's t-test for normally distributed variables and Fisher's exact tests for categorical variables. Normally distributed variables are reported as mean ± standard deviation, and nonnormally distributed variables as median and interquartile range. All analyses were conducted in SAS 9.4 (SAS Institute, Cary, NC). P-values ≤0.05 were considered statistically significant.

2. Results

From January 2009 through June 2016, a total of 16 children were identified who had IF, required >6 weeks of PN support, and subsequently developed IFALD. Table 1 shows patient demographics and intestinal anatomy. All of the 16 children were initially receiving PN and IL at a dose >1.5 g/kg/d. After developing IFALD, 8 patients were treated with IL and 8 were treated with Omegaven® at a median dose of 1 g/kg/d. The median age at initiation of lipid minimization was 6 and 9 months in the IL and Omegaven® groups, respectively. No difference in gestational age, gender, birth weight, or small bowel length was observed between groups.

There were no differences between groups in markers of liver function or serum liver enzyme levels between groups at the time of lipid minimization or when bilirubin levels normalized (Table 2), and in the Intralipid group the change in ALP ($p = 0.63$), ALT ($p = 0.08$), AST ($p = 0.07$), and GGT ($p = 0.07$) was not statistically significant during this time. However, in the Omegaven group, although the change in ALP ($p = 0.56$), and GGT ($p = 0.43$) was not statistically significant, ALT ($p = 0.02$) and AST ($p = 0.01$) did significantly decrease. The mean direct bilirubin prior to initiating either treatment was 7.8 ± 4.3 mg/dL and 7.5 ± 3.5 mg/dL ($p = 0.87$) in the IL and Omegaven® groups, respectively. All children in both groups achieved a normal direct bilirubin. Children in the IL group took a median of 113 days to achieve a direct bilirubin less than 0.5 mg/dL compared to 124 days in the Omegaven® group ($p = 0.49$). The trend in direct bilirubin levels throughout the study period for both groups is presented in Fig. 1.

The nutritional and growth parameters are detailed in Table 3. Patients in both groups were receiving similar PN support both at the initiation of lipid minimization and at the time of bilirubin normalization. The mean PN calories (kcal/kg/d) prior to starting lipid minimization

Table 1
Demographic and anatomic data for children with intestinal failure treated with lipid minimization.

	Intralipid (n = 8)	Omegaven® (n = 8)	p-value
Gestational age (weeks), mean ± SD[b]	36.3 ± 2.0	33.9 ± 4.2	0.17[a]
Age at initiation of therapy (months), mean ± SD	6.2 ± 7.0	9.4 ± 7.6	0.40[a]
Male gender, n (%)	5 (63)	4 (50)	1.00[b]
Birth weight (g), median (IQR)	2593 (2362–2958)	2612 (1668–3543)	1.00[a]
Diagnosis, n (%)[c]			N/A
Necrotizing enterocolitis	1 (13)	1 (13)	
Atresia	5 (63)	2 (25)	
Gastroschisis	2 (25)	1 (13)	
Volvulus	2 (25)	2 (25)	
Hirschsprung's Disease	0 (0)	1 (13)	
Other	1 (13)	2 (25)	
Length of small bowel (cm), median (IQR)	40 (28.5–140.8)	28 (17–77)	0.23[a]
Expected bowel (%), median (IQR)	30 (19.9–100)	23 (5–27)	0.16[a]
Presence of ICV, n (%)	6 (75)	5 (63)	1.00[b]
Time to normalization of direct bilirubin (days), median (IQR)	113 (42–163.5)	124 (96–212)	0.49

SD = standard deviation; IQR = interquartile range; PN = parenteral nutrition; ICV = ileocecal valve.
[a] Student's t-test was used for comparison.
[b] Fisher's exact test was used for comparison.
[c] Multiple patients had more than 1 diagnosis.

Table 2
Laboratory values for children with intestinal failure treated with lipid minimization.[a]

	Intralipid (n = 8)	Omegaven® (n = 8)	p-value[b]
Direct bilirubin (mg/dL), mean ± SD			
Initiation of therapy	7.8 ± 4.3	7.5 ± 3.5	0.87
Normalization of DBili	0.28 ± 0.05	0.29 ± 0.10	0.87
Albumin (g/L), mean ± SD			
Initiation of therapy	2.8 ± 0.5	2.7 ± 0.6	0.71
Normalization of DBili	2.9 ± 0.8	2.8 ± 0.5	0.73
ALP, mean ± SD			
Initiation of therapy	446 ± 286	483 ± 158	0.79
Normalization of DBili	312 ± 40	372 ± 184	0.47
ALT, mean ± SD			
Initiation of therapy	330 ± 262	309 ± 180	0.86
Normalization of DBili	168 ± 118	162 ± 84	0.91
AST, mean ± SD			
Initiation of therapy	273 ± 190	281 ± 130	0.93
Normalization of DBili	94 ± 53	91 ± 45	0.91
GGT, mean ± SD			
Initiation of therapy	344 ± 271	144 ± 38	0.13
Normalization of DBili	197 ± 188	274 ± 427	0.65

SD = standard deviation; DBili = direct bilirubin; ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; GGT = γ-glutamyl transferase.
Time to Direct Bilirubin Normalization During Lipid Minimization.
[a] All values summarized as mean ± SD.
[b] Student's test was used for comparison.

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