Parenteral Fish Oil as Monotherapy Prevents Essential Fatty Acid Deficiency in Parenteral Nutrition–dependent Patients

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**ABSTRACT**

**Objective:** The use of fish oil–based emulsions as the sole source of fat for patients receiving parenteral nutrition (PN) has raised concerns for the development of essential fatty acid deficiency (EFAD), hindering its adoption into clinical practice. The purpose of the present study was to examine fatty acid profiles of patients receiving no enteral energy, while completely dependent on PN and an intravenous fish oil–based lipid emulsion, for onset of EFAD and maintenance of growth.

**Patients and Methods:** Prospectively collected data from 10 patients were reviewed for evidence of EFAD, defined as a triene:tetraene ratio >0.2. Gestational age–adjusted z scores for length, growth, and head circumference at baseline were compared with the corresponding z scores at time of censoring. All of the patients received PN with a fish oil–based lipid emulsion at 1 g · kg⁻¹ · day⁻¹ as the sole source of fat energy for at least 1 month. The fish oil monotherapy was used under a compassionate use protocol.

**Results:** Median gestational age at the time of birth was 35 weeks, and median age at the start of treatment was 3.5 months. After a median time of 3.8 months on exclusive PN and fish oil–based lipid emulsion, none of the patients developed biochemical or clinical evidence of EFAD. z scores were not statistically different, indicating no growth impairment. Median direct bilirubin levels improved in 9 patients from 6.8 to 0.9 mg/dL (P = 0.009).

**Conclusions:** When dosed appropriately, fish oil–based lipid emulsions contain sufficient amounts of essential fatty acids to prevent EFAD and sustain growth in patients who are completely dependent on PN.

**Key Words:** essential fatty acid deficiency, fish oil, Omega-3, parenteral nutrition, parenteral nutrition–associated liver disease

(PJGN 2010;50: 212–218)

Parenteral nutrition (PN) is an established modality to provide the necessary nutrient requirements for patients with intestinal abnormalities or when the use of the gastrointestinal tract is contraindicated. PN is typically administered in conjunction with an intravenous lipid emulsion to provide an alternative to carbohydrates as a source of nonprotein energy, and to supply polyunsaturated fatty acids (PUFAs) to prevent essential fatty acid deficiency (EFAD) (1,2). In the United States, the only approved intravenous lipid emulsions are derived from either soybean oils alone or a combination of soybean and safflower oils. Recent evidence, however, suggests that these emulsions significantly contribute to the onset of PN-associated liver disease, which is associated with high morbidity and mortality (3–5).

PUFAs have many physiological functions, including providing the integrity and fluidity of cellular membranes, serving as major constituents of phospholipids, triglycerides, and cholesterol esters in plasma lipoprotein particles, and are precursors of numerous bioactive eicosanoids and prostanooids (6,7). Traditionally, alpha-linolenic acid (ALA, ω-3) and linoleic acid (LA, ω-6) are considered to be the only “essential fatty acids” because they cannot be synthesized in mammalian tissues and are required for normal physiological development, growth, and function (8). Other ω-3 and ω-6 PUFAs can be derived from these 2 fatty acid precursors by elongation and desaturation reactions. Eicosapentaenoic acid (EPA, ω-3), docosahexaenoic acid (DHA, ω-3), and arachidonic acid (AA, ω-6) are considered “conditionally essential fatty acids” because their production may be inadequate in selective conditions such as prematurity and rapid growth (9). Oleic acid (OA, ω-9) is a monounsaturated FA that can be synthesized by de novo lipogenesis in mammals. OA can be converted via intermediates to mead acid (MA, ω-9), which typically accumulates in conditions of EFAD. The ratio of this compound to AA, the triene:tetraene ratio, is used as a diagnostic marker for EFAD (10).

Although relatively rare, EFAD can occur in as little as a few days in infants, and within several weeks in older children and adults with chronic malnutrition and malabsorption. EFAD may also occur within weeks in patients receiving prolonged courses of PN with inadequate fat intake (11). Because of their limited fat stores, premature infants may develop EFAD in <1 week when
their intake of essential fatty acids is <4% to 5% of their total energy intake (12). EFAD may lead to dermatitis, growth retardation, hair loss, infertility, impaired vision, coagulopathies, susceptibility to infections, as well as to hepatosteatosis induced by de novo lipogenesis (10–13).

Recent investigation has focused on the hepatoprotective effects of fish oil as a monotherapy alternative to soybean oil (14–17). Fish oil–based lipid emulsions have been available in Europe and Asia for more than 10 years as a supplement, but their use as the sole source of fat energy, however, is not recommended by its manufacturer because of concerns that the low levels of the traditional essential fatty acids, LA and ALA, present in fish oils could lead to EFAD. Studies have shown that in a subset of pediatric patients, parenteral fish oil as monotherapy led to reversal of EFAD, improved liver function, and maintained adequate growth (14–17). Moreover, it has been shown that the ω-3 PUFAs such as ALA, EPA, and DHA that are more prevalent in fish oil compared with soybean oil, may play a role in reducing the amount of the ω-6 PUFA LA required to prevent EFAD (18). Skepticism, however, remains sufficient to hinder the adoption of fish oil–based emulsions as monotherapy into clinical practice (19).

To test the hypothesis that parenteral fish oil as monotherapy prevents EFAD in PN-dependent patients, we examined the fatty acid profiles and growth parameters of patients who were exclusively administered PN and a fish oil–based lipid emulsion for the onset of EFAD.

PATIENTS AND METHODS

Patients

The present study was approved by the Children’s Hospital Boston Committee on Clinical Investigation (protocol no. 05-04-048). From April 2005 to February 2009, infants who developed cholestasis (serum direct bilirubin ≥2 mg/dL) while receiving PN with soybean-based lipid emulsions were switched to a fish oil–based lipid emulsion (Omagaven Fresenius Kabi, Bad Homburg v.d.H., Germany) and prospectively studied under a compassionate treatment protocol. A subset of 10 patients (70% male) who exclusively received PN with the fish oil–based lipid emulsion as the sole source of fat energy for at least 1 month were included for analysis. When a baseline fatty acid profile was unavailable before the start of the fish oil therapy, the patient was considered ineligible for analysis. Patients were censored when they advanced to enteral feeding, and censoring was assumed independent of essential fatty acid status. Although we censored patients when they advanced to enteral feeds, some did receive minimal oral intake for comfort during the study period (patients 1, 2, 4, 7, and 9). Because of severe malabsorption from their microvillus inclusion disease, it was unlikely that patients 1 and 2 had any significant energy absorption from the Pedialyte (Abbott Nutrition, Columbus, OH) and breast milk that they received for comfort. Patient 7 received a few crackers per day but had a previous failed intestinal transplant that was subsequently explanted and literally had no gut. Patients 4 and 9 sporadically received Pedialyte during the study period, but this sugar- and electrolyte-based formula did not contribute to any fat energy.

Study Treatment

After obtaining informed consent, the soybean-based lipid emulsion, Intralipid (Fresenius Kabi, Uppsala, Sweden), was discontinued and treatment with the fish oil–based lipid emulsion, Omagaven was started. Intralipid is mainly composed of LA (ω-6), and only contains a small amount of ALA (ω-3). In contrast, Omagaven contains significant amounts of the ω-3 PUFAs EPA and DHA and only a small amount of ω-6 PUFAs (Table 1). All of the patients received Omagaven at a goal dose of 1 g·kg⁻¹·day⁻¹ that was infused more than 12 to 20 hours. Dosing was based on the previous use of fish oil–based lipid emulsions as monotherapy (14,15). Protein intake was 2.5 g·kg⁻¹·day⁻¹ for full-term infants and 3 to 3.5 g·kg⁻¹·day⁻¹ for premature infants. The initial rate of dextrose infusion was approximately 5 mg·kg⁻¹·min⁻¹, and because of the fact that we limited fat administration, extra energy intake was provided by increasing dextrose intake. Because Omagaven is not yet approved for use in the United States, approval was obtained from the Food and Drug Administration (IND 73,488) for its compassionate use.

Study Outcomes

The primary study outcome was the onset of EFAD, defined as a triene:tetraene ratio >0.2. Fatty acid profiles were measured from blood samples obtained before the start of Omagaven and weekly thereafter until direct serum bilirubin levels were <2 mg/dL,

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<th>TABLE 1. Comparison of the parenteral lipid emulsions per 10 g/100 mL.</th>
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AA = arachidonic acid; ALA = alpha-linolenic acid; DHA = docosahexaenoic acid; EPA = eicosapentaenoic acid; LA = linoleic acid; OA = oleic acid.

*Data as provided by manufacturers.
at which time fatty acid profiles were obtained monthly. All of the fatty acid analyses were performed at the same clinical laboratory (Mayo Laboratories, Rochester, MN). Direct bilirubin was measured using a modified Jendrassik-Grof assay. As a secondary study outcome, the onset of clinical parameters for EFAD, including dermatitis, hair loss, and growth impairment, was systematically recorded. z scores for length, weight, and head circumference, corrected for gestational age, were analyzed as anthropometric measurements for growth.

**Estimated Nutrient and Essential Fatty Acid Intake**

To gain insight into the energy intake derived from carbohydrate, protein, and fat during our study, we arbitrarily picked a time point of 1 month after the initiation of fish oil monotherapy. For the calculation, we used male sex, a median weight of 4.8 kg, height of 52 cm, and age of 4.5 months. Using the recommendations from the American Academy of Pediatrics for infants <10 kg (100 kcal·kg⁻¹·day⁻¹), we calculated an estimated daily energy requirement of 480 kcal·day⁻¹ (20). Using the information in Table 2, and given that the energy density of a 10% Omegaven emulsion is 1.12 kcal·mL⁻¹, we calculated that LA, ALA, EPA, DHA, and AA accounted for 0.8% to 5.6%, <1.6%, 10.3% to 22.7%, 11.6% to 24.8%, and 0.8% to 3.2% of fat energy, respectively, when given at a dose of 1 g·kg⁻¹·day⁻¹.

**Statistical Analysis**

z scores and direct bilirubin levels were expressed as median (range) and differences were assessed using a paired nonparametric Wilcoxon signed rank test. P < 0.05 was considered statistically significant. All of the data were collected in a computerized Microsoft Excel database (Microsoft Inc, Redmond, WA). The analysis was performed with SPSS version 16.0 (SPSS Inc, Chicago, IL) statistical software, and figures were created using GraphPad Prism version 5.0 (GraphPad Software Inc, La Jolla, CA) software.

**RESULTS**

The median gestational age at the time of birth was 35 weeks (range 24–38 weeks), and median age at the start of study treatment was 3.5 months (range 0.8–37 months). Because of the underlying intestinal abnormalities, all of the patients had inadequate intestinal length requiring PN (Table 2). All of the patients experienced significant cholestasis, indicated by direct bilirubin levels ranging from 2.5 to 12.8 mg/dL (median 6.8 mg/dL) at baseline (Table 2).

**Fatty Acid Analysis**

At baseline, all of the patients except patients 3 and 9 had fatty acid profiles comparable to the composition of the soybean-based lipid emulsion (Tables 1 and 3), characterized by high absolute and relative levels of the ω-6 PUFAs LA and AA, low levels of the ω-3 PUFAs EPA and DHA, and low ω-3:ω-6 ratios (Table 3). Patients 3 and 9, diagnosed with necrotizing enterocolitis (NEC), had already been switched to Omegaven therapy because of severe cholestasis for 1 and 3 months, respectively, and became eligible for the study when oral intake was withheld because of NEC-related complications. Therefore, their fatty acid profiles at baseline already showed elevated levels of EPA and DHA, decreased levels of LA, and high ω-3:ω-6 ratios (Table 3).

The fatty acid profiles gradually changed to the composition of the fish oil–based lipid emulsion during the study (Table 1). Fatty acid profiles after 3 and 6 weeks show decreasing levels of LA and AA, and increasing amounts of EPA and DHA (Table 3). All of the weekly fatty acid profiles showed a consistent pattern of gradual change to the composition of fish oil (data not shown).

**Onset of Essential Fatty Acid Deficiency**

At baseline, all of the patients’ triene:tetraene ratios were <0.2, hence, none of them had EFAD. After 1 week, the ω-3:ω-6 ratios had increased from a median 0.146 (range 0.045–3.667) to a median ratio of 0.915 (range 0.088–2.917) (Fig. 1A). Median ω-3:ω-6 ratios gradually increased during the study and remained between 1:1 to 2:1 in all of the patients. MA levels remained normal in all of the patients, indicating that none of the patients experienced EFAD-associated de novo lipogenesis (Fig. 1B). After a median time of 3.8 months (range 1.2–9.3 months) on exclusive PN along with a fish oil–based lipid emulsion, none of the patients developed biochemical evidence of EFAD before the end of the study period (Fig. 2A and B).

![Table 2](image-url)
During the course of the study, none of the patients experienced any clinical signs of EFAD. Specifically, we did not observe EFAD-associated dermatitis, hair loss, coagulopathies, or increased infection rates related to Omegaven monotherapy (data not shown). Additionally, patients did not experience growth retardation. Median baseline and end-of-study \( z \) scores for length for age were \(-2.1\) (range \(-4.8\) to \(-0.3\)) and \(-1.4\) (range \(-2.2\) to \(-0.3\)), respectively \((P = 0.236, \text{Fig. 3A})\). Median \( z \) scores for weight were \(-2.8\) (range \(-4.9\) to \(-1.8\)) at baseline and \(-2.0\) (range \(-4.8\) to \(-1.1\)) at the end of the study \((P = 0.932, \text{Fig. 3B})\). For head circumference, median baseline \( z \) scores were \(-1.4\) (range \(-3.9\) to \(-1.2\)) compared with \(-1.2\) (range \(-1.9\) to \(-2.5\)) at the end of the study \((P = 0.138, \text{Fig. 3C})\). Only patient 8 did not improve her growth rate during the 7.1 months that she was studied; however, she was also receiving postoperative chemotherapy after intestinal resection for neuroblastoma. All of her weekly triene:tetraene ratios were \(<0.05\) and she did not develop any clinical signs of EFAD.

### Improvement of Cholestasis

After a median time of 3.8 months (range 1.2–9.3 months) receiving exclusive PN and Omegaven monotherapy, median direct bilirubin levels improved in 90% of the patients from a median of 6.8 mg/dL (range 2.5–12.8 mg/dL) to a median level of 0.9 mg/dL (range 0.1–9.6 mg/dL; \(P = 0.009\)). Six of the 10 patients had their direct bilirubin normalized. Patients 5 and 10 had their direct bilirubin levels improved from 9.6 to 8.8 mg/dL and 8.4 to 5.6 mg/dL, respectively. Their direct bilirubin levels continued to decrease to normal levels after censoring (data not shown). Patient 8 received concomitant chemotherapy for neuroblastoma, but showed a major decrease in direct bilirubin from 12.8 to 2.4 mg/dL. Only patient 9 showed progression of his liver disease indicated by an increase in direct bilirubin from 7.5 mg/dL at baseline to 9.6 mg/dL after 5.6 weeks. Median time to reverse cholestasis with a fish oil-based lipid emulsion, however, was approximately 9.4 weeks (17). Before the initiation of Omegaven, this 24 week premature male experienced NEC, pneumonia, and central line sepsis, which are all risk factors for developing severe liver disease. In addition, during his hospital stay, this patient developed severe brain hemorrhage, resulting in severe cerebral atrophy and ultimately withdrawal of care.

### Estimated Nutrient and Essential Fatty Acid Intake

To gain insight into the energy intake derived from carbohydrate, protein, and fat during our study, we arbitrarily picked a...
time point of 1 month after the initiation of fish oil monotherapy. For the calculation, we used male sex, a median weight of 4.8 kg, height of 52 cm, and age of 4.5 months. Using the recommendations from the American Academy of Pediatrics for infants <10 kg, we calculated an estimated daily energy requirement of 480 kcal·day⁻¹ (20). Estimated energy intake from parenteral fat was 1 g·kg⁻¹·day⁻¹ = 11.2 kcal·g⁻¹·1 g·kg⁻¹·day⁻¹·4.8 kg·l day = 53.8 kcal (11.2%). Estimated energy intake from protein was 2.5 g·kg⁻¹·day⁻¹ = 4.0 kcal·g⁻¹·2.5 g·kg⁻¹·day⁻¹·4.8 kg·l day = 48.0 kcal (10.0%). Estimated energy intake from carbohydrates was therefore 480 – 53.8 – 48 = 378 kcal (23.2 g·kg⁻¹·day⁻¹ of carbohydrate; 78.8%). Using the estimated total daily energy intake for a 4.8-kg, 52-cm, 4.5-month-old male infant who received all fat energy derived from Omegaven, we calculated that we provided an estimated 0.09% to 0.63% LA, <0.18% ALA, 1.15% to 2.54% EPA, 1.30% to 2.78% DHA, and 0.09% to 0.36% AA of total estimated daily energy intake.

**DISCUSSION**

In our center, a parenteral fish oil–based lipid emulsion used as monotherapy in a subset of pediatric PN-dependent patients at a dose of 1 g·kg⁻¹·day⁻¹ has been shown to be safe and efficacious in reversing PN-associated liver disease and normalizing EFAD status (14–17). In addition to previously published articles by our group, this report adds important data regarding the safety of parenteral fish oil as monotherapy. In contrast to our earlier studies, we present a unique population of 10 PN-dependent infants who received no significant enteral energy and received all fats derived from intravenous fish oil. Although this patient population is even more prone to develop EFAD, our results are in line with our previously published data that patients receiving parenteral fish oil monotherapy do not develop EFAD (14). Moreover, we previously demonstrated that fish oil, when used at sufficient concentrations, can be used as the sole source of fat, displaying no adverse effects on growth and no evidence of EFAD in a 9-week murine model (18). Despite these results, skepticism remained that a fish oil–based lipid emulsion may not contain sufficient amounts of LA and ALA to prevent EFAD when used as a monotherapy. Our results show, for the first time, that Omegaven monotherapy as the sole source of fat in a subset of PN-dependent patients does not lead to the onset of clinical or biochemical EFAD.

Although physical signs and symptoms of EFAD in infants may not appear for 4 to 6 weeks, biochemical abnormalities generally appear in only 1 to 2 weeks (12). In our study, however, all of the patients were studied for a minimum of 6 weeks and none
of them showed clinical signs of EFAD. A cutoff point for the upper limit for the triene:tetraene ratio as a biochemical marker for EFAD was based on early experiments on rats that initially suggested it to be 0.4 (21). Further work in humans using the more accurate gas-liquid chromatography, however, showed that the upper limit should be 0.2 (22). Although others have argued that the upper limit should be as low as 0.025 (23), this distinction is somewhat semantic because clinical evidence of EFAD is not seen when the triene:tetraene ratio is <0.2. The upper limit, therefore, should be 0.2 because a lower ratio would actually overdiagnose patients with EFAD.

We also demonstrated that these patients did not experience growth retardation, indicated by gestational age–adjusted z scores for length, weight, and head circumference, while receiving the fish oil–based lipid emulsion. In a state of EFAD in which ω-3 and ω-6 PUFAs stores are depleted, MA is produced by de novo lipogenesis. Data from the fatty acid profiles showed that while receiving Omegaven, MA levels remained within the normal range, and the triene:tetraene ratios remained at <0.2. Moreover, the relative amount of ω-3 to ω-6 increased in all of the patients.

Although the median follow-up time was only 3.8 months, this period should exceed the time window for the onset of EFAD. By including only those with a minimum of 4 weeks receiving exclusive PN and intravenous Omegaven, we hope to eliminate any false-negatives in detecting EFAD. Moreover, by censoring these patients as soon as they advanced to any enteral feeding, we eliminated any possible confounding from enteral fat energy.

At baseline, all of the patients had significant liver disease (median direct bilirubin 6.8 mg/dL), as well as multiple other comorbidities, justifying their enrollment in the Omegaven monotherapy under a compassionate use protocol. At baseline, patients’ fatty acid profiles represented the composition of the parenteral lipid emulsions that they had been receiving. It has been suggested that patients with severe liver disease are deficient in long-chain PUFAs, and that supplementation may improve patients’ clinical condition by correcting this deficiency (24,25). Although none of the 8 patients who had received the soybean-based lipid emulsion were deficient in the total amount of long-chain PUFAs, they experienced a low, suboptimal ω-3:ω-6 ratio. Already after 1 week, fatty acid profiles had changed to the composition of fish oil, which has been shown to be less proinflammatory and less hepatotoxic (26–28).

Breast milk, which contains considerable amounts of long-chain PUFAs, is considered to provide the optimal form of nutrition for young infants. Because long-chain PUFAs accumulate mainly during the last trimester of pregnancy, preterm infants have limited body stores at birth, at a time when its requirement is high because of their rapidly growing state (29). Although a fish oil–based lipid emulsion does not provide the same amounts of fatty acids as breast milk, it contains relatively high levels of EPA and DHA that may play an important role in the development of critical organs and cognitive function (29). These effects may be particularly important in preterm infants who receive their entire energy intake from PN and a parenteral lipid emulsion.

In our study, we calculated that an estimated daily energy intake of 0.09% to 0.63% LA, <0.18% ALA, 1.15% to 2.54% EPA, 1.30% to 2.78% DHA, and 0.09% to 0.36% AA was enough to prevent EFAD. The estimated amount of ω-3 PUFAs that we provided is higher than reported by Bjerve et al (30), who estimated that the minimal daily requirement of ω-3 PUFAs was approximately 0.1% to 0.2%. Our patients, however, were growing, young infants (some premature), with significant comorbidities and a higher need for ω-3 PUFAs, whereas the patients that Bjerve et al described were relatively healthy, immobile adults fed by gastric tube. Although we provided <0.18% of ALA, our patients received a significantly higher amount of the downstream ω-3 PUFAs EPA and DHA, ensuring proper physical and mental development (29). Our data does require a note of caution because we calculated an estimated daily energy intake based on the median data derived from our study sample. Because this calculation is dependent on infants’ weight, height, and age, our numbers are presented as a representative snapshot of our study sample, and may not be generalized to the pediatric population as a whole.

CONCLUSIONS

In conclusion, we have demonstrated for the first time that a fish oil–based lipid emulsion as monotherapy contains sufficient amounts of essential fatty acids to prevent EFAD and sustain adequate growth in children who are completely dependent on
PN. A randomized, controlled, double-blind clinical trial, such as the one that is under way at our institution (NCT00512629), comparing the conventional soybean-based Intralipid with the fish oil–based Omegaven as the sole source of parenteral lipid, will be imperative in the current debate about the efficacy and safety of parenteral fish oil–based lipid emulsions (31). The results will also determine its role as monotherapy in PN-dependent patients.

Acknowledgments: The authors are grateful to Danielle Arsenault and Elizabeth Robinson for their contribution.

REFERENCES