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A Comparison of Two Intravenous Lipid Emulsions: Interim Analysis of a Randomized Controlled Trial

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Abstract

Objective—To assess the safety and efficacy of a fish-oil based intravenous fat emulsion (FIFE) in reducing the incidence of cholestasis in neonates compared to the traditional soybean oil-based intravenous fat emulsion (SIFE).

Methods—A double-blind randomized controlled trial was conducted. Nineteen neonates were enrolled (10 SIFE; 9 FIFE). Nutritional assessments and laboratory studies were serially obtained for the duration of PN support or until 6-months corrected gestational age. Neurodevelopmental outcomes were assessed at 6 and 24-months corrected age.

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Trial Registry Number: NCT 00512629; **URL:** <http://clinicaltrials.gov/ct2/show/NCT00512629>

Conflict of Interest Disclosure: A license agreement for the use of Omegaven[®] has been signed by Boston Children's Hospital and Fresenius Kabi and a patent has been submitted by Children's Hospital Boston on behalf of Mark Puder and Kathleen Gura.

Results—There were no differences between groups in demographic characteristics with an overall median age of 2 days, gestational age of 36-weeks and birth weight of 2410g. There were no differences between groups in baseline laboratory values other than alkaline phosphatase (lower in FIFE group), or in the duration of parenteral nutrition, amount of enteral intake or the number of operative procedures. The incidence of cholestasis amongst enrolled patients was significantly lower than expected resulting in early study termination and an inability to assess for differences in the incidence of cholestasis. The FIFE was associated with no increased risk of growth impairment, coagulopathy, infectious complications, hypertriglyceridemia or adverse neurodevelopmental outcomes. No patient developed essential fatty acid deficiency.

Conclusion—The FIFE at 1g/kg/day was well tolerated in the neonates recruited for this study. Given the necessary early termination of this study, a follow-up trial with revised eligibility criteria is necessary to determine whether the provision of a FIFE decreases the incidence of PN-cholestasis compared to the traditional SIFE.

Keywords

neonatal; parenteral nutrition; cholestasis; lipid emulsion; fish oil; soybean oil; parenteral nutrition associated liver disease; fatty acid; omega-3; omega-6

INTRODUCTION

Parenteral nutrition (PN) is a life-saving therapy for patients unable to absorb adequate enteral nutrients. Unfortunately, long-term PN has many potential complications, with one of the most severe being hepatobiliary dysfunction, commonly referred to as PN-associated liver disease (PNALD) or PN-cholestasis.

There are numerous established risk factors for PNALD including prematurity, low birth weight, prolonged duration of PN, central venous catheter-related sepsis and a diagnosis of gastroschisis, jejunal atresia, or necrotizing enterocolitis^{1, 2}. The intravenous fat emulsion (IFE) traditionally administered with PN in the United States is soybean oil-based and rich in omega-6 fatty acids, and there is data that suggests that omega-6 fatty acids may play an important role in the development of PNALD³⁻⁵. Recently, a fish-oil based IFE (FIFE; Omegaven®, Fresenius Kabi, Bad Homburg, Germany) has been shown to be effective in reversing cholestasis and normalizing liver function tests in patients with PNALD⁶⁻⁸. While these studies suggest that the FIFE is safe and effective for use in children *with* PNALD, no study to date has evaluated the safety and efficacy of a FIFE in the prevention of PNALD.

We conducted a randomized controlled trial to determine whether the administration of a FIFE is safe and effective in reducing the incidence of cholestasis in neonates compared to the traditional SIFE and herein report an interim analysis.

MATERIALS AND METHODS

Study Design

After Institutional Review Board (IRB Protocol #06-03-0105) approval, we conducted a randomized, controlled, double-blind clinical trial at Boston Children's Hospital. This trial is registered at clinicaltrials.gov (NCT 00512629).

Eligibility Criteria

Neonates and infants (<3 months age) with baseline direct bilirubin of <1.0mg/dL and a gastrointestinal disease requiring surgical intervention who were expected to be PN-dependent for ≥21 days were eligible.

Infants were excluded for prior exposure to an IFE, having an allergy to any component of the IFEs, enrollment in another clinical trial involving an investigational drug and intention to transfer to another institution within 3 months. In addition, those with a baseline International Normalized Ratio (INR) >1.5 (>2 if ≥1 week of age) or triglyceride level >400mg/dL and those with a hemolytic disorder, liver disease or shock requiring vasopressor support, extracorporeal membrane oxygenation and/or nitric oxide treatment were excluded. Patients who had undergone an intestinal lengthening procedure were not eligible.

Recruitment and Randomization

Eligibility criteria for each patient were reviewed by a multidisciplinary team. Neonates were recruited at the time of initial ILE initiation, which was typically within the first few days of life. Following informed consent, subjects were randomly assigned a computer-generated list of random numbers and were randomly assigned to the control (SIFE) or experimental (FIFE) group in a 1:1 ratio. Patients, parents, physicians, dieticians and nurses were blinded to the treatment allocation for the duration of the study. Members of the department of pharmacy aware of the randomization and identically packaged the IFEs.

Interventions/Outcomes

Patients received standard medical, surgical, and nutritional support. Both IFEs were provided at 1g/kg/day and this dose was kept constant throughout the study period. All patients remained on their assigned IFE until weaned from PN unless crossed-over to the other study arm. Patients with persistently elevated direct bilirubin (>2mg/dL for ≥2 continuous weeks) were considered treatment failures and were crossed over to the other study arm.

Patient demographics and baseline characteristics were recorded. Baseline nutritional assessment, laboratory studies and liver ultrasound were obtained. These were repeated on a weekly basis for the duration of PN support (or until 6-months corrected gestational age, whichever occurred first) with the exception of coagulation profiles (obtained bi-weekly) and abdominal ultrasound (repeated at 6-months corrected gestational age). All fatty acid analyses were performed at the same clinical laboratory (Mayo Clinic, Rochester MN) using

gas chromatography-mass spectrometry stable isotope dilution analysis. All data collection except neurodevelopmental testing was terminated at 6-months corrected age.

A trained psychologist administered the Bayley Scales of Infant and Toddler Development, 3rd edition (BSID-III) motor, cognitive, and language scales⁹ at 6 and 24-months corrected age. Parents completed the Parent Report of Children's Abilities (PARCA-R), a questionnaire that assesses verbal and non-verbal cognition¹⁰, at 24 months corrected age.

Study Drugs

SIFE (Intralipid®): Intralipid® is FDA approved for use in children and is manufactured by Fresenius Kabi, Uppsala, Sweden and marketed by Baxter Healthcare, Deerfield, IL. Supplies of Intralipid® were purchased from the local pharmaceutical wholesaler.

FIFE (Omegaven®): Omegaven® is not FDA approved for use in the United States. An IND application (IND 73,488) was issued by the FDA and supplies of Omegaven® were purchased from the manufacturer, Fresenius Kabi AG in Bad Homburg v.d.h., Germany.

Primary Aim

To determine whether the incidence of cholestasis, defined as a serum direct bilirubin >2mg/dL for 2 consecutive weeks, differs between the SIFE and FIFE groups.

Secondary Aims

To evaluate the safety and tolerability of the FIFE compared to the standard SIFE in the neonatal population. Safety evaluation of the FIFE involved assessment of mortality and adverse event rate. Documented adverse events included: infections, cardiopulmonary arrest, and incorrect IFE dosing. Additional safety evaluation included an analysis and comparison of growth parameters, bleeding complications, transfusion requirements, laboratory studies and neurodevelopmental outcomes.

Sample Size

Based on prior experience at our institution we expected the incidence of cholestasis amongst recruited subjects to be between 30-80%. To detect a reduction in the incidence of cholestasis of 55% assuming a 70% incidence of cholestasis in the SILE group, with a two-sided 5% significance level and a power level of 80%, a sample size of 15 patients per group was necessary. Given prior experience we estimated that it would take 2 years to recruit 30 patients.

Due to the very low incidence of cholestasis amongst the 19 subjects enrolled over a 2-year period, the decision was made to perform an interim analysis followed by potential revision of study design.

Data Analysis

All continuous data are presented as median [inter-quartile range, IQR]. Continuous variables were compared using the Wilcoxon rank-sum test, while categorical variables were compared using Fisher's exact test. All analyses were performed on an intention-to-treat

basis. Significance was assessed using a two-sided 5% alpha level. All laboratory measurements are represented at baseline and week 4 due to the small number of patients with data beyond 4 weeks. Weight-for-age, length-for-age, and head-circumference-for-age Z-scores^{11, 12} are presented from baseline to week 5 due to the small number of patients with data beyond week 5. A generalized estimating equation was used to investigate between-group differences and changes over time. Comparisons were made between groups using a Wilcoxon rank-sum test and within groups across time using a Wilcoxon signed-rank test. Neurodevelopmental outcomes were compared across treatment groups, after adjusting for age, by the method of Sen and Adichie^{13, 14}.

RESULTS

Over a 2-year period (July 2007-June 2009), 26 eligible patients were identified and 19 were enrolled. Ten patients were randomized to the SIFE group and nine to the FIFE group. Eight (80%) patients in the SIFE group and 6 (67%) in the FIFE group completed the 6-month follow-up. Five patients (26%) were lost to follow-up (Figure 1).

Baseline Characteristics

There were no statistically significant differences in baseline patient characteristics between the 2 groups (Table 1). On baseline liver ultrasound, 6 (43%) patients had ascites and 6 (43%) had abnormal liver echotexture and there were no differences between groups (data not shown). There were no differences between groups in baseline laboratory studies other than alkaline phosphatase, which was lower in the FIFE group [75 (72, 83) vs. 105 (89, 133)U/L, $P=0.03$], although, values for all patients were within the normal range of 110-400 U/L (Table 2). There were no differences in baseline plasma fatty acid (FA) concentrations and no patient had evidence of biochemical essential fatty acid deficiency (Table 3).

Group Characteristics while on PN

Groups were comparable with regards to several factors known to impact the incidence of PNALD including the duration of IFE support, enteral intake and the number of operative procedures, blood transfusions and bloodstream infections (Table 1).

Primary Outcome (Efficacy in the Prevention of Cholestasis)

The incidence of cholestasis among enrolled patients was significantly lower than expected and enrollment was terminated early to allow for an interim analysis of the data and potential study revision. The interim analysis demonstrate no difference in the maximum direct bilirubin between groups while on PN, with a median value of 0.7 (0.4, 1.6)mg/dL in the SIFE group and 0.4 (0.2, 1.3)mg/dL in the FIFE group ($P=0.32$). No significant differences were seen between groups in any laboratory markers of liver function at week 4 (Table 2), or in liver ultrasound characteristics at 6-months corrected age (not shown). One patient in each group developed cholestasis and both were crossed-over.

Secondary Outcome (Safety)

Growth—There were no statistically significant differences between groups in weight-for-age, length-for-age or head circumference-for-age Z-scores^{11, 12} (Figure 2). There was a

notable downward trend in the weight-for-age Z-score in the SIFE group that was not seen in the FIFE group (Figure 2A), although the difference did not reach statistical significance.

Bleeding Risk—No patient had any bleeding complications. There was no difference between groups in the number of patients requiring operative or non-operative blood product transfusions (Table 1) or in the hematocrit values, platelet counts or coagulation profiles (Table 2). The INR at week 4 was higher in the FIFE compared to the SIFE group [1.19 (1.13, 1.20) vs. 1.05 (1.03, 1.09), $P=0.02$] although this difference was not clinically significant and all values remained in the normal range (Table 2).

Hypertriglyceridemia—No patient in either group developed persistent hypertriglyceridemia (serum triglyceride $>300\text{mg/dL}$) or a significant derangement of the lipid profile (Table 2).

Infection Risk—Eight (42%) patients had at least 1 positive blood culture during the study period. There was no difference between groups with 4 patients in each group with 1 positive blood culture ($P=1.00$) (Table 1).

Fatty Acid Profiles—Notable changes in the plasma FA profiles were seen over time (Table 3). Normative ranges are provided but it must be noted that these are determined based on population studies focused on individuals consuming a standard Western diet. Although the total FA content remained similar between the SIFE and FIFE groups, there was an increase over time (baseline to week 4) in the total omega-3 FA content in the FIFE group (median increase of 1.4 (0.9, 0.18) $\mu\text{mol/L}$, Wilcoxon signed-rank test $P=0.03$) and a similar increase in the omega-6 FA content in the SIFE group (median increase of 1.2 (0.8, 1.3) $\mu\text{mol/L}$, Wilcoxon signed-rank test $P=0.06$). The omega-3 FAs that most notably contributed to the rise in the FIFE group were docosahexaenoic acid (DHA), eicosapentaenoic acid (EPA) and docosapentaenoic acid (DPA). Similarly, the increase in the omega-6 FA content in the SIFE was mostly attributable to an increase in the concentration of linoleic acid (LA), gamma linoleic acid (GLA) and dihomo-gamma linoleic acid (DGLA). No patient developed biochemical essential fatty acid deficiency.

Neurodevelopmental Outcomes—There were no differences between groups in cognitive, language or motor outcomes (BSID-III) or in verbal or non-verbal cognition (PARCA-R) (Table 4).

Adverse Events—There were no deaths or major adverse events. Infectious and bleeding complications are presented above. Two patients on the SIFE were briefly incorrectly infused with the FIFE without complication.

DISCUSSION

This is the first study to evaluate the use of FIFE monotherapy as the initial IFE in neonates and we chose to recruit relatively healthy neonates. Unlike most neonates receiving PN who develop PNALD, none of our patients were extremely premature or low birth-weight. We also specifically excluded patients with major associated comorbidities. Thus, given the

known risk factors for the development of PN-cholestasis², these recruitment criteria led to the enrollment of a group of patients with a very low incidence of cholestasis and a lower incidence than was expected. Although, an alternative explanation is that the incidence of cholestasis was low because both ILEs were provided at the relatively reduced dose of 1g/kg/day, we would argue that this is less likely as we have recently published data from our institution demonstrating that neonates who receive the soybean-oil based ILE at 1g/kg/day have the same incidence of cholestasis as those who receive this ILE at a dose of 2-3g/kg/day¹⁵. As a result, the number of patients recruited at the time of this interim analysis was insufficient to reveal differences in the incidence of cholestasis between groups. Overall, only one patient in each treatment arm developed a persistently elevated direct bilirubin and was crossed-over. Based on the low incidence of cholestasis in the cohort of neonates recruited for this study, a follow-up randomized controlled trial with broadened inclusion criteria is necessary to truly determine whether the FIFE reduces the incidence of PN-cholestasis as compared to the SIFE when administered at an equivalent dose.

This study does, however, provide important evidence that the FIFE was well tolerated in the cohort of neonates recruited in this study. Providing adequate nutrition to support rapid growth and development is of utmost importance in the newborn period. We observed no detrimental effect of the FIFE on weight gain, linear or head growth, nor did we see any evidence of poorer cognitive or motor outcomes at 6 or 24-months. Interestingly, our results demonstrate that the Bayley scores of the infants assessed were similar to the expected population mean of 100 ± 15 (standard deviation)⁹. A substantial body of literature suggests that omega-3 FAs are essential for the growth and development of the neonate¹⁶⁻¹⁹ and that DHA intake may be essential for optimal functional maturation of the retina and visual cortex^{20, 21}. The increased omega-3 FA in the serum of neonates on the FIFE may thus translate to cognitive and visual benefits when administered long-term, especially in the preterm infant who is relatively deficient in DHA.

Additional safety concerns regarding the FIFE have been raised in the literature. There are reports of coagulopathy²² in the adult population and concerns regarding a higher risk of infection²²⁻²⁵, neither of which was observed in this study. We saw no evidence of bleeding complications or clinically significant derangements of any laboratory measure of coagulation although further longer-term studies are necessary. Additionally, we found no predisposition to bloodstream infections. This is important as infectious complications in this cohort of patients can be life threatening and can predispose to worsening liver function. Taken together, our findings are in agreement with prior reports documenting the safe use of FIFE under a compassionate use protocol in the pediatric population^{7, 8}.

The interim analysis of this randomized controlled trial suggests that the FIFE was well tolerated in the neonatal population recruited in this study with no observed increased risk of growth impairment, coagulopathy, infectious complications, hypertriglyceridemia or adverse neurodevelopmental outcomes. The significant increase in the serum omega-3 FA content in neonates on the FIFE may have a beneficial long-term impact on cognitive development and visual acuity for the preterm infant. The lack of an observed detrimental effect with the FIFE observed in this study paves the way for a follow-up randomized controlled trial with

revised eligibility criteria in order to accurately determine whether the provision of a FIFE is associated with a lower incidence of PN-cholestasis.

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Abbreviations

BSID	Bayley Scales of Infant and Toddler Development
DGLA	dihomo-gamma linoleic acid
DHA	docosahexaenoic acid
DPA	docosapentaenoic acid
EPA	eicosapentaenoic acid
FA	fatty acid
FIFE	fish oil based intravenous fat emulsion
GLA	gamma linoleic acid
INR	International Normalized Ratio
IL	interleukin
IQR	interquartile range
IFE	intravenous fat emulsion
LA	linoleic acid
PARCA-R	Parent Report of Children's Abilities
PN	parenteral nutrition
PNALD	parenteral nutrition associated liver disease
SIFE	soybean oil based intravenous fat emulsion

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CLINICAL RELEVANCY STATEMENT

In the United States the only intravenous fat emulsion approved by the Food and Drug Administration is soybean oil-based, although, a fish oil-based lipid emulsion is available for compassionate use in the setting of parenteral nutrition-associated cholestasis. This randomized controlled trial is the first to compare the soybean-oil and fish-oil lipid emulsions as the *initial* lipid for neonates. The results from the interim analysis indicate that the fish-oil lipid emulsion was associated with no increased risk of growth impairment, coagulopathy, infection, hypertriglyceridemia or adverse neurodevelopmental outcomes. This interim analysis paves the way for and highlights the need for a follow-up trial with revised eligibility criteria to determine whether the provision of a FIFE decreases the incidence of PN-cholestasis compared to the traditional SIFE.

Figure 1. Patient Flow Diagram

Twenty-six patients were assessed for eligibility and 19 were enrolled in the study. All analyses with the exception of neurodevelopmental and liver ultrasound outcomes were based on variables measured during PN-dependence, thus all 19 randomized patients (n=10 SIFE; n=9 FIFE) were included in the analysis on an intention-to-treat basis.

Neurodevelopmental outcomes at 6 and 24 months and liver ultrasound outcomes at 6 months were limited to the subset of patients who were seen in follow-up and agreed to have these tests completed.

Figure 2. Anthropometric Z scores

Median (IQR) weight-for-age Z-score (A), length-for-age Z-score (B) and head circumference-for-age Z-score (C) from time of IFE initiation (study week 0) to week 5 of IFE administration. The tables show the number of subjects with data at each study week. No significant differences were found between groups at any time point.

Table 1**Patient Characteristics**

	SIFE (n=10)	FIFE (n=9)	P
<i>Baseline Characteristics</i>			
Age at PN initiation (days)	2.0 (2.0, 3.0)	2.0 (2.0, 3.0)	0.66
Gestational age (weeks)	34.5 (34.0, 36.0)	36.0 (36.0, 37.0)	0.24
Birth weight (g)	2250 (1900, 2500)	2450 (2370, 2545)	0.25
Female gender	6 (60)	4 (44)	0.66
Race			1.00
White	8 (80)	8 (89)	
Black	2 (20)	1 (11)	
Diagnosis			0.39
Gastroschisis	4 (40)	6 (67)	
Jejuno-ileal atresia	3 (30)	0 (0)	
Duodenal atresia	1 (10)	1 (11)	
Midgut volvulus	2 (20)	1 (11)	
Necrotizing enterocolitis	0 (0)	1 (11)	
Prior operative intervention	8 (80)	7 (78)	1.00
Prior blood product transfusion	5 (50)	7 (78)	0.35
Mechanical ventilation	8 (80)	8 (89)	1.00
Prior/current antibiotic use	8 (80)	9 (100)	0.47
<i>Characteristics on PN</i>			
Duration of IFE (days)	36.5 (29.0, 76.0)	38 (32.0, 58.0)	0.97
Mean daily enteral intake (kcal)	60.2 (35.7, 69.9)	61.0 (46.2, 81.8)	0.66
Subjects undergoing an operative procedure	6 (60)	6 (67)	1.00
Transfusions			
Subjects requiring an operative transfusion	2 (20)	2 (22)	1.00
Subjects requiring a non-operative transfusion	6 (60)	5 (56)	1.00
Blood stream infection (number/subject)			1.00
Zero	6 (60)	5 (56)	
One	3 (30)	2 (22)	
Two	1 (10)	1 (11)	
Four	0 (0)	1 (11)	

Data presented as either median (IQR) or number of patients (%) as appropriate.

Table 2

Laboratory Studies

	Baseline			Week Four		
	SIFE	FIFE	P	SIFE	FIFE	P
Complete Blood Count	n=10	n=9		n=7	n=7	
WBC ($\times 10^3/\mu\text{L}$)	12.8 (8.7, 13.5)	12.4 (6.9, 14.7)	0.72	7.1 (5.1, 10.4)	11.3 (5.4, 25.8)	0.33
Hematocrit (%)	36.4 (32.1, 46.6)	44.7 (40.8, 47.4)	0.18	21.9 (18.2, 25.0)	26.3 (21.5, 29.8)	0.22
Platelet count ($\times 10^3/\mu\text{L}$)	235 (192, 346)	218 (161, 349)	0.90	422 (260, 546)	447 (292, 578)	0.53
Coagulation Profile	n=10	n=9		n=6	n=7	
INR	1.18 (0.99, 1.25)	1.16 (0.95, 1.60)	0.94	1.05 (1.03, 1.09)	1.19 (1.13, 1.20)	0.02
PTT (sec)	41.8 (30.8, 54.1)	45.0 (29.5, 48.6)	0.50	29.2 (24.7, 33.5)	34.3 (28.3, 37.3)	0.45
Fibrinogen (mg/dL)	327 (254, 399)	349 (251, 537)	0.66	284 (241, 356)	250 (235, 341)	0.63
Liver Function Tests	n=10	n=9		n=7	n=7	
Direct bilirubin (mg/dL)	0.3 (0.2, 0.3)	0.2 (0.2, 0.5)	0.73	0.3 (0.2, 1.0)	0.3 (0.1, 1.0)	0.70
AST (U/L)	36 (28, 63)	45 (27, 48)	1.00	39 (23, 56)	29 (25, 48)	0.75
ALT (U/L)	9 (6, 21)	21 (11, 29)	0.11	25 (13, 39)	18 (15, 40)	1.00
Alkaline phosphatase (U/L)	105 (89, 133)	75 (72, 83)	0.03	351 (320, 559)	255 (199, 291)	0.06
GGTP (U/L)	65 (36, 104)	67 (48, 108)	0.90	153 (114, 218)	100 (36, 294)	0.62
Albumin (g/dL)	2.0 (1.9, 2.6)	1.9 (1.7, 2.2)	0.34	3.1 (2.8, 3.3)	2.6 (2.4, 3.4)	0.42
Prealbumin (mg/dL)	6.3 (4.5, 6.9)	5.7 (5.4, 8.3)	0.60	10.2 (8.1, 12.7)	11.2 (8.4, 11.9)	0.85
Lipid Panel	n=10	n=9		n=7	n=7	
Triglycerides (mg/dL)	63 (41, 79)	62 (48, 91)	0.57	69 (28, 74)	58 (45, 110)	0.62
Cholesterol (mg/dL)	75 (57, 89)	79 (70, 105)	0.66	95 (91, 110)	89 (70, 160)	0.80
HDL (mg/dL)	16.6 (12.1, 18.9)	15.7 (12.6, 18.3)	0.78	29.8 (22.1, 34.5)	21.3 (11.2, 36.3)	0.71
VLDL (mg/dL)	13 (9, 16)	12 (9, 18)	0.77	14 (6, 15)	12 (9, 22)	0.71
LDL (mg/dL)	44 (30, 56)	53 (41, 59)	0.37	55 (53, 68)	53 (32, 115)	1.00

Data presented as median (IQR). Laboratory values at baseline (IFE initiation) and at week 4 of IFE administration.

Table 3**Plasma Fatty Acid Profiles**

	Baseline			Week Four		
	SIFE (n=9)	FIFE (n=9)	<i>P</i>	SIFE (n=5)	FIFE (n=6)	<i>P</i>
Alpha-linolenic acid, ALA 18:3n-3 (μmol/L)	5 (4,10)	14 (7, 18)	0.08	64 (60, 77)	26 (20, 51)	0.03
Linoleic acid, LA 18:2n-6 (μmol/L)	673 (628, 697)	755 (429, 913)	0.44	1885 (1838, 2149)	893 (535, 1422)	0.03
Arachidonic acid, AA 20:4n-6 (μmol/L)	829 (567, 943)	683 (651, 901)	1.00	685 (679, 837)	421 (230, 489)	0.06
Docosahexaenoic acid, DHA 22:6n-3 (μmol/L)	262 (126, 290)	202 (117, 303)	0.86	184 (183, 334)	713 (516, 1148)	0.02
Eicosapentaenoic acid, EPA 20:5n-3 (μmol/L)	18 (12, 26)	15 (13, 25)	0.97	47 (39, 54)	697 (505, 935)	0.02
Docosapentaenoic acid, DPA 22:5n-3 (μmol/L)	30 (16, 33)	30 (25, 56)	0.73	64 (57, 77)	125 (109, 158)	0.06
Gamma linoleic acid, GLA 18:3n-6 (μmol/L)	14 (12, 22)	24 (10, 37)	0.37	44 (39, 48)	10 (8, 13)	0.02
Dihomo-gamma linoleic acid, DGLA 20:3n-6 (μmol/L)	87 (78, 112)	85 (78, 97)	1.00	106 (104, 125)	41 (35, 60)	0.02
Oleic acid, OA 18:2n-9 (μmol/L)	1070 (1034, 1533)	1127 (1058, 1313)	0.54	914 (792, 983)	1036 (840, 1122)	0.34
Mead acid, MA 20:3n-9 (μmol/L)	26 (24, 28)	30 (21, 45)	0.52	15 (14, 17)	10 (8, 12)	0.04
Pristanic acid, PA 19:0 (μmol/L)	0.01 (0.01, 0.02)	0.01 (0.01, 0.02)	0.89	0.02 (0.01, 0.02)	0.70 (0.53, 0.92)	0.02
Stearic acid, SA 18:0 (μmol/L)	569 (480, 797)	541 (513, 683)	1.00	609 (588, 683)	522 (491, 730)	0.26
Palmitic acid, PAL 16:0 (μmol/L)	1133 (991, 1345)	1095 (1046, 1296)	0.44	1263 (1259, 1405)	1173 (1098, 1345)	0.26
Total n-3 FAs (mmol/L)	0.3 (0.2, 0.3)	0.3 (0.2, 0.4)	0.89	0.4 (0.3, 0.5)	1.6 (1.0, 2.4)	0.02
Total n-6 FAs (mmol/L)	1.6 (1.4, 1.8)	1.8 (1.3, 2.0)	0.69	2.9 (2.8, 3.1)	1.4 (0.9, 2.0)	0.04
Total Saturated FA ,SFA (mmol/L)	1.9 (1.6, 2.5)	1.9 (1.7, 2.1)	0.57	2.1 (2.1, 2.2)	1.9 (1.8, 2.5)	0.30
Total Monounsaturated FA, MUFA (mmol/L)	1.8 (1.5, 2.5)	2.1 (1.7, 2.2)	0.54	1.5 (1.3, 1.8)	1.5 (1.4, 2.0)	0.72
Total Polyunsaturated FA, PUFA (mmol/L)	2.0 (1.6, 2.2)	2.1 (1.5, 2.5)	0.83	3.3 (3.1, 3.7)	2.8 (2.4, 4.4)	0.53

	Baseline			Week Four		
	SIFE (n=9)	FIFE (n=9)	<i>P</i>	SIFE (n=5)	FIFE (n=6)	<i>P</i>
Total FA (mmol/L)	5.5 (5.0, 7.1)	5.8 (5.4, 6.7)	0.63	7.0 (6.7, 7.7)	6.2 (5.4, 9.3)	0.43
Triene:Tetraene ratio	0.030 (0.028,0.037)	0.046 (0.028,0.078)	0.46	0.020 (0.020,0.022)	0.029 (0.018,0.033)	0.34

Data presented as median (IQR). Fatty acid profiles at baseline (IFE initiation) and at week 4 of IFE administration.

Table 4

Neurodevelopmental Outcomes

	SIFE	FIFE	<i>P</i> *
<i>Bayley Scores of Infant Development (BSID)</i>			
6 months	105 (100, 105)	100 (95, 100)	0.08
Cognitive (n=5 SIFE, 6 FIFE)	97 (94, 106)	94 (91, 97)	0.43
Language (n=5 SIFE, 5 FIFE)	97 (97, 103)	94 (79, 103)	0.55
Motor (n=5 SIFE, 5 FIFE)			
24 months			
Cognitive (n=6 SIFE, 4 FIFE)	95 (85, 115)	93 (88, 98)	0.76
Language (n=5 SIFE, 4 FIFE)	106 (91, 118)	111 (100, 121)	0.56
Motor (n=6 SIFE, 4 FIFE)	99 (88, 103)	101 (94, 109)	0.76
<i>Parent Report of Children's Abilities – R (PARCA-R)</i>			
24 months			
Non-verbal cognition (n=5 SIFE, 4 FIFE)	26 (25, 28)	29 (23, 33)	1.00
Linguistic skills (n=5 SIFE, 4 FIFE)	33 (29, 92)	77 (64, 99)	0.30
Parent Report Composite Score (n=5 SIFE, 4 FIFE)	59 (52, 120)	98 (87, 125)	0.30

Data presented as median (IQR).

* *P*-value from a nonparametric analog to analysis of covariance, after adjusting for age.