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Nutrition

Essential fatty acid deficiency, olive oil-based intravenous lipid emulsion, and genetic polymorphisms: A pediatric randomized controlled trial

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Abstract

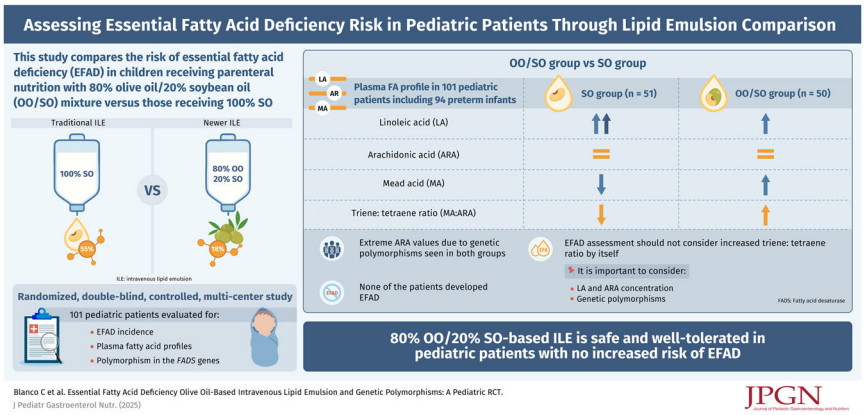
Objectives: There is a concern that decreasing soybean oil (SO) content in intravenous lipid emulsions (ILEs) may increase the risk for essential fatty acid deficiency (EFAD). This study evaluates the risk of EFAD in pediatric patients who were expected to require parenteral nutrition for at least 7 days with an 80% olive oil/20% SO ILE (OO/SO group) versus a 100% SO ILE (SO group).

Methods: This randomized, double-blind, controlled, multicenter study evaluated 101 pediatric patients including 94 preterm infants. The primary outcome was the incidence of EFAD, including the analysis of the plasma fatty acid (FA) profiles and genetic polymorphism in the FA desaturase genes in patients with extreme arachidonic acid values.

Results: Treatment duration was 10.3 ± 7.8 and 11.3 ± 9.4 days in the OO/SO and SO groups respectively. No EFAD was observed. Linoleic acid values increased in both groups but to a lesser extent in the OO/SO group. Arachidonic acid values remained stable within the two groups. The changes in mead acid value were opposite in the two groups, demonstrating an increase in the OO/SO group and a decrease in the SO group, leading to similar changes in the triene:tetraene ratio (T:T). Genetic polymorphisms were frequently observed in patients presenting extreme arachidonic acid values in both groups.

Conclusions: The use of an 80% OO/20% SO ILE is well tolerated, safe, and does not increase the risk of EFAD in pediatric patients. The assessment of EFAD should not only consider the T:T but also the complete FA profile and genetic polymorphisms.

Trial Identification Number and URL: NCT04555044, https://clinicaltrials.gov/study/NCT04555044?term=NCT04555044&rank=1



KEYWORDS

fat emulsions, parenteral nutrition, premature infants

1 | INTRODUCTION

Linoleic acid (LA) and alpha-linolenic acid (ALA) are essential fatty acids (EFAs) for humans.[1–3] EFA deficiency (EFAD) primarily occurs when fat intake or absorption is severely limited in the setting of depleted fat stores. Because of their high requirements, infants may develop EFAD within a few days if an intravenous lipid emulsion (ILE) is omitted from parenteral nutrition (PN).[3–5] Biochemical characteristics are secondary to insufficient availability of n-6 and n-3 polyunsaturated fatty acids (PUFAs) and traditionally includes an elevated plasma triene:tetraene ratio (T:T), specifically mead acid to arachidonic acid (ARA) ratio, also known as the Holman Index. Other biochemical manifestations of EFAD are considered nonspecific and may include elevated liver enzymes, hyperlipidemia, thrombocytopenia, and altered platelet aggregation.[1,2,6,7]

An ILE should be an integral part of any pediatric PN, either exclusive or complementary to enteral feeding, providing 25%–50% of nonprotein calories.[3,8] A minimum LA intake of 0.25 and 0.1 g/kg/day is recommended to prevent EFAD in preterm infants and in term infants and children respectively.[3] The first safe and efficient ILE consisted of 100% soybean oil (SO) which contains large amounts of LA and ALA (Table 1). However, experimental and clinical research have shown that 100% SO ILE (SO-ILE) were not ideal and new composite ILEs have been developed to decrease the proportion of SO.[2,3,7,9,10] Olive oil (OO) has the potential to improve overall health reducing the risk of noncommunicable diseases.[11–13] These benefits are attributed to the nutritional composition of OO, in particular its high n-9 monounsaturated fatty acids (MUFA) content (i.e., oleic acid) and some minor compounds such as polyphenols.[11–13] Oleic acid is also the most abundant fatty acid (FA) in human milk.[14] Recent PN evidence suggests that the use of an 80% OO/20% SO ILE (OO/SO) is well tolerated, provides efficient nutritional support, appears to support the innate immune system, is associated with fewer infections, induces less lipid peroxidation, and is not associated with increased hepatobiliary or lipid disturbances.[12,13] As the OO/SO-ILE includes less LA than SO-ILE (~18% vs. ~55% respectively, Table 1), the objective of this study was to evaluate the risk of developing EFAD when using an OO/SO ILE and providing less LA (OO/SO group) versus using a SO-ILE in pediatric patients, including preterm infants.

What is Known?

- Essential fatty acids (EFAs) are mainly supplied from soybean oil (SO) during parenteral nutrition (PN).
- EFA deficiency (EFAD) may develop within a few days during PN in infants, especially with omission of an intravenous lipid emulsion (ILE).

What is New?

- Olive oil-based ILE did not increase the risk of EFAD when compared to a 100% SO ILE in pediatric patients.
- The complete fatty acid profile should be analyzed, in particular arachidonic acid, when assessing the risk of EFAD, and not only the triene-to-tetraene ratio.
- Genetic polymorphisms need to be assessed when evaluating EFAD.

TABLE 1 Fatty acid content (mean) for 100% soybean oil and 80% olive oil/20% soybean oil intravenous lipid emulsions.

Fatty acid(s)	100% soybean oil (%)	80% olive oil/ 20% soybean oil (%)
Total saturated fatty acids	15.6	16.6
Myristic acid (14:0)	0.1	0.0
Palmitic acid (16:0)	11.0	13.0
Stearic acid (18:0)	3.9	3.3
Total monounsaturated fatty acids	22.8	63.4
Palmitoleic acid (16:1n-7)	0.1	0.9
Oleic acid (18:1n-9)	20.9	59.7
Vaccenic acid (18:1n-7)	1.3	1.7
Gondoic acid (20:1n-9)	0.2	0.2
Total polyunsaturated fatty acids	61.7	20.0
Linoleic acid (18:2n-6)	54.7	18.6
γ-Linolenic acid (18:3n-6)	ND	ND
α-Linolenic acid (18:3n-3)	6.7	1.7
Arachidonic acid (20:4n-6)	0.2	0.2
Eicosapentaenoic acid (20:5n-3)	ND	ND
Docosahexaenoic acid (22:6n-3)	0.1	0.1

Note: Adapted from Giuffrida et al.[14]

Abbreviation: ND, not detected.

2 | METHODS

2.1 | Population

This randomized, double-blind, controlled, phase 4 study (NCT04555044) was developed in accordance with the Food and Drug Administration (FDA) for expanding the indication of Clinolipid to pediatric patients in the United States. The study was performed between January 2021 and November 2022 in pediatric inpatients expected to require PN for at least 7 days. At study entry, PN was to represent at least 80% of targeted energy requirements in preterm infants and at least 70% of targeted energy requirements in full-term infants and children <18 years. Exclusion criteria included preterm infants <24 weeks of gestation or birth weight <750 g, known hypersensitivity to ILE, liver disease including cholestasis, hypertriglyceridemia >400 mg/dL, patients who required or were expected to require propofol for sedation, and patients who are not expected to survive hospitalization.

2.2 | Intervention

The investigational product was a mixture of refined 80% OO/20% SO (Clinolipid 20%, Baxter Healthcare Corporation). It was compared to standard of care 100% SO ILE (Intralipid 20%, Fresenius Kabi). The FA content of each ILE is described in Table 1.

The ILE dosing schedule was to start lipid on first day of PN at 1 g/kg/day and to increase the lipid dose by 1 g/kg/day up to 2.5–3 g/kg/day in preterm and term infants <1 year, 2–3 g/kg/day children 1–10 years, and 1–2 g/kg/day in adolescents 10–18 years.

2.3 | Outcomes and methods

The primary outcome was the incidence of EFAD, defined using a plasma T:T value above 0.4. Biochemical EFAD was confirmed in the context of low LA, low ARA, and high mead acid in plasma. Clinical EFAD was diagnosed in the presence of any clinical features of EFAD (dermatitis, diarrhea, perianal irritation, growth and development failure, recurrent infections, irritability, and/or poor wound healing).[1,2,7]

Patients with a T:T between 0.2 and 0.4 were considered as indeterminate considering it may be seen in patients with adequate LA intake to prevent EFAD and in patients with low LA intake that are evolving toward EFAD. In such patients, EFAD was considered if any clinical features of EFAD were present or if the LA and ARA levels were both low, and the treatment was adapted for increasing the LA intake after unblinding the pharmacist who prepared the ILE. If no clinical feature of EFAD was present with both the ARA levels and the LA intake within the normal range, then the risk of EFAD was not considered. Patients with a T:T below 0.2 were considered as having normal EFA status.

An analysis of the complete plasma FA profile was assessed in the central laboratory according to the Mayo Clinic Laboratories method.[15] Blood was collected after a 4-h ILE interruption at screening/baseline and every 15 (±2) days up to the end of treatment (EoT).

To assess the role of FA desaturase 1 and 2 (FADS1/2) gene polymorphism in extreme ARA values, buccal swab samples were also analyzed at the central laboratory in 20 patients, the 10 patients (five in each group) with the lowest ARA values and the 10 patients (five in each group) with the highest ARA values at any point during the study.

2.4 | Statistics

Patients were assigned to the two treatment groups with a 1:1 randomization ratio according to a central

dynamic randomization scheme stratified by site and age group (preterm infants, full-term neonates <1 month of age, infants 1–<12 months of age, children 1–<10 years of age, adolescent 10–<18 years of age).

A sample size of 100 pediatric patients (50 in each of the two treatment groups), including neonates, was decided with the FDA for this phase 4 trial based on the feasibility of timely enrollment of patients for generating reference data and summary descriptive statistics, rather than on a formal power calculation.

The descriptive statistical analyses were performed using SAS®, SAS/GRAPH®, and SAS/STAT® software, Version 9.4 of SAS for Windows, copyright© 2016 SAS Institute Inc, on a Microsoft Windows Server.

2.4.1 | Ethics statement

This study was approved by the East Carolina University & Medical Center Institutional Review Board (Greenville, NC), the University of Tennessee Health Science Center Institutional Review Board (Memphis, TN), and the WCG Institutional Review Board (Puyallup, WA) that served for the University of Texas Health Science Center (San Antonio, TX), University of Mississippi Medical Center (Jackson, MS), Utah Valley Hospital (Provo, UT), AdventHealth for Children (Orlando, FL), and Tufts University School of Medicine (Boston, MA). A written informed consent form was signed by the patients or their legal representative. The procedures were performed in accordance with the ethical standards of the US 21 Code of Federal Regulations Part 312, the Declaration of Helsinki, and Good Clinical Practice ICH E6.

3 | RESULTS

3.1 | Demographics

A total of 101 patients were enrolled at seven hospitals, 50 in the OO/SO group and 51 in the SO group. Demographic and baseline characteristics were similar in the two groups (Table 2). Ninety-four patients (93.1%) were preterm infants,53 (52.5%) being very low birth weight (1000–1499 g), and 32 (31.7%) extremely low birth weight (ELBW, <1000 g). Despite randomization, the OO/SO group had more ELBW patients than the SO group (38.0% vs. 25.5%). Other differences included a greater percentage of males in the OO/SO group than the SO group (68.0% vs. 43.1%).

Among the 94 preterm infants, median (min, max) age at consent was 1 (0–8) and 1 (0–6) day in the OO/SO and SO group respectively. Median (min, max) gestational age and birth weight were 28.7 (24.7–36.0) and 29.0 (25.0–35.6) weeks, and 1110 (765–1869) and 1130 (765–2200) g in the OO/SO and SO group respectively.

3.2 | Treatment exposure

Treatment exposure was similar and compliant with the study protocol in the two study treatment groups. Standard of care 100% SO ILE was administered as pre-study treatment in 44 patients (44%), 21 patients in the OO/SO group and 23 patients in the SO group.

The mean ± standard deviation (SD) study treatment duration was 10.3 ± 7.8 and 11.3 ± 9.4 days in the OO/SO and SO groups, respectively. During the study period, the mean ± SD parenteral lipid daily intake was 2.3 ± 0.8 and 2.4 ± 0.8 g/kg/day in the OO/SO and SO groups, respectively. During the study treatment, the cumulative enteral intake was 234 ± 115 kcal/kg in the OO/SO group and 198 ± 126 kcal/kg in the SO group, representing 39.4% and 35.1% of total cumulative intakes, respectively. Overall daily intakes were aligned with the study protocol and nutritional recommendations as summarized in Supporting Information S1: Figure S1 that shows the progression of administered total and enteral intakes.

3.3 | Primary outcome

No patient developed EFAD, clinically or biochemically, at any time-point during the study period.

3.4 | FA profile

Total FAs, saturated FAs, monounsaturated FAs (MUFAs), and n-6 and n-3 PUFAs increased in the two groups from baseline to EoT (Table 3). Compared to the SO group, the OO/SO group showed a higher increase in MUFAs and a lower increase in n-6 PUFAs.

The individual FA changes from baseline to EoT are presented in Figure 1. The plasma LA values increased from baseline to EoT in the two treatment groups, but the increase in the OO/SO groups (504.5 ± 961.44 µmol/L, geometric mean 86.3%) was less than in the SO group (1039.2 ± 816.24, geometric mean 131.0%). Similarly, an increase in plasma ALA values were observed in both groups but to a lower extent in the OO/SO group than in the SO group (3.6 ± 66.02 vs. 29.5 ± 47.64, geometric mean 186.6% vs. 271.6%). Plasma ARA values remained stable in the two groups demonstrating a geometric mean change of –2.6% and –1.9% in the OO/SO and SO groups, respectively. Both groups showed an increase in oleic acid with a higher increase in the OO/SO group than in the SO group (687.6 ± 781.75 vs. 205.6 ± 513.69 µmol/L, geometric mean 56.2%

TABLE 2 Demographic and baseline characteristics.

Characteristic		80% OO/20% SO group *N* = 50 *n* (%)	100% SO group *N* = 51 *n* (%)	Total *N* = 101 *n* (%)
Sex	Female	16 (32.0)	29 (56.9)	45 (44.6)
	Male	34 (68.0)	22 (43.1)	56 (55.4)
Race	American Indian or Alaska Native	3 (6.0)	0	3 (3.0)
	Asian	2 (4.0)	2 (3.9)	4 (4.0)
	Black or African American	21 (42.0)	20 (39.2)	41 (40.6)
	Native Hawaiian or other Pacific Islander	1 (2.0)	0	1 (1.0)
	White	19 (38.0)	23 (45.1)	42 (41.6)
	Other	2 (4.0)	4 (7.8)	6 (5.9)
	Not reported	2 (4.0)	2 (3.9)	4 (4.0)
Ethnic group	Hispanic or Latino	3 (6.0)	5 (9.8)	8 (7.9)
	Not Hispanic or Latino	44 (88.0)	42 (82.4)	86 (85.1)
	Not reported	3 (6.0)	4 (7.8)	7 (6.9)
Diagnosis for parenteral nutrition	Prematurity	46 (90.2)	46 (85.2)	92 (87.6)
	Gastroschisis	0	3 (5.6)	3 (2.9)
	Enteropathies including inflammatory gastrointestinal diseases	0	1 (1.9)	1 (1.0)
	Feeding intolerance	1 (2.0)	0	1 (1.0)
	Meconium ileus	1 (2.0)	0	1 (1.0)
	Necrotizing enterocolitis	1 (2.0)	0	1 (1.0)
	Persistent pulmonary hypertension	1 (2.0)	0	1 (1.0)
	Preterm infant with feeding intolerance	1 (2.0)	0	1 (1.0)
	Preterm infant with gastroschisis	0	1 (1.9)	1 (1.0)
	Sepsis	0	1 (1.9)	1 (1.0)
	Short bowel syndrome	0	1 (1.9)	1 (1.0)
	Small for gestational age	0	1 (1.9)	1 (1.0)
Age group	Preterm neonate (born <37 weeks of gestation)	47 (94.0)	47 (92.2)	94 (93.1)
	Full term neonate (born ≥37 weeks of gestation to <1 month of age)	2 (4.0)	2 (3.9)	4 (4.0)
	Infant (1–<12 months of age)	0	0	0
	Child (1–<10 years of age)	1 (2.0)	1 (2.0)	2 (2.0)
	Adolescent (10–<18 years of age)	0	1 (2.0)	1 (1.0)
Weight at birth	Normal (>2500 g)	1 (2.0)	2 (3.9)	3 (3.0)
	Low (1500–2499 g)	4 (8.0)	6 (11.8)	10 (9.9)
	Very low (1000–1499 g)	25 (50.0)	28 (54.9)	53 (52.5)
	Extremely low (<1000 g)	19 (38.0)	13 (25.5)	32 (31.7)
	N/A[a]	1 (2.0)	2 (3.9)	3 (3.0)

Note: Multiple diagnoses for parenteral nutrition were allowed, so *n* may be greater than number of subjects.

Abbreviations: OO, olive oil; SO, soybean oil.

[a]Includes the two children aged 1–<10 years and the one adolescent aged 10–<18 years.

TABLE 3 Change in FA profile from baseline and EoT in the 80% OO/20% SO group ($N = 50$) and the 100% SO group ($N = 51$).

	Treatment group	Baseline	EoT
Total FAs (mmol/L)	OO/SO	6.79 ± 2.052	8.85 ± 1.923
	SO	6.81 ± 1.971	8.51 ± 1.453
Total saturated FAs (mmol/L)	OO/SO	2.43 ± 0.567	3.10 ± 0.734
	SO	2.36 ± 0.567	2.90 ± 0.470
Total MUFAs (mmol/L)	OO/SO	1.81 ± 0.614	2.61 ± 0.668
	SO	1.83 ± 0.683	2.00 ± 0.475
Total PUFAs (mmol/L)	OO/SO	2.55 ± 1.180	3.12 ± 0.788
	SO	2.60 ± 0.974	3.59 ± 0.757
Total n-3 PUFAs (mmol/L)	OO/SO	0.19 ± 0.127	0.20 ± 0.071
	SO	0.22 ± 0.138	0.25 ± 0.094
Total n-6 PUFAs (mmol/L)	OO/SO	2.32 ± 1.084	2.86 ± 0.752
	SO	2.34 ± 0.873	3.31 ± 0.690

Abbreviations: EoT, end of treatment; FA, fatty acid; MUFAs, monounsaturated fatty acids; OO, olive oil; PUFAs, polyunsaturated fatty acids; SO, soybean oil.

vs. 17.0%). Plasma mead acid value changes differed between the two groups. The OO/SO group demonstrated an increase (15.4 ± 38.14 μmol/L, geometric mean 38.7%) while the SO group demonstrated a decrease (10.6 ± 21.02 μmol/L, geometric mean −25.6%).

The EoT distribution of the FA profile values in neonates (<1 months of age, $n = 98$) is presented in Supporting Information S1: Table S1. The changes from baseline to EoT in neonates showed similar trends in the entire cohort. The FA profiles of neonates <1000, 1000–1499, and ≥1500 g, and in infants and children show similar trends without differences between groups (data not shown).

The median (interquartile range), minimum, and maximum values of all plasma ARA results ($n = 205$) observed during the study in the entire cohort were 932 (798–1112), 366, and 1756 μmol/L, being similar in the two groups. Within the lowest (1st quartile) of ARA values, 42% were observed at baseline. Among the ones observed after baseline, 37% were in the OO/SO group and 63% in the SO group. Within the highest (4th quartile) ARA values, 63% were observed at baseline. Among the ones observed after baseline, 53% were in the OO/SO group and 47% in the SO group.

3.5 | T:T

The mean T:T changes from baseline to EoT followed the same trend as mead acid in the two groups, as ARA changes were similar. Mean T:T changes showed an increase (0.018 ± 0.044, geometric mean 42.3%) in the OO/SO group and a decrease (0.010 ± 0.0175, geometric mean −23.8%) in the SO group.

A T:T value between 0.2 and 0.4 was observed in one patient from the OO/SO group, a small-for-gestational age very preterm infant (29.3 weeks and 830 g at birth). The T:T increased from 0.054 at baseline to 0.253 at EoT. The study treatment was administered from 1 day of age, after 1 day of prestudy treatment with 100% SO ILE, up to Day 13, and the EoT blood sampling was performed on Day 15. The ILE-dosing was in accordance with the study protocol (Supporting Information S1: Table S2). No clinical feature of EFAD was reported. The itemized FA profile changes for this patient are shown in Supporting Information S1: Table S3. The ARA levels remained within reference range while mead acid increased above the reference range. The result from the FADS1 and FADS2 gene polymorphism analysis was positive: heterozygous for rs174553 FADS1 allele and heterozygous for rs99780 FADS2 allele.

Due to a trend for higher T:T values in the OO/SO group, the three patients who demonstrated an increased T:T value between 0.1 and 0.2 were also analyzed. None have developed clinical features of EFAD. All demonstrated an increase in their ARA values, not suggesting any risk of EFAD (Supporting Information S1: Table S4).

3.6 | Genetic polymorphisms in FADS1 and FADS2 genes

Of the 20 patients with extreme ARA values, 14 (70%) presented genetic polymorphisms in FADS1 and/or FADS2 genes, 6 among the 10 patients with the highest ARA values and 8 among the 10 patients with the lowest ARA patients. All were preterm infants with similar population characteristics. Mean age, gestational age, and birth weight were 1.60 ± 1.265 and 0.70 ± 0.823 days, 29.9 ± 2.7 and 30.0 ± 1.25 weeks, and 1.24 ± 0.45 and 1.16 ± 0.19 kg in the lowest and highest ARA subgroups, respectively. These lowest and highest ARA values were mainly observed at baseline, in six (60%) patients from the lowest ARA subgroups and in eight (80%) patients from the highest ARA subgroups. The lowest ARA values were observed after baseline in two (40%) and three (60%) patients in the OO/SO and SO subgroups, respectively. The detailed FADS1 and FADS2 gene polymorphism results and the patient and FA profile characteristics of

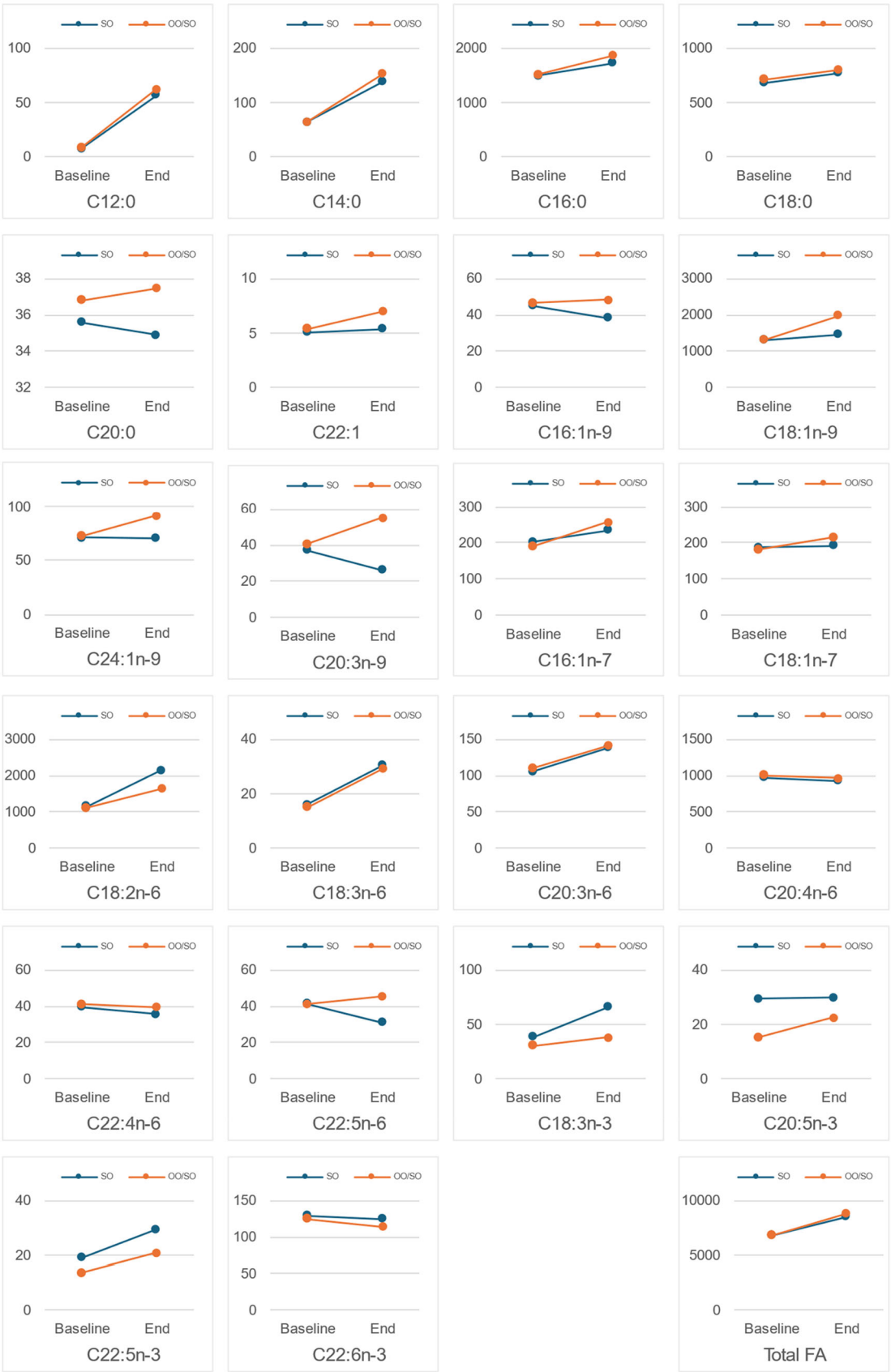


FIGURE 1 Baseline and end of treatment fatty acid profile mean values (μmol/L) in the 80% olive oil/20% soybean oil group ($N = 50$) and the 100% soybean oil group ($N = 51$).

the 20 analyzed patients are described in Supporting Information S1: Table S5.

4 | DISCUSSION

This pediatric clinical trial showed that reducing the SO content to 20% in an OO-based ILE did not increase the risk of EFAD when compared to 100% SO ILE during PN, maintaining similar ARA levels. It also showed reduced LA increase and higher mead acid plasma values. The study confirms the importance of assessing the whole FA profile—in particular ARA—when evaluating EFAD.[2,16,17] The diagnosis of EFAD traditionally focuses on an elevated T:T considering the numerator (triene/mead acid) increases when the denominator (tetraene/ARA) decreases. However, changes in the numerator or denominator alone may also occur secondary to dietary changes or the FA composition of the ILE.[2,10,17] It is known that plasma oleic acid content is increased by OO-based ILE when compared to 100% SO ILE.[2,10,17,18] As oleic acid can easily be metabolized into mead acid, the T:T tends to be higher in these patients, potentially exceeding population-based reference ranges.[2,10,17] There is some controversy in the literature as to whether the T:T is still the best criterion to diagnose EFAD during PN.[2,10,17] In patients receiving an ILE, the whole FA profile and not only the T:T should be interpreted to assess the risk of EFAD taking into account the FA composition of the ILE.[2] As another example, the presence of fish oil in an ILE and its high n-3 PUFA content also impact both the ARA and mead acid values, both tending to be lower when compared to other ILEs, especially ARA.[10,16,19,20] Several studies have assessed EFAD focusing on the single T:T value without reporting precisely the individual FA values, in particular ARA and mead acid.[21–23] Such an assessment of EFAD considering only the T:T value may be inaccurate and misleading.[2,17] An increase in mead acid not accompanied by a decrease in ARA should not be considered as EFAD.[2,17] Several experts have recently discussed the importance of ARA highlighting its key structural role, in particular in infants.[24–27] Maintaining an appropriate concentration of ARA is arguably more important than simply maintaining the T:T when assessing the risk of EFAD.[2,3,10,24,28]

In addition, laboratory reference ranges for FAs are influenced by the diet in the reference population, most frequently a western-type diet rich in LA. Such a diet is associated with low mead acid value inducing low T:T reference range that should not be used as a threshold for indicating EFAD, especially during PN.[2] The diagnosis of EFAD with certainty requires that the T:T ratio is elevated because LA levels are low enough to result in a decreased production of ARA and an increased production of mead acid.[2,29]

In this study, no cases of EFAD were observed but one patient from the OO/SO group exhibited a T:T value that increased to 0.253. The T:T increase was mainly due to a high increase in mead acid, while the ARA remained within the reference range. This patient also had polymorphisms for both the FADS1 and FADS2 genes and these variants are known to significantly influence the plasma ARA values.[30–32] Variants in the FADS 1/2 genes modify the activity of PUFA desaturation leading to lower or higher ARA values in plasma and tissues, as demonstrated by their high prevalence in the 20 patients with extreme ARA values.[30–32] In the case of the patient with a T:T of 0.253, it is known that both rs174553 FADS1 allele and rs99780 FADS2 allele polymorphisms are associated with decreased level of ARA.[31] Therefore, this study confirms the key role of FADS1 and FADS2 in the synthesis of LC-PUFAs, especially ARA. It highlights the importance of assessing FADS gene polymorphisms when assessing EFAD, and not only to the T:T. This is indeed of high importance as variants in the FADS gene cluster not only modify the activity of PUFA desaturation and the lipid composition in human blood and tissue, but also influence health conditions such as eczema, asthma, and cognition.[30–32]

This study has several limitations. It was descriptive and had a limited sample size. The overall short duration of the intervention implies that the risk of EFAD has not been assessed in children requiring long-term PN. Nonetheless, the patients included in the study were representative of the overall pediatric inpatients that receive PN.[33,34]

The ideal FA profile remains unknown, particularly in preterm infants who are at higher risk of EFAD. The role of FADS1/2 gene polymorphisms also needs to be better described when assessing EFAD as this study confirms the high prevalence of polymorphisms in patients with extreme ARA values.[30–32] Finally, some important changes in the FA profiles are also observed during the first weeks of life.[35] A rapid increase in the concentration of LA and ALA and a rapid decrease of traditional EFAD biomarkers (mead acid and T:T) and several n-6 PUFAs have been observed in red blood cells during the first weeks of life.[35] Therefore, more studies are required to better define the optimal concentrations of EFAs in infants, especially in light of the recent evidence supporting the key role of ARA.[24–27]

5 | CONCLUSION

This trial data demonstrated that the 80% OO/20% SO ILE did not increase the risk of EFAD in pediatric patients during PN when compared to a 100% SO ILE in actual routine practice, as documented by the duration of this trial and at the doses studied. The results are

valid for the overall pediatric patients and may not apply for patients who require long-term total PN and lipid dosing is minimized. The observation of stable ARA concentration between both study groups suggests that the risk of EFAD is similar between the two ILEs, especially in preterm infants. This study confirms the importance of assessing the whole FA profile during PN as the plasma FA profiles of the patients may be influenced by the ILE composition. Particular attention should be dedicated to ARA values and genetic polymorphisms when assessing EFAD, and not only to the T:T. Further studies are necessary to define the optimal FA concentration in pediatric patients during PN.

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CONFLICTS OF INTEREST STATEMENT

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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