Long-term efficacy and safety of a new olive oil–based intravenous fat emulsion in pediatric patients: a double-blind randomized study[1,2]

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ABSTRACT

Background: A new intravenous lipid emulsion (ILE) prepared from a mixture of soybean and olive oils contains only long-chain triacylglycerols, with a low proportion (20%) of polyunsaturated fatty acids and 60% monounsaturated fatty acids.

Objective: The goal of this randomized, double-blind clinical trial was to assess in children the efficacy and safety of this new ILE compared with a control group receiving a soybean-oil emulsion.

Design: Eighteen children received for 2 mo 24% of nonprotein energy ($1.80\ g \cdot kg \cdot^{-1} \cdot d^{-1}$) either as the new ILE or a soybean oil–based emulsion. Assessments were performed on days −30, 0, 30, and 60 and the changes (day 60 − day 0) assessed by analysis of variance.

Results: There were no significant differences in triacylglycerol, apolipoproteins A-I and B, or HDL cholesterol between the 2 groups, whereas total and LDL cholesterol were higher in the soybean oil group on day 60. The pattern of 20:4n−6 in erythrocyte membranes did not change significantly, nor did the ratio of 20:3n−9 to 20:4n−6. On day 60, 18:1n−9 was significantly higher in the olive oil group, the ratio of Σn−6 > C_{18} + 18:3n−6 to 18:2n−6 was 2.20 ± 0.09 in the olive oil group and 1.33 ± 0.16 in the soybean-oil group, and Σn−3 > C_{18} was 3.83 ± 0.30 in the olive oil group and 4.03 ± 0.33 in the soybean-oil group. The peroxidation index was lower after the olive oil treatment.

Conclusions: The olive oil–based emulsion was well tolerated, maintained a normal EFA status, and may be more suitable for prevention of lipid peroxidation than the soybean-oil–based emulsion. *Am J Clin Nutr* 1999;70:338–45.

KEY WORDS Intravenous fat emulsion, lipids, olive oil, soybean oil, parenteral nutrition, pediatrics, children

INTRODUCTION

Parenteral nutrition is an efficient and often life-saving therapy in pediatric patients with severe gastrointestinal diseases (1). Glucose has long been considered the main energy substrate in neonates and children. Intravenous lipid emulsions (ILEs) are currently widely used and their benefits in pediatric patients are well documented (2–5). ILEs serve as a major source of energy by reducing the potential side effects of a high glucose intake (6–8), providing the required essential fatty acids (EFAs) (9–11), and improving nitrogen balance (12–16). Two types of lipid emulsions are currently used for adult as well as pediatric patients: *1*) ILEs prepared from soybean oil that are composed of long-chain triacylglycerols (LCTs), 62% of which are polyunsaturated fatty acids (PUFAs), and *2*) ILEs composed of 50% medium-chain triacylglycerols (MCTs) and 50% LCT soybean oil, not corresponding to usual lipid intakes in healthy subjects, containing 30% of total fatty acids as PUFAs. A new ILE prepared from a mixture of soybean oil and olive oil contains only LCTs and has a lower proportion (20%) of PUFAs and 60% monounsaturated fatty acids (MUFAs). In previous clinical studies, this olive oil–based emulsion was used in children as a short-term treatment and results showed efficacy and a good clinical and biological safety profile in children (17). The advantage of this ILE is a reduction in the risks related to an excessive intake of PUFAs, such as increased lipid peroxidation, inhibition of the synthesis of higher homologues of EFAs, alteration of membrane structures, and impairment of immune function (18–21). In addition, this new ILE provides a balanced and sufficient intake of the different classes of fatty acids and prevents or corrects EFA deficiency (17).

The objective of the present study was to assess, in children requiring prolonged parenteral nutrition, the long-term efficacy and safety of a new olive oil–based fat emulsion compared with that of a soybean-oil emulsion given to a control group. The study was performed after a 30-d equilibration period.

SUBJECTS AND METHODS

Patient selection

The study included 20 children who required prolonged parenteral nutrition (>3 mo) to meet ≥80% of their protein-energy requirements. The children required parenteral nutrition because of the following conditions: short-bowel syndrome (n = 8),

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TABLE 1
Composition of the 2 lipid emulsions

	Olive oil	Soybean oil
Olive oil (g/L)	160	—
Soybean oil (g/L)	40	200
Egg phosphatidates (g/L)	12	12
Sodium oleate (g/L)	0.3	—
Glycerol (g/L)	22.5	22.5
Major fatty acids (% by wt)		
16:0	13	11
18:0	3	4
18:1n−9	60	21
18:2n−6	18	53
18:3n−3	2	7
α-Tocopherol (mg/L)	30	14

intractable diarrhea (n = 8), and chronic intestinal pseudo-obstruction (n = 4). Patients with type 1 diabetes, renal insufficiency, abnormal liver function, or any metabolic disorder were excluded as were those receiving carnitine supplements, anticoagulants, steroids, or immunosuppressive agents. The protocol of the study was approved by the Human Ethical Committee of the Necker-Enfants Malades University. Written, informed consent was obtained for each patient after the study was explained to the patients and their parents.

Parenteral nutrition

Carbohydrate intake was adjusted on the basis of lipid intakes, which represented 20–40% of nonprotein energy. The patients received an amino acid solution identical to that given in the equilibration period: 250–500 mg $N \cdot kg^{-1} \cdot d^{-1}$ as Vaminolac (Upjohn-Pharmacia, Saint Quentin en Yvelines, France) or Vintene (Baxter Clintec, Maurepas, France).

Water and electrolytes were adjusted on the basis of age requirements and intestinal losses. The doses of vitamins and trace elements were standardized on the basis of recommended intakes (1). Daily intakes of vitamins A, C, and E were provided as follows: 53 μg (175 IU) retinol/kg body wt, 6.25 mg ascorbic acid/kg body wt, and 0.50 mg α-tocopherol/kg body wt, respectively. Vitamin and trace element intakes were not modified during the study unless there was an urgent clinical or biological need to. Vitamin K (50 mg) was provided once monthly.

Study protocol

The 20 patients underwent a 30-d equilibration period, during which their parenteral nutrition regimen included the administration of the lipid emulsion Medialipide 20% (B Braun, Boulogne, France), which was composed of 50% MCTs and 50% LCTs. The equilibration period was designed to individually adjust a stable regimen of energy and protein intakes and to select the dose rate of lipid emulsion so that the lipid intake represented ≥20% (40% maximum) of the total nonprotein energy intake weekly. At the end of the equilibration period, 18 (ages 1–9 y) of the 20 patients were randomly assigned to either a treatment (n = 9) or to a control group (n = 9). Two patients were not eligible for randomization: one patient had a worsening of his gastrointestinal condition and withdrew for personal reasons and one patient's bilirubin concentration increased on day −30 to unacceptable concentrations.

Randomization was performed according to the method of minimization for assigning patients to treatment and control groups (22, 23). During the 2-mo randomization period, the safety and efficacy of a new olive oil–based ILE (ClinOleic 20%; Baxter Clintec) was compared with those of a soybean-oil–based emulsion (Intralipid 20%; Upjohn-Pharmacia) (**Table 1**). Tested products used in both the equilibration and study periods were prepared by the hospital pharmacist in blinded ethylene vinyl acetate bags identified by the treatment number on the label. Neither the patient nor the investigator knew which lipid emulsion was administered. For both periods, lipid emulsions were administered with an infusion pump at a maximum rate of 0.25 $g \cdot kg^{-1} \cdot h^{-1}$ from between 1800 and 2000 to between 0600 and 0800 3–5 d/wk.

Efficacy and safety measurements

Clinical indexes

Any abnormal manifestation was noted, eg, headache, emesis, and fever. The following indexes were determined on day −30, day 0, and every 30 d thereafter or at treatment withdrawal: triceps skinfold thickness with a skinfold caliper (Holtain Ltd, Crymych, United Kingdom), weight, height, and midarm circumference.

Biological indexes

All blood samples were obtained 4–6 h after the end of the glucose-amino acid infusion and ≥24 h after the end of all ILE infusions. Safety indexes included measures of blood urea nitrogen, glucose, creatinine, plasma electrolytes, total and conjugated bilirubin, serum aspartate transaminase, serum alanine transaminase, alkaline phosphatase, and γ-glutamyltransferase, which were measured on day −30, day 0, and every 30 d thereafter or at treatment withdrawal. Prothrombin time was determined and a hemogram [hemoglobin concentration, hematocrit, and white blood cell (WBC), red blood cell (RBC), and platelet counts] completed on day −30, day 0, and at treatment withdrawal.

Plasma total cholesterol, HDL-cholesterol, LDL-cholesterol, phospholipid, and triacylglycerol concentrations were assayed by using enzymatic methods. Apolipoproteins A-I and B were assayed by automatic immunoturbidimetry. Total bile acids in serum, α-tocopherol (vitamin E), and albumin were also measured. Plasma and RBC fatty acids were determined as described previously (24) by using gas-liquid chromatography on a Carlo Erba Chromatograph (Erba Sciences, Paris) equipped with a polar capillary column (Omegawax; Supelco Inc, Bellefonte, PA) and a flame ionization detector. Results were expressed as the sum of upper derivatives of linoleic acid (Σn−6 > C_{18} + 18:3n−6), the sum of upper derivatives of α-linolenic acid (Σn−3 > C_{18}), triene (20:3n−9), and as the ratio of 20:3n−9 to tetraene (20:4n−6). The peroxidation index was assessed by measuring the maximal amount of formed thiobarbituric acid–reactive substances (TBARS) after an oxidative stress induced in vitro by phenylhydrazine on the precipitated RBC membranes (RBC-TBARS), LDL (LDL-TBARS), and total LDL + VLDL (LV-TBARS) (25–27). The precipitation method has been evaluated and validated when serum triacylglycerol values are low by positive correlation with electrophoresis, analytic ultracentrifugation, and with the Friedewald formula (28–30).

Statistical analysis

Results are expressed as means ± SEMs. All variables recorded at inclusion (day 0) and thereafter were compared between groups. Data were entered twice and all data were audited manually to ensure accuracy. SAS (SAS Institute Inc,

TABLE 2
Baseline characteristics of the study population[1]

	Olive oil (n = 9)	Soybean oil (n = 9)
Age (y)	4 ± 1.1	3 ± 1.0
>2 y (n)	4	4
≤2 y (n)	5	5
Male:female	4:5	5:4
Ethnicity (n)		
White	6	7
Black	1	0
Other	2	2
Weight (kg)	17.4 ± 2.7	15.2 ± 1.8
Height (cm)	96.9 ± 7.0	95.6 ± 6.2
Midarm circumference (cm)[2]	15.9 ± 1.0	16.0 ± 0.8
Triceps skinfold thickness (mm)[2]	7.5 ± 1.1	7.0 ± 0.7

[1] $\bar{x}$ ± SEM. There were no significant differences between groups.
[2] Olive oil group: n = 4; soybean-oil group: n = 8.

Cary, NC) for WINDOWS was used for the analyses. Data for the 2 groups were compared by using a Student's t test or Wilcoxon's rank-sum test. A two-factor repeated-measures analysis of variance was applied to the difference between values on days 0 and 30 and between values on days 0 and 60 to compare the biological course of patients receiving olive oil–based emulsions with those receiving soybean-oil–based emulsions over the 2-mo treatment period. If any differences between groups at baseline had a P value < 0.10, an analysis of covariance with baseline as the covariate was performed on the repeated measures obtained with values on days 30 and 60. For the blood indexes, a Student's t test or Wilcoxon's rank-sum test was used to analyze the differences between baseline (day 0) and day 60 values. A P value of 0.05 was considered significant.

RESULTS

Comparability at baseline

Baseline (day 0) characteristics of the subjects, including demographic data, are presented in **Table 2**. There were no significant differences between the 2 groups in age, sex, ethnicity, weight, height, midarm circumference, or skinfold thickness.

At baseline, nutrient intakes and the duration of previous parenteral nutrition were not significantly different between the 2 groups, nor were the mean durations of the equilibration and double-blind periods of treatment (**Table 3**). During the double-blind period, the average daily amount (per kg/d) of lipids and energy provided to the patients was 1.92 g (range: 1.41–2.95 g) and 72.1 ± 6.5 kJ, respectively, in the olive oil group and 1.69 g (range: 0.93–2.28 g) and 63.7 ± 5.6 kJ, respectively, in the soybean-oil group. The cumulative dose of lipids (daily lipid intake × duration of treatment) was not significantly different between the 2 groups: 106.9 ± 9.8 g/kg (range: 77–168 g/kg) in the olive oil group and 92.9 ± 10.5 g/kg (range: 49–151 g/kg) in the soybean-oil group. During the double-blind period, intravenous intakes of lipids, nitrogen, carbohydrates, nonprotein energy, total energy, and vitamins were not significantly different between the 2 groups.

At baseline, there were no significant differences in lipid profiles (total cholesterol, HDL cholesterol, phospholipids, triacylglycerol, and apolipoproteins A-I and B) between the 2 groups (**Table 4**). At baseline, the fatty acid profiles of the plasma phospholipid fractions (**Table 5**) were not significantly different between the 2 groups, except for 18:3n−3, which was significantly lower in the soybean-oil group (P = 0.030). There were no significant differences in RBC phospholipid fractions between the 2 groups, except for 20:5n−3 and Σn−3 > C_{18}, which were significantly lower in the soybean-oil group (**Table 6**). Blood counts, biliary acid concentrations, α-tocopherol concentrations, and results of liver function tests were not significantly different between the 2 groups (**Table 7**).

Double-blind period

Analysis of safety and efficacy

Adverse events (eg, catheter-related sepsis) occurred between days 30 and 60 in 1 patient in the olive oil group and in 2 patients in the soybean-oil group, but were resolved completely. There were no significant differences between groups in clinical indexes (weight, height, midarm circumference, and triceps skinfold thickness) or in measures of biological safety, including blood urea nitrogen, glucose, creatinine, plasma electrolytes, and total and conjugated bilirubin. Measures of liver function (serum aspartate transaminase, serum alanine transaminase, alkaline phosphatase, and γ-glutamyl transferase), prothrombin time (data not shown), hemogram, and concentrations of biliary acids, α-tocopherol, and albumin were not significantly different between the 2 groups (Table 7).

Lipid profile

A significant treatment effect was observed for total cholesterol, which was lower in the olive oil group than in the soybean-oil

TABLE 3
Comparison of energy and nutrient intakes[1]

	Olive oil (n = 9)	Soybean oil (n = 9)
Duration of parenteral nutrition (mo)	34 ± 14	34 ± 12
Duration of equilibration period (d)	34 ± 1.7	41 ± 5.2
Duration of double-blind period (d)	56 ± 1.1	55 ± 2.8
Lipid intakes ($g \cdot kg^{-1} \cdot d^{-1}$)	1.92 ± 0.17	1.69 ± 0.15
Nitrogen intake ($g \cdot kg^{-1} \cdot d^{-1}$)	0.32 ± 0.03	0.27 ± 0.02
Carbohydrates intake ($g \cdot kg^{-1} \cdot d^{-1}$)	13.2 ± 0.7	12.6 ± 0.9
Nonprotein parenteral energy intake ($kJ \cdot kg^{-1} \cdot d^{-1}$)	292 ± 16	275 ± 19
Total parenteral energy intake ($kJ \cdot kg^{-1} \cdot d^{-1}$)	326 ± 19	304 ± 21
Oral energy intake ($kJ \cdot kg^{-1} \cdot d^{-1}$)	37 ± 17	56 ± 21

[1] $\bar{x}$ ± SEM. There were no significant differences between groups.

TABLE 4
Effect of treatment on plasma lipid concentrations[1]

	Olive oil			Soybean oil			*P*[2]		
	Day 0	Day 30	Day 60	Day 0	Day 30	Day 60	Treatment	Time	Treatment × time
Total cholesterol (mmol/L)[3]	3.96 ± 0.43	3.89 ± 0.32	3.67 ± 0.48	3.40 ± 0.22	3.54 ± 0.20	3.91 ± 0.31	0.0465	NS	NS
HDL cholesterol (mmol/L)[4]	0.82 ± 0.13	0.82 ± 0.16	0.73 ± 0.11	0.88 ± 0.14	0.96 ± 0.17	0.74 ± 0.18	NS	0.018	NS
LDL cholesterol (mmol/L)[5]	2.62 ± 0.46	2.47 ± 0.32	2.39 ± 0.51	1.73 ± 0.25	1.99 ± 0.29	2.60 ± 0.53	0.0537[6]	NS[6]	0.0185[6]
Phospholipids (mmol/L)[7]	2.36 ± 0.20	2.42 ± 0.16	2.45 ± 0.24	2.27 ± 0.09	2.44 ± 0.12	2.58 ± 0.15	NS	NS	NS
Triacylglycerol (mmol/L)[8]	1.09 ± 0.15	1.18 ± 0.20	1.12 ± 0.26	1.06 ± 0.08	1.01 ± 0.10	1.18 ± 0.18	NS	NS	NS
Apolipoprotein A-I (g/L)	0.75 ± 0.05	0.75 ± 0.08	0.71 ± 0.05	0.76 ± 0.07	0.79 ± 0.08	0.76 ± 0.07	NS	NS	NS
Apolipoprotein B (g/L)	0.82 ± 0.10	0.80 ± 0.07	0.78 ± 0.13	0.72 ± 0.06	0.67 ± 0.06	0.76 ± 0.06	NS	NS	NS

[1] $\bar{x}$ ± SEM; n = 9.
[2] Two-way repeated-measures ANOVA.
[3] Olive oil group: n = 8; soybean-oil group: n = 8.
[4] Olive oil group: n = 7; soybean-oil group: n = 5.
[5] Olive oil group: n = 6; soybean-oil group: n = 5.
[6] ANCOVA with day 0 as covariate.
[7] Olive oil group: n = 7; soybean-oil group: n = 7.
[8] Olive oil group: n = 9; soybean-oil group: n = 8.

group (Table 4). Analysis of covariance showed that there was a significant time-by-treatment effect for LDL cholesterol.

Fatty acids in plasma phospholipids

There were significant differences between groups (Table 5). Oleic acid (18:1n−9) and the ratio of Σn−6 > C_{18} + 18:3n−6 to 18:2n−6 were significantly higher and 18:2n−6 and eicosapentaenoic acid (20:5n−3) were significantly lower in the olive oil group than in the soybean-oil group.

Fatty acids in red blood cell phospholipids

In RBCs, there were significant effects of treatment. The ratio of Σn−6 > C_{18} + 18:3n−6 to 18:2n−6 and 18:1n−9 were significantly higher and 18:2n−6 was significantly lower in the olive oil group than in the soybean-oil group (Table 6).

Peroxidation index

There were significant main effects of treatment on some peroxidation indexes. More LV-TBARS formed in the soybean-oil group than in the olive oil group and the ratios of LDL-TBARS to LDL (cholesterol + phospholipids + triacylglycerol) and of LV-TBARS to LV (cholesterol + phospholipids + triacylglycerol) were higher in the soybean-oil group (**Table 8**). The same trend was observed with LDL-TBARS, although the trend was not significant.

DISCUSSION

The objective of this double-blind randomized study was to evaluate, for the first time in a long-term study of children aged <10 y, the tolerability and the biological effects of a new ILE prepared from a mixture of soybean oil and olive oil (ClinOleic). This ILE is low in PUFAs, especially 18:2n−6, but high in MUFAs, especially 18:1n−9. The only previous similar clinical studies were short term and involved the administration of an ILE enriched with olive oil (CT 6/3; Clintec-Nutrition-Cernep, Velizy, France) and no equilibration period (17, 31–34). Because our patients required long-term parenteral nutrition, a placebo treatment was not ethically acceptable. Thus, we decided to compare the olive oil–based ILE with a soybean-oil–based ILE now used (33, 34).

The 30-d equilibration period was intended to standardize energy and protein intakes before starting the comparative period. For the equilibration period, we selected an "older" product (with a different PUFA content) consisting of a 50-50 mixture of MCTs and LCTs (Medialipide). This ILE has been used in newborns (35, 36) and has been shown to have long-term tolerability in children (37). After a 1-mo period of initial screening, there was no significant difference between the 2 randomized groups receiving either the olive oil-based emulsion or the reference soybean-oil–based emulsion, in terms of age, indication, and duration of prior parenteral nutrition intakes. In addition, there was no significant difference with respect to the biological indexes assessed in this study. Under these conditions, the substitution of the MCT and LCT emulsion administered during the equilibration period controlled for the effects of the parenteral nutrition itself. Long-term (averaging 2.5 y) parenteral nutrition is actually associated with moderate abnormalities in liver function tests, which were observed at baseline in the study population.

During the prolonged administration of the olive oil–based and the reference soybean-oil–based ILEs, no clinical symptoms warranted the discontinuation of therapy. The minor side effects observed could not be attributed to the olive oil–based ILE because these side effects occurred during the equilibration period as well as during the administration of both ILEs. There was no significant difference between the 2 ILEs with respect to weight gain, fluid and electrolyte balances, and hematologic indexes, as confirmed in previous short-term studies in adults and children (17, 31–34). The clinical tolerability of this new olive oil–based ILE was similar to that of the reference soybean-oil–based ILE, which has been used widely in children, term infants, and premature infants for many years (2–5). Results of liver function tests and serum bile acid concentrations did not differ significantly between the 2 groups. These findings contrast with those of other studies, which showed a significant decrease in biliary flow during the administration of ILEs with a high PUFA content (38, 39). However, our results agree with those observed in adult patients who received either a soybean-oil– or olive oil–based ILE, between whom there was no significant difference (40).

Plasma lipid profiles in the 2 groups were not significantly different, except for total and LDL-cholesterol concentrations.

TABLE 5
Effect of treatment on the composition of plasma phospholipid fatty acids[1]

	Olive oil (n = 9)			Soybean oil (n = 8)			P^2		
Fatty acid	Day 0	Day 30	Day 60	Day 0	Day 30	Day 60	Treatment	Time	Treatment × time
16:0 (%)	33.87 ± 1.49	35.06 ± 1.37	35.69 ± 1.17	35.34 ± 0.85	33.95 ± 1.38	34.45 ± 0.81	NS	NS	NS
18:0 (%)	16.99 ± 0.61	15.21 ± 0.68	14.69 ± 0.39	16.84 ± 0.55	15.99 ± 0.88	16.63 ± 0.54	NS	NS	NS
18:1n−9 (%)	10.69 ± 0.67	14.26 ± 0.57	14.49 ± 0.49	9.21 ± 0.46	10.58 ± 0.77	9.88 ± 0.33	0.0002[3]	NS[3]	0.0685[3]
18:2n−6 (%)	16.64 ± 0.42	14.73 ± 0.71	13.94 ± 0.69	17.61 ± 1.06	20.54 ± 0.91	20.17 ± 1.45	0.0001	NS	NS
18:3n−3 (%)	0.26 ± 0.04	0.18 ± 0.01	0.16 ± 0.01	0.16 ± 0.02	0.30 ± 0.10	0.22 ± 0.02	0.0807[3]	NS[3]	NS[3]
20:5n−3 (%)	0.50 ± 0.02	0.42 ± 0.03	0.40 ± 0.03	0.44 ± 0.05	0.42 ± 0.05	0.42 ± 0.04	0.0249	NS	NS
22:5n−3 (%)	0.76 ± 0.06	0.54 ± 0.05	0.58 ± 0.04	0.65 ± 0.07	0.48 ± 0.05	0.50 ± 0.04	NS	NS	NS
22:6n−3 (%)	2.17 ± 0.22	2.02 ± 0.16	2.05 ± 0.16	1.78 ± 0.13	2.06 ± 0.16	1.91 ± 0.15	NS	NS	NS
20:3n−9 (%)	0.75 ± 0.26	0.45 ± 0.04	0.45 ± 0.03	0.45 ± 0.03	0.43 ± 0.05	0.48 ± 0.06	NS	NS	NS
20:4n−6 (%)	9.56 ± 0.65	9.32 ± 0.21	9.64 ± 0.68	9.91 ± 0.79	8.58 ± 0.65	8.27 ± 0.65	0.0949	NS	NS
Ratio of 20:3n−9 to 20:4n−6	0.088 ± 0.035	0.049 ± 0.004	0.048 ± 0.003	0.048 ± 0.005	0.054 ± 0.009	0.060 ± 0.006	NS	NS	NS
Σn−3 > C_{18} (%)	3.43 ± 0.30	2.98 ± 0.20	3.03 ± 0.19	2.86 ± 0.20	2.96 ± 0.19	2.82 ± 0.21	NS	NS	NS
Σn−6 > C_{18} + 18:3n−6	13.46 ± 0.83	12.91 ± 0.34	13.29 ± 0.73	13.89 ± 0.92	11.72 ± 0.73	11.80 ± 0.85	NS	NS	NS
Ratio of Σn−6 > C_{18} + 18:3n−6 to 18:2n−6	0.816 ± 0.058	0.890 ± 0.044	0.963 ± 0.053	0.825 ± 0.086	0.589 ± 0.059	0.640 ± 0.105	0.0001	NS	NS

[1] $\bar{x}$ ± SEM.
[2] Two-way repeated-measures ANOVA.
[3] ANCOVA with day 0 as covariate.

Normal plasma triacylglycerol concentrations reflect the good plasma clearance of ILEs. In the present study, triacylglycerol concentrations were normal during the administration of the olive oil–based ILE, in agreement with results of in vitro studies in which hydrolysis by endothelial lipoprotein lipase was not influenced by the fatty acid composition of an ILE with a high content of 18:1n−9 (41).

Exchanges of esterified cholesterol (LDL and HDL) between ILE and lipoproteins have been studied extensively (42–45). In this study, total and LDL-cholesterol concentrations were significantly different between the 2 groups; however, HDL-cholesterol and apolipoprotein A-I and B concentrations were not significantly different. This effect of the olive oil–based ILE needs to be confirmed in patients receiving long-term parenteral nutrition. Indeed,

TABLE 6
Effect of treatment on the compositon of red blood cell fatty acids[1]

	Olive oil (n = 9)			Soybean oil (n = 8)			P^2		
Fatty acid	Day 0	Day 30	Day 60	Day 0	Day 30	Day 60	Treatment	Time	Treatment × time
16:0 (%)	29.59 ± 1.98	32.77 ± 1.18	31.57 ± 1.54	33.32 ± 1.51	31.55 ± 0.77	30.13 ± 1.17	0.0970	NS	NS
18:0 (%)	19.50 ± 0.41	17.93 ± 0.64	17.40 ± 0.33	19.16 ± 0.64	17.78 ± 0.43	18.65 ± 0.51	NS	NS	NS
18:1n−9 (%)	13.98 ± 0.46	16.84 ± 0.38	17.53 ± 0.36	13.37 ± 0.19	13.71 ± 0.27	13.75 ± 0.30	0.0003	NS	NS
18:2n−6 (%)	11.03 ± 0.82	8.59 ± 0.50	7.98 ± 0.47	11.01 ± 0.68	12.63 ± 0.78	12.89 ± 0.80	0.0020	NS	NS
18:3n−3 (%)	0.23 ± 0.03	0.20 ± 0.04	0.19 ± 0.03	0.20 ± 0.04	0.25 ± 0.03	0.24 ± 0.03	NS	NS	NS
20:5n−3 (%)	0.41 ± 0.03	0.50 ± 0.23	0.27 ± 0.03	0.27 ± 0.05	0.37 ± 0.04	0.33 ± 0.04	NS[3]	NS[3]	NS[3]
22:5n−3 (%)	1.56 ± 0.17	1.22 ± 0.12	1.35 ± 0.12	1.18 ± 0.12	1.26 ± 0.07	1.32 ± 0.12	0.0996	NS	NS
22:6n−3 (%)	2.63 ± 0.27	2.09 ± 0.15	2.21 ± 0.21	1.98 ± 0.20	2.47 ± 0.28	2.38 ± 0.20	NS[3]	NS[3]	NS[3]
20:3n−9 (%)	0.43 ± 0.05	0.65 ± 0.18	0.34 ± 0.04	0.42 ± 0.05	0.65 ± 0.29	0.46 ± 0.07	NS	NS	NS
20:4n−6 (%)	12.92 ± 0.94	11.84 ± 0.53	12.82 ± 0.75	11.84 ± 0.88	11.92 ± 0.41	12.18 ± 0.97	NS	NS	NS
Ratio of 20:3n−9 to 20:4n−6	0.035 ± 0.005	0.056 ± 0.016	0.028 ± 0.004	0.035 ± 0.003	0.053 ± 0.023	0.038 ± 0.007	NS	NS	NS
Σn−3 > C_{18} (%)	4.59 ± 0.42	3.81 ± 0.31	3.83 ± 0.30	3.43 ± 0.34	4.09 ± 0.29	4.03 ± 0.33	NS[3]	NS[3]	NS[3]
Σn−6 > C_{18} + 18:3n−6	17.80 ± 1.31	15.90 ± 0.77	17.39 ± 1.03	15.97 ± 1.12	16.09 ± 0.33	16.48 ± 1.19	NS	NS	NS
Ratio of Σn−6 > C_{18} + 18:3n−6 to 18:2n−6	1.70 ± 0.19	1.91 ± 0.15	2.20 ± 0.09	1.47 ± 0.10	1.31 ± 0.10	1.33 ± 0.16	0.0117	0.0588	NS

[1] $\bar{x}$ ± SEM.
[2] Two-way repeated-measures ANOVA.
[3] ANCOVA with day 0 as covariate.

TABLE 7
Effect of treatment on routine biological blood indexes[1]

	Olive oil		Soybean oil		
	Day 0	Day 60	Day 0	Day 60	*P*
Alanine transaminase (U/L)	42.6 ± 8.0	57.4 ± 14.7	47.3 ± 15.5	72.9 ± 17.0	NS[2]
Aspartate transaminase (U/L)	40.9 ± 7.6	51.3 ± 13.5	57.7 ± 26.3	52.8 ± 10.8	NS[2]
Alkaline phosphatase (IU/L)	276 ± 55	295 ± 52	273 ± 29	262 ± 29	0.0915[3]
Total bilirubin (μmol/L)	10.9 ± 3.6	12.7 ± 3.4	9.1 ± 3.0	11.9 ± 4.2	NS[3]
γ-Glutamyl transferase (IU/L)[4]	27.0 ± 6.4	26.6 ± 6.2	27.4 ± 4.7	29.4 ± 4.1	NS[3]
Hemoglobin (g/L)[4]	118 ± 2.7	110 ± 2.9	114 ± 3.6	108 ± 3.6	NS[3]
Hematocrit[5]	0.354 ± 0.007	0.325 ± 0.007	0.351 ± 0.013	0.330 ± 0.013	NS[3]
RBC ($\times 10^{12}$/L)[5]	4.44 ± 0.11	4.10 ± 0.15	4.80 ± 0.14	4.60 ± 0.15	NS[2]
WBC ($\times 10^{9}$/L)[5]	7.95 ± 1.38	6.63 ± 1.00	10.25 ± 1.25	11.78 ± 1.84	0.0540[3]
Platelets ($\times 10^{9}$/L)[4]	262 ± 31	268 ± 36	276 ± 43	266 ± 47	NS[2]
Biliary acids (μmol/L)	8.22 ± 2.47	15.33 ± 7.60	7.44 ± 1.45	7.67 ± 1.34	NS[2]
α-Tocopherol (mg/L)	8.42 ± 0.55	9.25 ± 0.62	8.57 ± 0.54	8.78 ± 0.99	NS[3]
Albumin (g/L)	41.0 ± 1.9	39.5 ± 1.6	39.4 ± 1.1	39.7 ± 1.1[6]	NS[3]

[1] $\bar{x}$ ± SEM; $n = 9$ unless otherwise indicated. RBC, red blood cells; WBC, white blood cells.
[2] Wilcoxon rank-sum test on the difference between days 60 and 0.
[3] Student's two-sample *t* test on the difference between days 60 and 0.
[4] Olive oil group: $n = 8$; soybean-oil group: $n = 7$.
[5] Olive oil group: $n = 8$; soybean-oil group: $n = 6$.
[6] Values missing for 2 patients at day 60, values at day 30 used.

it is now established that consumption of diets such as the Mediterranean diet, which have a high content of MUFAs (primarily from olive oil), leads to a decrease in plasma total and LDL-cholesterol concentrations and to either maintenance of or an increase in plasma HDL-cholesterol concentrations (46, 47). The antiatherogenic effect of MUFA-rich oils is now recognized (48–55). Moreover, a diet low in PUFAs reduces peroxidation effects, whose role in atherogenesis is critical.

Despite the low content of PUFAs in the new olive oil–based emulsion compared with the reference emulsion used in the present study, its prolonged administration did not significantly alter the plasma fatty acid profile, especially that of tetraene, which otherwise would have suggested a deficiency of EFAs. In a previous study, children who received an olive oil–based emulsion short term showed either no EFA deficiency or the resolution of an EFA deficiency (17). In the present study, the increase in plasma and RBC 18:1n−9 concentrations and the decrease in 18:2n−6 concentrations in children who received the olive oil–based emulsion reflected the high 18:1n−9 content of this emulsion. The soybean-oil–based ILE contained 54% 18:2n−6 and 8% l8:3n−3. The minimum intake of 18:3n−6 should be 1–2% of the total energy intake (11). Administration of 0.2–0.4 g lipids $\cdot$ kg^{-1} $\cdot$ d^{-1} from the soybean-oil–based ILE used in this study would be required for a child with a total energy intake of 418.4 kJ (100 kcal) $\cdot$ kg^{-1} $\cdot$ d^{-1} to meet this recommended intake. In this study, children received an average intake of 1.69 g lipids $\cdot$ kg^{-1} $\cdot$ d^{-1} intravenously from the soybean-oil–based emulsion; therefore, their EFA requirements were exceeded. Excessive intakes of 18:2n−6 can decrease the activity of Δ^6-desaturase, alter the metabolism of EFAs, and increase the effects of peroxidation (46–49).

TABLE 8
Effect of treatment on peroxidation indexes[1]

	Olive oil ($n = 9$)			Soybean oil ($n = 8$)			*P*[2]		
Fatty acid	Day 0	Day 30	Day 60	Day 0	Day 30	Day 60	Treatment	Time	Treatment × time
LDL-TBARS (μmol/L)	71.39 ± 10.33	54.78 ± 9.93	55.06 ± 9.21	48.66 ± 5.25	46.13 ± 4.90	63.03 ± 5.66	NS[3]	0.0633[3]	0.0917[3]
LV-TBARS (μmol/L)	99.88 ± 14.86	77.25 ± 12.49	83.69 ± 15.57	72.01 ± 7.01	78.72 ± 9.81	104.63 ± 12.65	0.0027	0.0752	NS
LDL-C:LDL-PL	2.90 ± 0.49	2.25 ± 0.18	2.74 ± 0.22	2.05 ± 0.16	2.65 ± 0.32	2.64 ± 0.40	0.0908	NS	NS
RBC-TBARS (mmol/L)	61.50 ± 8.46	44.34 ± 5.58	56.00 ± 6.02	52.50 ± 6.71	48.06 ± 4.88	55.03 ± 5.17	NS	0.0069	NS
RBC-C (mmol/L)	1.85 ± 0.18	1.96 ± 0.24	1.92 ± 0.16	2.05 ± 0.16	1.95 ± 0.18	1.92 ± 0.19	NS	NS	NS
RBC-PL (mmol/L)	1.10 ± 0.13	1.27 ± 0.13	1.29 ± 0.10	1.28 ± 0.13	1.13 ± 0.10	1.19 ± 0.12	0.0917	NS	NS
RBC-TBARS:RBC-C	33.70 ± 3.88	24.31 ± 2.97	29.39 ± 2.65	26.59 ± 3.31	24.78 ± 1.06	29.34 ± 1.77	NS	0.0363	NS
RBC-TBARS:RBC-PL	61.93 ± 13.28	36.14 ± 3.71	43.34 ± 3.50	42.66 ± 5.26	42.70 ± 2.30	46.86 ± 1.31	NS	0.0558	NS
LDL-TBARS:LDL (C + PL + TG)	24.45 ± 2.17	18.75 ± 1.44	22.80 ± 3.92	20.95 ± 2.37	22.39 ± 3.56	25.32 ± 2.72	0.0262	0.0879	NS
LV-TBARS:LV (C + PL + TG)	24.72 ± 2.33	18.81 ± 1.68	22.71 ± 4.16	22.16 ± 2.61	22.06 ± 2.29	28.40 ± 4.23	0.0146	0.0335	NS

[1] $\bar{x}$ ± SEM. TBARS, thiobarbituric acid–reactive substances; C, cholesterol; PL, phospholipids; RBC, red blood cells; LV, LDL + VLDL; TG, triacylglycerol.
[2] Two-way repeated-measures ANOVA.
[3] ANCOVA with day 0 as covariate.

It was shown in a 28-d animal study that the soybean-oil–based ILE used in the present study resulted in a greater accumulation of peroxidation products than did the olive oil–based ILE (56). In the present study, concentrations of peroxidation products formed in vitro (eg, LV-TBARS, LDL-TBARS:total LDL, and LV-TBARS:LV) were significantly higher in the soybean-oil group than in the olive oil group. The peroxidation process increases the hydrophilic characteristics of membrane phospholipids and modifies their structure and function in RBC membranes. However, in this long-term study, hemoglobin concentrations did not differ significantly between the 2 groups. The effects of peroxidation were also observed in the circulating lipoproteins, although these lipoproteins carry liposoluble vitamins, especially α-tocopherol, which has antioxidative properties. In this study, plasma α-tocopherol concentrations were significantly different between the 2 groups, although the olive oil–based ILE contained a greater amount than the soybean-oil–based ILE (57). When excessive peroxidation occurs, oxidized LDL is no longer recognized by the LDL receptor and can then be captured by macrophages. Macrophage activation syndromes have been reported during the long-term administration of ILEs prepared from soybean oil (58, 59).

An excessive intake of PUFAs can therefore be avoided by using an ILE with a high content of 18:1n−9. Moreover, use of such an ILE decreases the risk of peroxidation and free radical production, which are potentially toxic to the cell membrane structure, circulating lipoproteins, and the reticuloendothelial system. In patients dependent on long-term parenteral nutrition, olive oil–based ILEs might beneficially modify the lipid profile and reduce the risk of atherogenic disease.

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