Parenteral Nutrition of Preterm Infants with a Lipid Emulsion Containing 10% Fish Oil: Effect on Plasma Lipids and Long-Chain Polyunsaturated Fatty Acids

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Objective To compare plasma lipids in preterm infants given a new lipid emulsion containing 10% fish oil, 50% medium-chain triacylglycerols, and 40% soybean oil, compared with a standard preparation containing 50:50 medium-chain triacylglycerols: soybean oil.

Study design Preterm infants weighing <1250 g at birth (n = 47) were randomly assigned to receive parenteral nutrition with a fish oil lipid (n = 23) or soybean oil (n = 24). Plasma lipid classes and plasma and red blood cell fatty acids were determined by gas chromatography in cord blood and on postnatal days 7 and 14.

Results On day 7, the infants receiving fish oil lipid had significantly lower plasma phospholipids, cholesterol esters, and free cholesterol but similar triglyceride concentrations. They also had significantly higher phospholipid docosahexaenoic acid (2.77 ± 0.08 versus 2.46 ± 0.01 mol%, $P < .01$) and eicosapentaenoic acid (1.58 ± 0.01 versus 0.25 ± 0.01 mol%, $P < .01$) as well as lower arachidonic acid (10.64 ± 0.29 versus 11.93 ± 0.29 mol%, $P < .01$) compared with those receiving soybean oil. Similar differences were found in red blood cells.

Conclusions The fish oil lipid emulsion was well tolerated, and infants receiving fish oil had lower plasma lipids and improved fatty acids status. The effect of these changes on inflammation, growth, and neurodevelopment should be explored. *(J Pediatr 2011;159:33-8)*.

Docosahexaenoic acid (DHA) is the most abundant n-3 long-chain polyunsaturated fatty acid (LC-PUFA) in cell membranes, especially in the retina and central nervous system, and its accretion occurs primarily during the last trimester of pregnancy and in the early postnatal months.[1,2] Infants born prematurely are thus deprived of the intrauterine DHA supply. Furthermore, physiological DHA requirements for tissue accretion are highest in the perinatal period and are thought to be largely dependent on the dietary supply. In randomized clinical trials, DHA supplements favorably affect both visual and cognitive development in preterm infants fed formulas or human milk supplemented with LC-PUFA, especially in those infants who receive high-dose DHA.[3-5] DHA supplementation of preterm formula lipid blends has become standard practice. However, currently used fat emulsions for the parenteral nutrition of preterm infants do not provide n-3 LC-PUFA. Recently, fish oil containing lipid emulsions for adult and pediatric parenteral nutrition became available in Europe and in the United States and may have beneficial effects, especially in adult surgical patients.[6,7] Data in infants are limited. A lipid emulsion containing 10% fish oil was well tolerated and effective in ameliorating parenteral nutrition–associated liver disease in children with short bowel syndrome.[8,9] Information in preterm infants is even more limited. Tomsits et al[10] found that a 15% fish oil lipid emulsion was well tolerated and that g-glutamyl transferase plasma concentration were lower in relatively large preterm infants in comparison with the conventional lipid emulsion group. They also found in red blood cells increased eicosapentaenoic acid (EPA) and lower linoleic acid and linolenic acid levels.

We reasoned that the n-3 LC-PUFA of a fish oil lipid emulsion, given to extremely low birth weight preterm infants immediately after birth, would be a good source of DHA, which is thought to promote neurodevelopment and visual function, as well as of EPA, which could favorably modulate inflammation. This randomized pilot study was designed to compare the effects of a new preparation containing 10% fish oil versus a standard lipid emulsion on the plasma lipid classes and on fatty acid (FA) composition of plasma phospholipids, plasma triglycerides and of red blood cells (RBC) in the extremely small preterm infants

ARA	Arachidonic acid
DHA	Docosahaexaenoic acid
EPA	Eicosapentaenoic acid
FA	Fatty acid
LC-PUFA	Long-chain polyunsaturated fatty acid
MCT	Medium chain triglyceride
RBC	Red blood cell

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The authors declare no conflicts of interest.

 10.1016/j.jpeds.2010.12.052

receiving total parenteral nutrition as part of standard care from the first day of life.

Methods

In this single-center, pilot study, preterm infants were recruited from the NICU of "G. Salesi" Children's Hospital, Ancona, Italy, between September 2007 and May 2008.

Neonates with a birth weight of 500 to 1249 g, who routinely receive parenteral nutrition from the first hour of life, were consecutively enrolled. Informed consent was obtained prenatally or after birth, and random assignment was performed by sealed envelope system in the first minutes of life. Exclusion criteria were severe malformations, inborn errors of metabolism, and severe sepsis. Infants were randomly assigned to receive a new lipid emulsion consisting of a physical mixture of 10% fish oil, 50% medium-chain triacylglycerols (MCT), and 40% soybean oil or a standard product containing 50:50 MCT:soybean oil (**Table I**; available at www.jpeds.com). The emulsions contained similar amounts of phospholipids and other components but differed with a greater DHA and EPA content in the fish oil product (2.3% and 2.6%, respectively), compared with trace amounts in the standard emulsion.

The infants were started on total parenteral nutrition with glucose, amino acids, and lipids at about 1 hour after birth, according to NICU protocol. The lipid emulsions were infused at doses of 0.5, 1.0, 1.5, 2.0, and 2.5 $gkg^{-1}d^{-1}$ from postnatal day 0 to day 5, respectively. The higher dose was then infused until day 7, when parenteral nutrition tapering was begun, until day 18, when it was stopped. Minimal enteral feeding with human milk or LCP-containing formula was provided from day 0 to day 7, the maximum amount supplied being 8 $mL \cdot kg^{-1} \cdot d^{-1}$ from day 1 to day 4, and 16 $mL \cdot kg^{-1} \cdot d^{-1}$ from day 5 to day 8. Oral feeding was gradually increased from day 9 to reach full oral feeds by day 18.

Plasma and RBC FA composition was analyzed in 0.5 mL EDTA-blood collected at birth from the umbilical cord and on day 7 (total parenteral nutrition) and day 14 (partial parenteral nutrition).

The study was in accordance with the principles of the Helsinki Declaration and was reviewed and approved by the local ethics committee. Written informed consent was obtained from both parents.

Analytic Method

Plasma lipid classes and their FA composition were analyzed as described previously.[11] Briefly, lipids were extracted from plasma according to Folch et al[12] after addition of appropriate internal standards for each lipid class. Lipid classes were isolated by thin-layer chromatography; plasma phospholipids, and triglyceride FA were transesterified with HCl methanol. Separation and identification of the individual FA methyl esters was performed by capillary gas chromatography.[11] Data for plasma FA with chain lengths from C8 to C24 carbon atoms were calculated both as mole percent and as absolute plasma concentrations (mg/dL). RBCs were separated from plasma by three centrifugations with an isotonic EDTA solution (pH 7.35), resuspended in isotonic pyrogallol, and stored at –80°C until analysis. RBC fatty acids were extracted according to Folch et al,[11] with some modifications. The FA were methylated with HCl-methanol and measured by gas chromatography.

Safety Data and Growth

All patients had routine biochemistry and hematology determinations. Vital signs were recorded hourly, and adverse events were collected through the study. Daily weight and weekly head circumference and recumbent length were also recorded as part of routine care. Gains and individual SD scores were computed using Italian reference data with dedicated proprietary software (Neotools, Interactive.com srl, Milano, Italy).

Statistical Analysis

Data are expressed as group means ± SD for clinical variables and as group means ± SEM for all analytic variables, except for the EPA/arachidonic acid (ARA) ratio (mean ± SD). The clinical characteristics of the two groups were compared using the *t* test. Data were analyzed by two-way, repeated-measures ANOVA, Mann-Whitney, and Wilcoxon tests. Significance was set at .05.

All statistical analyses were performed using SPSS (v 15.0; SPSS Inc, Chicago, Illinois) and Microsoft Excel (v 2000; Microsoft Corp, Redmond, Washington) softwares.

Results

Overall, 48 preterm infants were recruited and randomly assigned to the fish oil containing lipid emulsion (n = 24) or

Table III. Mean nutrient and daily energy parenteral nutrition intakes (mean ± SD) from day 0 to day 7

Characteristics	Study group (n = 23)	Control group (n = 24)	*P*
Parenteral nonprotein energy supply	50.6 ± 6.5	46.7 ± 8.0	.10
IV Carbohydrates ($g \cdot kg^{-1} \cdot d^{-1}$)	9.0 ± 1.1	8.3 ± 1.4	.04
IV Protein ($g \cdot kg^{-1} \cdot d^{-1}$)	2.8 ± 0.5	2.4 ± 0.7	.31
IV Fat ($g \cdot kg^{-1} \cdot d^{-1}$)	1.8 ± 0.2	1.7 ± 0.4	.21
IV ARA ($mg \cdot kg^{-1} \cdot d^{-1}$)	11.7 ± 1.7	8.4 ± 1.1	.00
IV DHA ($mg \cdot kg^{-1} \cdot d^{-1}$)	41.7 ± 5.9	2.9 ± 0.6	.00
IV EPA ($mg \cdot kg^{-1} \cdot d^{-1}$)	44.2 ± 5.9	Traces	.00
Enteral nonprotein energy (%)	13.1%	13.3%	.81

n = 47.