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Comparison of 5 intravenous lipid emulsions and their effects on hepatic steatosis in a murine model ☆

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Abstract

Background: Plant-based intravenous lipid emulsions have been shown to contribute to parenteral nutrition–associated liver disease (PNALD). There is mounting evidence that fish oil–based emulsions may prevent this liver injury. This study compares 5 emulsions with different fat compositions and their effect on hepatic steatosis, one of the first hits in PNALD.

Methods: C57BL/6J mice were placed on a fat-free diet and randomized into 5 equal groups. Each group received one of the commercially available intravenous lipid emulsions (Intralipid [Baxter/Fresenius Kabi, Deerfield, Ill], Liposyn II [Hospira Inc, Lake Forest, Ill], ClinOleic [Baxter/Clintec Parenteral SA, Cedex, France], SMOFlipid [Fresenius Kabi, Bad Homburg, Germany], or Omegaven [Fresenius Kabi Deutschland GmbH]) or normal saline. Liver enzymes, degree of steatosis, and fatty acid compositions were analyzed after 19 days.

Results: Intralipid, Liposyn II, ClinOleic, and SMOFlipid groups all demonstrated moderate steatosis with hepatic fat contents of 17.4%, 21.9%, 22.5%, and 12.6%, respectively. Omegaven mice, however, had normal livers. Saline control mice developed biochemical evidence of essential fatty acid deficiency (EFAD). Lipid supplementation with Intralipid, Liposyn II, and Omegaven prevented the onset of biochemical EFAD, whereas administration of ClinOleic and SMOFlipid did not.

Conclusion: The fish oil–based lipid emulsion Omegaven prevented hepatic steatosis and EFAD in this murine model. ω-3 fatty acids may be efficacious in preventing PNALD and should be explored in the development of novel lipid emulsions.

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Since its introduction in the mid-1960s [1], parenteral nutrition (PN) has been a life-saving measure for patients with intestinal failure. Although it has dramatically changed the standard of nutritional care throughout the world, its use is associated with multiple complications such as central line infections and electrolyte abnormalities [2]. The most devastating complication of long-term PN use is PN-associated liver disease (PNALD), which may occur in up to 60% of infants who receive a prolonged course of PN [3]. PNALD is characterized by varying degrees of hepatic steatosis, steatohepatitis, hepatocellular injury, and cholestasis, which may progress to cirrhosis and ultimately liver failure.

Intravenous lipids are a vital component of PN and provide a source of nonprotein, noncarbohydrate calories; maintain integral components of cell membranes; and prevent the development of essential fatty acid deficiency (EFAD) [4]. Lipid emulsions provide what has been traditionally considered the 2 essential fatty acids, linoleic acid (LA) and α-linolenic acid (ALA). These fatty acids are important precursors of eicosanoids and prostaglandins, and are imperative in many biochemical pathways [5].

Currently, Intralipid (100% soybean oil) (Baxter/Fresenius Kabi, Deerfield, Ill) and Liposyn II (50% soybean oil, 50% safflower oil) (Hospira Inc, Lake Forest, Ill) are the only 2 lipid emulsions approved by the Food and Drug Administration in the United States. Both products are composed of high amounts of the ω-6 polyunsaturated fatty acids (PUFAs) LA and a limited amount of the ω-3 fatty acid ALA (Table 1).

Worldwide, there are several alternative lipid emulsions such as ClinOleic (Baxter/Clintec Parenteral SA, Cedex, France), a lipid emulsion composed of 80% olive oil and 20% soybean oil. Compared to Intralipid and Liposyn II, it is abundant in monounsaturated fatty acids (MUFAs) mostly in the form of oleic acid found in olive oil, lower amounts of PUFA, and only long-chain triglycerides [6].

Another alternative lipid emulsion approved for use in Europe is SMOFlipid (Fresenius Kabi, Bad Homburg, Germany), which is composed of 30% soybean oil, 30% medium-chain triglycerides, 25% olive oil, and 15% fish oil [7]. The inclusion of olive oil increases the amount of MUFAs, whereas the addition of fish oil, more specifically, docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA), increases the amount of ω-3 fatty acids.

The only available lipid emulsion composed of 100% fish oil is Omegaven (Fresenius Kabi Deutschland GmbH, Bad Homburg, Germany). Omegaven has a very low concentration of LA, but does contain a moderate amount of its downstream product, arachidonic acid (AA) (Table 1). Although it is not recommended to be used as monotherapy by the manufacturer, Omegaven has been used at the authors' institution in both infants and children with promising results [8,9].

Although the etiology of PNALD is multifactorial, the development of hepatic steatosis is thought to be the first step, and recent findings suggest that the composition of the intravenous lipid emulsion administered with PN may contribute to this liver injury [10,11]. There is mounting evidence in both animal models [12] and clinical trials [8,9,13] that fish oil–derived ω-3 fatty acid supplementation may prevent and/or alleviate the liver injury. This study aims to elucidate the effects of 5 different lipid emulsions on the development of steatosis and EFAD.

Table 1 Comparison and characteristics of 5 parenteral lipid emulsions (10 g fat/100 mL)

Product	Intralipid	Liposyn II	ClinOleic	SMOF lipid	Omegaven
Manufacturer	Baxter Healthcare/ Fresenius Kabi	Hospira	Baxter Healthcare/ Parenteral SA	Fresenius Kabi	Fresenius Kabi
Oil source (g)					
Soy bean	10	5	2	3	0
Safflower	0	5	0	0	0
MCT	0	0	0	3	0
Olive oil	0	0	8	2.5	0
Fish oil	0	0	0	1.5	10
α-Tocopherol (mg/L)	38	NP	32	200	150-296
Phytosterols (mg/L)	348 ± 33	383	327 ± 8	47.6	0
Fat composition (g) [a]					
Linoleic	5.0	6.5	0.9	2.9	0.1- 0.7
α-Linolenic	0.9	0.4	0.1	0.3	< 0.2
EPA	0	0	0	0.3	1.28 – 2.82
DHA	0	0	0	0.05	1.44 – 3.09
Oleic	2.6	1.8	.8	2.8	0.6 - 1.3
Palmitic	1.0	0.9	0.7	0.9	0.25 – 1
Stearic	0.35	0.34	0.2	0.3	0.05 – 0.2
Arachidonic	0	0	0.03	0.05	0.1 – 0.4

[a] All data have been provided by the manufacturer. MCT indicates medium-chain triglycerides; NP, not provided.