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# Parenteral Nutrition – Lipid Emulsions and Potential Complications



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**Intravenous lipid emulsions (ILE) have become a crucial component of parenteral nutrition providing a source of essential fatty acids as well as non-protein calories. However, their use, especially in the long-term setting has been associated with significant complications such as intestinal failure associated liver disease and dyslipidemia. This has led to the quest to identify a lipid emulsion that not only decreases the prevalence of these complications, but can also provide beneficial physiologic effects. Multiple plant and fish based sources of ILE have been identified and are in use throughout the world. The present review focuses on the benefits and adverse effects associated with soybean oil (SO) ILE in addition to discussion of subsequent generations of ILE.**

## INTRODUCTION

Intravenous lipid emulsions (ILE) are a key component of parenteral nutrition (PN), providing a source of essential fatty acids (EFA) as well as non-protein calories. Development of a stable ILE took decades of work by leaders in the field before the introduction of the first stable ILE (Lipomul<sup>®</sup>; 15% cotton seed, 4% soy phospholipids, 0.3% ploxamer).<sup>1,2</sup> Unfortunately, due to adverse effects felt to be from the emulsifying agent, as well as a non-extractable toxic substance in cottonseed oil, Lipomul<sup>®</sup> was removed from the market.<sup>3</sup> Subsequently, work by Wretling and Schubert led to the introduction of a soybean oil (SO)

based ILE as a 10% SO solution.<sup>4</sup> Since that initial introduction, significant modifications have taken place in subsequent generations of ILE, largely in an effort to reduce omega-6 fatty acid (FA) concentrations.

### Soybean Oil Based ILE (Generation 1)

SO ILE are composed of SO triglycerides enveloped by a phospholipid emulsifier allowing the triglyceride core to remain soluble in an aqueous PN mixture, similar to a chylomicron-like particle.<sup>2</sup> The emulsifiers are typically provided in excess amounts to ensure that particles maintain a size of 200-600 nanometers (nm), thus allowing them to pass through the smallest capillaries.<sup>5</sup> Due to this, a typical composition of first generation ILE is 10-30% SO, 1.2% egg yolk phospholipids, and 2.25% glycerin with calorie content ranging from 10-11 kcal/g depending on concentration.<sup>2,6</sup> Therefore ILE provide an excellent source of calories allowing for a reduction in the amount of dextrose used in PN. This

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distribution of calories is important because, after the technique of “hyperalimentation” in the US with a solution of glucose, fibrin hydrolysate, vitamins, and minerals was introduced by Drs. Wilmore and Dudrick, reports began linking the high dextrose, fat-free PN to hyperosmolar, hyperglycemic, non-ketotic diabetic coma, hypoglycemia, hepatic enzyme elevations, fatty liver, and essential fatty acid deficiency (EFAD).<sup>6-8</sup> Meguid et al. subsequently performed a pivotal study showing that providing one-third of daily calories as SO ILE (10% Liposyn<sup>®</sup>) was associated with lower metabolic complications in 23 men, leading to a gradual change in the U.S. to include ILE in PN.<sup>8</sup>

In addition to serving as a calorie source, SO ILE also contain robust amounts of essential fatty acids, linoleic acid (18:2n-6) and  $\alpha$ -linolenic acid (18:3n-3), all of which play a key role in structural stability of membranes, as well as in generation of cellular signaling molecules.<sup>9</sup> Humans lack the ability to synthesize these fatty acids and must obtain them from plant sources such as seed oils.<sup>10</sup> Minimal PN requirements of linoleic acid to prevent EFAD have been estimated to be at least 1% of total calories, with optimal levels being 3-4%, whereas  $\alpha$ -linolenic acid requirements are even less at 0.2-0.5% of total calories.<sup>9,11</sup> Given that Intralipid<sup>®</sup> contains 20% SO, with 52% of the fat as linoleic acid, only 2.9-8.7g/day of lipid or 29-87 mL of Intralipid<sup>®</sup> would be required to meet the essential fatty acid needs of a 60 kg individual receiving 25 kcal/kg/day.<sup>9</sup>

Despite these benefits, the high ratio of n-6 to n-3 polyunsaturated fatty acids (PUFA) in SO ILE can have adverse effects. These 18-carbon fatty acids are used to make 20- and 22-carbon derivatives including arachidonic acid (AA, 20:4n-6) and eicosapentaenoic (EPA, 20:5n-3) and docosahexaenoic (DHA, 22:6n-3).<sup>2,11</sup> AA can be further metabolized to give rise to pro-inflammatory eicosanoids (2-series prostaglandins and thromboxanes, and 4-series leukotrienes).<sup>6,10,12,13</sup> On the other hand, EPA, which originates from n-3 PUFAs, tends to generate less pro-inflammatory 3-series prostaglandins and thromboxanes, as well as the 5-series leukotrienes. In addition to these pro-inflammatory metabolites, SO ILE have also been noted to lead to reduced clearance of the reticuloendothelial system (RES), a key player in the phagocytosis of microorganisms, tissue debris, and particulate matter.<sup>14</sup> With provision of SO ILE at a rate of 0.13 g/kg/hr over 10 hrs daily for 3 days, RES clearance fell by an average of 40%.<sup>14</sup> In a 60kg individual, this would amount to

39 mL/hr of 20% lipid emulsion, which typically has 50g per 250 ml.

SO ILE can also lead to increased LDL and triglyceride levels as well as a decrease in HDL levels. This is due to the liposomes created from excess phospholipid emulsifier acquiring cholesterol and apolipoproteins from HDL in exchange for phospholipids.<sup>15,16</sup> The capacity of HDL to handle this phospholipid influx is saturable, and if infusion rates exceed this capacity, liposomes begin to accumulate in plasma where they can continue to be enriched in cholesterol and begin to show characteristics of lipoprotein-X (Lp-X).<sup>17</sup> It is important to note that 20% ILE tend to have lower phospholipid to triglyceride ratios compared to 10% ILE, resulting in faster phospholipid clearance. Twenty percent ILE are predominantly used in clinical practice.<sup>18</sup>

Another common complication of PN is intestinal failure associated liver disease (IFALD) affecting 30-60% of children and 15-40% of adults requiring long-term SO ILE.<sup>2</sup> IFALD tends to vary in clinical presentation and can include hepatic steatosis, cholestasis, cholelithiasis, and hepatic fibrosis.<sup>19</sup> Although, the etiology of IFALD seems multifactorial, some studies have revealed a correlation between parenteral lipid intake of  $\geq 1$  g/kg/day with higher phytosterol levels.<sup>20</sup> Additionally, elevated levels of phytosterols from SO ILE may be another contributing factor as higher phytosterol levels correlate with severity of IFALD.<sup>21</sup> Typically, only a small percentage (5-10%) of dietary phytosterols are absorbed and play a beneficial role by inhibiting enteral absorption of cholesterol. Unfortunately, with parenteral administration, increased levels of phytosterols enter the circulation leading to higher concentrations as they cannot be converted to bile acids.<sup>22</sup>

### Soybean Oil and Medium Chain Triglycerides (SO:MCT 50:50) (Generation 2)

The search for improved sources of ILE following widespread use of SO lipids first led to the use of medium chain triglycerides (MCT). Similar to other triglycerides, MCTs have a glycerol backbone with fatty acids attached, typically composed of between 6 (capric) and 12 (lauric) carbon atoms compared to the 13-21 carbon chains of long chain triglycerides (LCTs).<sup>23</sup> In addition to being hydrolyzed faster by pancreatic lipases, MCTs are not incorporated into chylomicrons, and are thus rapidly delivered directly to the liver via portal circulation.<sup>23</sup> In contrast to LCTs,

**Table 1. Currently Approved ILE in the United States**

Product	Lipid Source	n-6:n-3 ratio	Phytosterols mcg/mL	A-tocopherol level (mg/L)	Linoleic (% weight)	a-Linolenic (% weight)
Intralipid® (Baxter)	100% Soybean oil	7:1	343 ± 6	38	44-62	4-11
Clinolipid® (Baxter)	20% soybean oil 80% Olive Oil	NA	NA	NA	13.8-22	0.5-4.2
Smoflipid® (Fresenius Kabi)	30% soybean oil 30% MCT 25% olive oil 15% fish oil	2.5:1	179 ± 10	200	21.4	2.5

NA- not available

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once delivered to the cell, MCTs are able to passively cross the mitochondrial membrane due to their water-soluble properties and proceed directly for oxidation.

Based largely on these theoretical advantages of MCTs demonstrated primarily in animal models, ILE formulations have included combination MCT/LCT for the past 30 years in Europe. A number of small short-term studies have shown MCT ILE to be beneficial compared to SO ILE in terms of liver function tests, phospholipid to triglyceride ratio, and recovery of RES, although some studies reveal minimal benefit.<sup>24-27</sup> Additionally, a larger prospective RCT showed that MCT/LCT use resulted in phospholipid profiles similar to healthy controls at the end of 4 weeks compared to 100% LCT.<sup>28</sup> Due to the limited data on MCT (in any PN formulations - MCT/ LCT or pure MCT), there is a need for longer-term studies to evaluate the safety and efficacy of these ILE formulations.

**Olive Oil (OO) Containing ILE (Generation 3)**

In the third generation of ILEs, OO was introduced as an alternative lipid source. OO was seen as a potential substitute for SO because it contains higher amounts of monounsaturated fatty acids (MUFA) and less n-6 PUFAs.<sup>29</sup> During the 1990s, ClinOleic®20% became available and was comprised of 80% OO and 20% SO.<sup>30</sup> Since 18.5% of the fat is linoleic acid, 81-240ml per day would be needed to meet daily EFA needs. Concerns were raised that patients may not get these doses and may develop EFAD.<sup>31</sup> Despite data showing a significant reduction in α-linolenic acid and higher Mead acid levels, there was no clinical evidence of EFAD and triene:tetraene ratios remained normal.<sup>31</sup> Studies comparing OO/SO ILE to SO ILE have noted

less deterioration of liver enzymes, better phospholipid profile, and improvement in some clinical variables such as ventilator days.<sup>32-34</sup>

**Fish-Oil (FO) Containing ILE (Generation 4)**

The latest generation of ILE have reduced the SO content by either completely switching to fish oil (FO) alone (Omegaven®; Fresenius Kabi) or using FO in combination with other sources of triglycerides (Smoflipid®; 30% SO, 30% MCT, 25% OO, and 15% FO or Lipoplus; 50% MCT, 40% SO, and 10% FO). FO is an ideal choice for use in ILE given its high content of n-3 PUFA, α-tocopherol, and minimal amounts of plant phytosterols.<sup>35</sup> Omegaven® is currently the only ILE composed entirely of FO, but is not approved for routine use or commercially available in the U.S., and instead is available under study protocols or under a compassionate-use allowance through the FDA for treatment of IFALD.<sup>35</sup> Smoflipid®, on the other hand has recently been approved by the FDA and is now commercially available in the U.S.

Numerous studies have shown significant improvement or reversal of IFALD with the use of FO ILE in the pediatric and adult population.<sup>36,37</sup> Heller et al. studied the impact of combining FO (0.2 g/kg/day Omegaven®) with SO (0.8g/kg/day of 10% Lipovenoes®) versus SO alone (10% Lipovenoes®) in 44 post abdominal surgery patients and noted that the combination of FO with SO resulted in significant decrease in liver enzymes and bilirubin levels.<sup>38</sup> Klek et al. conducted a 4 week-long trial randomizing 73 patients with stable intestinal failure to either Smoflipid® or SO ILE (Intralipid®) and noted that mean ALT, AST,

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and total bilirubin concentrations were significantly lower in the Smoflipid® group.<sup>42</sup>

All 3 FO ILE tend to have higher levels of  $\alpha$ -tocopherol (~200mg/L) raising plasma concentrations compared to SO ILE.<sup>42,43</sup> A-tocopherol is an antioxidant from the Vitamin E family that is capable of scavenging free radicals that form from peroxidation of lipids, especially PUFAs and can result in cell damage.<sup>44</sup> In addition to raising  $\alpha$ -tocopherol concentrations, patients receiving FO ILEs also tend to have lower n-6 PUFA and higher n-3 PUFA concentrations, producing a less pro-inflammatory profile.<sup>43</sup> Metry et al. noted a significantly lower IL-6 level in surgical ICU patients randomized to Smoflipid® compared to Intralipid® on both day 4 and 7 of the trial.<sup>45</sup>

Beyond these liver and anti-inflammatory benefits, studies have also revealed metabolic benefit as patients randomized to Lipoplus® had a greater reduction in free-fatty acids, smaller rise in triglyceride levels, and less reduction in HDL after ~7 days of use compared to the Lipofundin® group.<sup>47</sup> Wu et al. also noted lower triglyceride levels on day 6 in patients randomized to Smoflipid® versus Lipovenoes®.<sup>48</sup>

Of note, most of these trials are very short term and further studies on the long-term impact of FO ILE needs to be evaluated. One area of concern is the development of EFAD given the lower ratio of n-6 PUFAs. Fortunately, clinical trials thus far have revealed that although triene:tetraene ratios do rise, they did not exceed threshold for EFAD if the dose of ILE is  $\geq 1$ g/kg/day.<sup>49,50</sup> Mead acid levels also remained low again confirming that the rise in Mead acid levels may be largely due to the composition of ILE. An important contributor to the lack of EFAD with fish oil ILE may be their higher content of AA, which is typically derived from linoleic acid.<sup>51</sup>

## CONCLUSION

In summary, significant advances have been made since the initial development and administration of ILE. We have progressed from searching for ILE that are non-toxic, to development of ILE that have beneficial properties other than being a source of non-protein, non-carbohydrate calories. Moving forward, additional research is necessary to expand our knowledge regarding the use of later generation of ILE in disease specific situations. The benefits with long-term use also need to be delineated, as much of current research has focused

on short-term trials in small cohorts. In order to continue to provide the best care possible to our patients, we need to continue work in this field to not only reduce the risk of harm, but also continue to find ILE that will improve outcomes. ■

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