Optimal composition of intravenous lipids

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Abstract

The provision of energy from a lipid source is an essential component of any parenteral nutrition (PN) therapeutic regimen in the appropriate clinical setting. All available sources of intravenous lipid emulsions have a low osmolarity but they strongly differ in their immunologic effects and their effects on oxidative stress, liver injury and mitochondrial function. The ω–9/ω–6 lipid emulsion with its relative immune-neutrality and also the newer fish oil admixtures are lipid emulsions that can be used in most critically ill and non-critically ill patients. Despite extensive research and encouraging progress in the availability of such lipid emulsions, there is still need for a lipid emulsions that could be advantageous in patients with real hyperinflammation.

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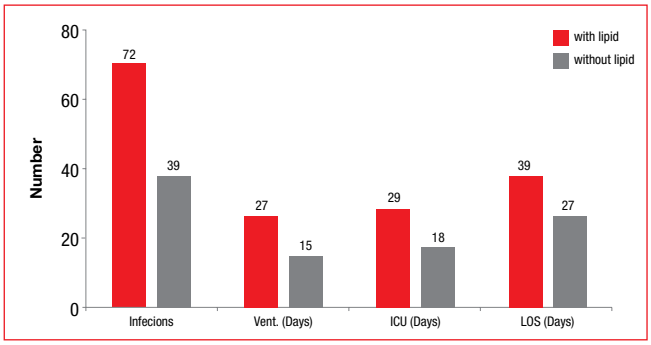
The composition of an intravenous (IV) lipid emulsion is of great importance in parenteral nutrition (PN) therapy, as most of its effects depend on the kind of fatty acids included and their respective ratio to each other. Today´s lipid emulsions may include four classes of different fatty acids (FA), namely ω–6 long chain polyunsaturated fatty acids, ω–3 long chain polyunsaturated fatty acids, ω–9 long chain monounsaturated fatty acids and medium chain saturated fatty acids. All these fatty acids present a source of energy with a low osmolarity but they strongly differ in their immunologic effects and their effects on oxidative stress, liver injury and mitochondrial function. For this review the effects of the different admixtures will be discussed following the time line of their landmark introduction into clinical practice.

The first lipid emulsion for parenteral application was a 100% soy bean oil-based emulsion introduced in 1961. There were two reasons for the development of this type of lipid emulsion. Firstly, soy bean oil contains the two essential ω–6 fatty acids, linoleic acid and linolenic acids, and secondly, soy bean oil was readily available. Very soon after its introduction into clinical practice its immunologic properties came into discussion[1] and with its widespread use concerns were raised regarding its immune-compromising effects and the increased risk of infections.[2,3] Today, there is consistent evidence from human and animal *in vitro* and *ex vivo* studies showing that ω–6 fatty acids or a soy bean oil-based emulsion inhibit lymphocyte proliferation,[4,5] decrease natural and lymphokine activated killer cell acitivity,[6,7] decrease chemotaxis and random migration of granulocytes[8–10] and negatively affect the reticuloendothelial system.[11,12]

Despite these impressive experimental results, some smaller trials in malnourished or paediatric patients[13–15] and one large clinical trial in bone marrow transplanted patients[16] found no significant difference between patients who received a parenteral ω–6 emulsion and those who did not. One smaller crossover study even reported an immunorestorative effect of the lipid emulsion.[17] In contrast, the study reported by Battistella[18] randomised 60 trauma patients with a severity score of 27 and an APACHE II score of 23 to 10 days of postoperative PN with our without an ω–6 emulsion. Patients who received the lipid emulsion had a longer length of hospitalisation (39 vs 27 days), a longer length of stay in the intensive care unit (29 vs 18 days) and more days of mechanical ventilation (27 vs 15) (Figure 1) The group which received the lipid emulsion also had a significantly reduced natural and lymphokine activated killer cell activity and a higher number of infections (72 vs 39). Although this trial is somewhat biased by the fact that the group which did not receive the lipid emulsion also received 25% less energy, these negative results made the Canadian, the European and also the American guideline committee recommend that – at least – intensive care patients should not receive pure ω–6 lipid emulsions as part of their PN regimens.

Figure 1: Battistella FD et al. Lipid emulsion in trauma victims (Figure was created using data from this publication)[18]



In order to reduce the amount of ω–6 fatty acids in a lipid emulsion, medium chain triglycerides were introduced into clinical practice in 1984. These fatty acids with a chain length of 8 resp. 10 carbon atoms are derived from coconut oil. *In vitro* and *ex vivo* studies could show that a 50/50 admixture of ω–6 FA and MCT (ω–6/MCT) could prevent the inhibition of lymphocyte proliferation,[19] that natural killer cell activity was less reduced,[20] and that the expression of adhesion molecules [21,22] as well as the phagocytic capacity of the RES were increased.[23,24] On the other hand it was also shown that the phagocytic capacity for *C. albicans* was significantly reduced.[25,26]

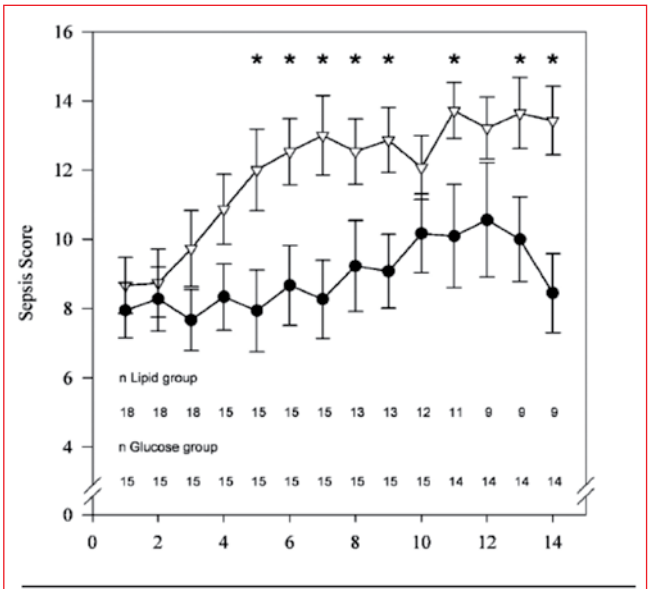
Seven smaller trials[19,27–32] in patients with ARDS, acquired immune deficiency syndrome, sepsis or undefined critically ill patients showed no significant difference in any important outcome parameter. One of two medium size trials (n = 72) showed less intra-abdominal infections and a trend towards reduced mortality in malnourished surgical patients[33] and the other one a significantly greater rise in retinol binding protein and nitrogen balance in septic patients.[34] However, as there are no harmful results, ω–6/MCT lipid emulsions are still in use and may still be used in critically ill patients.

The next step in the development of intravenous lipid emulsions was a further reduction in the ω–6 FA content to 20% and the completion with ω–9 oleic acid from olive oil (OO) – which was introduced in 1996. The concern with this new emulsion was that the low content of ω–6 FA might lead to a deficiency in essential FAs. This concern was partly addressed by a study in children reported by Munck[35] which documented that such a lipid emulsion could reduce the C20:3 content – a sign of essential acid deficiency – over 15 days as well as ω–6 FA. There are also experimental studies that showed that ω–9 FA or a lipid emulsion based on ω–9 FA (ω–9/ω–6) did not inhibit lymphocyte proliferation,[35,36] did not reduce the expression of activation markers on granulocytes[21,35,37] and that it had almost no effect on the release of proinflammatory cytokines.[38–41] Thus, its effect on most immunologic parameters was almost neutral.

This ω–9/ω–6 emulsion was evaluated in six trials in preterm infants[42–48] and in three trials in paediatric patients.[35,49–51] All trials showed a good short and (some studies) long term tolerability and no signs of essential fatty acid deficiency. In adults, this ω–9/ω–6 emulsion was administered over three to six months in home parenteral nutrition.[52–54] Besides seven mostly smaller trials in various patients, this emulsion was also studied in one observational[55] and two controlled trials[56,57] in critically ill patients. The trial reported by Huschak[57] randomised 33 severe multiple trauma patients to either high dose ω–9/ω–6 (75% of non-protein energy) or normal dose ω–6 FA (37% of non-protein energy). They found a significant shorter length of ventilation and a significantly shorter length of stay in the ICU in the high dose ω–9/ω–6 group (Figure 2). The trial reported by Garcia-de-Lorenzo[56] also found significantly less abnormalities in liver function in the ω–9/ω–6 group.

The next lipid emulsion – introduced in 1991 – was based on ω–3 fatty acids derived from fish oil (FO). In many *in vitro* and *ex vivo* studies it could be shown that ω–3 fatty acids had strong anti-inflammatory and immunosuppressive effects, already documented in various diseases such as rheumatoid arthritis, inflammatory bowel disease and asthma. Thus lipid emulsion inhibited lymphocyte proliferation,[58–61] decreased natural killer cell activity[6,62] as well as monocyte chemiluminescence, chemotaxis and adhesion to

Figure 2 : Huschak G et al.[57] Olive oil based nutrition in multiple trauma patients



	Lipid group (*n*=18)	Glucose group (*n*=15)	*p*[a]
Length of mechanical ventilation (days)	13.0±8.9 (3–35)	20.4±7.0 (9–29)	0.01
Length of stay in the ICU (days)	17.9±11.2 (3–42)	25.1±7.0 (12–37)	0.04
Length of stay in the acute care hospital (days)	80.4±84.4 (3–274)	84.5±71.7 (26–297)	0.88

[a] Student's *t* test

endothelial cells[63–65] and it reduced the release of proinflammatory cytokines.[66–68]

As the ω–3 fatty acids emulsion (ω–3) was never licensed for a standalone use but had to be administered in addition to another lipid emulsion, there are only few experimental clinical studies on the use of pure ω–3.[69–71] In these, its main effect was to modulate cytokine and leukotriene release (Figure 3).

As far as the admixture of ω–3 to other lipids is concerned, an important experiment was performed by Grimm et al[72] in 1994. They performed allogenic heart transplantations in inbred rats and fed them postoperatively with different lipid emulsions: fish oil, soybean oil, safflower oil or a mixture of safflower with fish oil with a ratio of 2.1:1. The rejection time of the allograft was significantly prolonged with fish oil but also with safflower or soybean oil. However, the mixture of safflower with fish oil induced a rejection time which was comparable to control animals (Figure 4). This experiment was the base for the ω–6:ω–3 ratio in the supplemental use of ω–3 with ω–6 and also for all lipid emulsions containing fish oil which were introduced after 2005.

It might be concluded from these data that an admixture with the described ω–6:ω–3 ratio is mostly immune-neutral. However, experimental data on the immunologic effect of these latest lipid emulsions are very rare. De Nardi et al[73] found yet a significant increase in macrophages that had engaged in phagocytosis with ω–6/MCT and ω–6/MCT/FO. However, there was no increase with ω–6/MCT/FO/OO.

There are many clinical studies concerning the addition of fish oil to lipid emulsions. They can be divided into studies using the admixture of pure ω–3 to other lipids, studies using ω–6/MCT/FO, or studies using ω–6/MCT/FO/OO.

Figure 3 : Meyer K et al.[67] Parenteral nutrition with fish oil modulates cytokine response in patients with sepsis

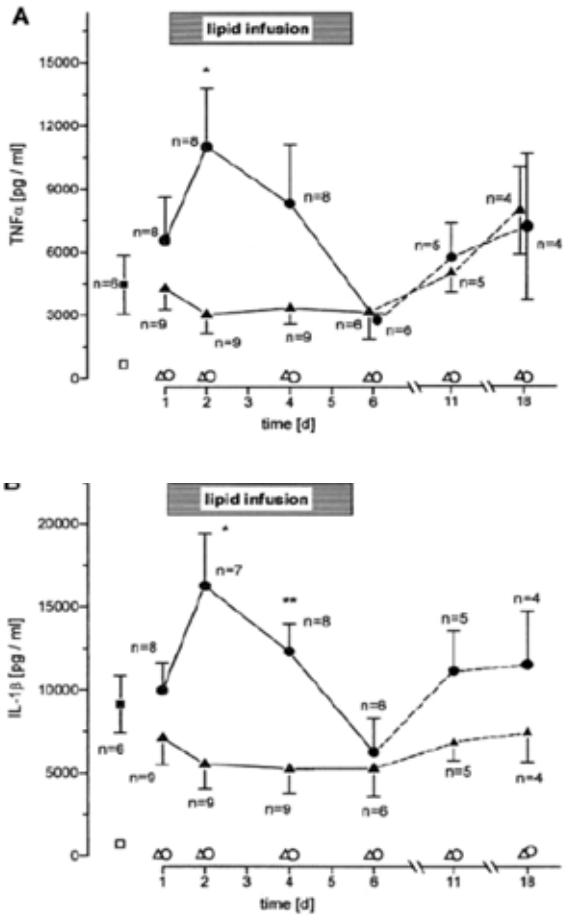
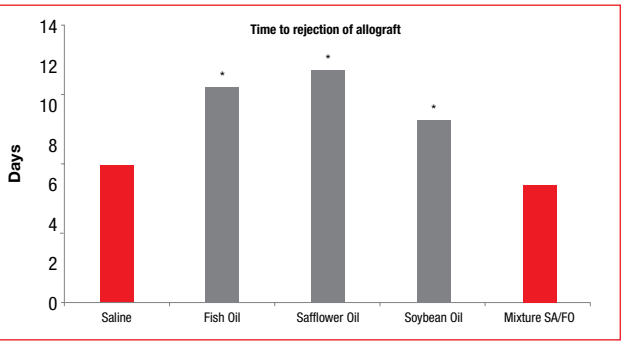


Figure 4: Grimm H et al.[72] Immunoregulation by parenteral lipids (Figure was created using data from this publication)



There are two observational[74,75] and nine randomised controlled[76–83] trials on the admixture of pure ω–3 FA to other lipids. While none of the randomised trials showed a significant improvement in survival or length of stay, the observational trial reported by Heller et al[74] showed that FO had the most favorable effects on survival, infection rates and length of stay when administered in doses between 0.1 and 0.2 g/kg/day.

The eight studies which evaluated ω–6/MCT/FO[84–91] also didn't show any significant effect on outcome except the trial reported by Wichmann et al[87] which showed a significant decrease in the length of stay (17.2 vs 21.9 days).

Of the three studies evaluating ω–6/MCT/FO/OO,[92–94] the study reported by Mertes et al[93] showed a trend towards a reduced length of hospital stay (15.7 +/- 6.3 vs 17.8 +/- 13.2 days). Piper et al[92] compared ω–6/MCT/FO/OO to ω–9/ω–6 and found at day two and five significantly lower levels of liver enzymes in the ω–6/MCT/FO/OO group. However, the importance of this result is limited by the fact that the higher levels found with ω–9/ω–6 also were only slightly above normal range.

In conclusion, ω–9/ω–6 with its relative immune-neutrality is a lipid emulsion that can be used in most critically ill and non-critically ill patients. The addition of fish oil in the newer ω–6/MCT/FO or ω–6/MCT/FO/OO emulsions certainly has advantages compared to pure ω–6 or ω–6/MCT and these emulsions can also be used in most patients. However, the drawback is that the immune-modulatory potential of these emulsions is rather low as the fish oil content is too low to exert a greater effect. So there is still need for a lipid emulsion that could be advantageous in patients with real hyperinflammation.

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