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Lipids for intravenous nutrition in hospitalised adult patients: a multiple choice of options

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Lipids used in parenteral nutrition provide energy, building blocks and essential fatty acids. Traditionally, these lipids have been based on *n*-6 PUFA-rich vegetable oils particularly soyabean oil. This may not be optimal because soyabean oil may present an excessive supply of linoleic acid. Alternatives to use of soyabean oil include its partial replacement by medium-chain TAG, olive oil or fish oil, either alone or in combination. Lipid emulsions containing these alternatives are well tolerated without adverse effects in a wide range of hospitalised adult patients. Lipid emulsions that include fish oil have been used in parenteral nutrition in adult patients' post-surgery (mainly gastrointestinal). This has been associated with alterations in patterns of inflammatory mediators and in immune function and, in some studies, a reduction in length of intensive care unit and hospital stay. These benefits are emphasised through recent meta-analyses. Perioperative administration of fish oil may be superior to post-operative administration. Parenteral fish oil has been used in critically ill adults. Here, the influence on inflammatory processes, immune function and clinical endpoints is not clear, since there are too few studies and those that are available report contradictory findings. However, some studies found reduced inflammation, improved gas exchange and shorter length of hospital stay in critically ill patients if they receive fish oil. More and better trials are needed in patient groups in which parenteral nutrition is used and where fish oil may offer benefits.

Surgery: Critical illness: Fish oil: Olive oil: Inflammation

There is currently great interest in the nature of the lipid component of parenteral nutrition and much discussion of what its composition should be. In the 1960s and 1970s soyabean oil became established as the lipid component of parenteral nutrition[1–3] and mixtures of soyabean oil and so-called 'medium-chain TAG' (a derivative of coconut oil or palm kernel oil) were introduced in the mid-1980s[4,5]. Globally, soyabean oil and mixtures of soyabean oil and medium-chain TAG remain the major lipids used in parenteral nutrition. The mid-1990s saw the introduction of olive oil and fish oil into parenteral nutrition, with products providing various combinations of soyabean oil, medium-chain TAG, olive oil and fish oil now available. This review will discuss the rationale for the inclusion of olive oil and fish oil in parenteral nutrition and will present the evidence currently available from clinical trials using these new lipid emulsions in hospitalised adult patients. The review will not discuss home parenteral nutrition or neonatal and paediatric uses, although there have been considerable developments in those areas with regard to the lipid emulsions that might be used. The material presented herein builds upon previous review articles of this subject[6–9], and includes a number of additional studies of relevance and discussion of several recent meta-analyses.

Abbreviation: ICU, intensive care unit.

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Table 1. Common names, short hand nomenclature and typical sources of fatty acids used in intravenous nutrition

Common name	Short hand nomenclature	Typical source
Caprylic acid	8:0	Coconut oil
Capric acid	10:0	Coconut oil
Palmitic acid	16:0	Olive oil, Soyabean oil, Fish oil
Oleic acid	18:1*n*-9	Olive oil, Soyabean oil
Linoleic acid	18:2*n*-6	Soyabean oil
α-Linolenic acid	18:3*n*-3	Soyabean oil
EPA	20:5*n*-3	Fish oil
DHA	22:6*n*-3	Fish oil

Fatty acids

Fatty acids are hydrocarbon chains with a carboxyl group at one end and a methyl group at the other. The carboxyl group is reactive and readily forms ester links with alcohol groups, for example, those on glycerol or cholesterol, in turn forming acylglycerols (e.g. TAG, phospholipids) and cholesteryl esters. Fatty acid chain lengths vary from two to thirty or more and the chain may contain double bonds. Fatty acids containing double bonds in the hydrocarbon chain are referred to as unsaturated fatty acids; a fatty acid containing one double bond is called a MUFA while one containing two or more double bonds is called a PUFA. Fatty acids have common and systematic names. They are also referred to by a shorthand nomenclature that denotes the number of carbon atoms in the chain, the number of double bonds and the position of the first double bond relative to the methyl (*n*) carbon. The *n*-3 and *n*-6 fatty acids are so-called because the first double bond is on carbon number 3 or 6, respectively, counting the methyl carbon as carbon number one. The simplest *n*-6 fatty acid is linoleic acid (18:2*n*-6) and the simplest *n*-3 fatty acid is α-linolenic acid (18:3*n*-3). Linoleic and α-linolenic acids cannot be synthesised in animals, including human subjects. They are classical essential fatty acids. In contrast, SFA and MUFA can be synthesised *de novo* in human subjects. Although mammalian cells cannot synthesise linoleic and α-linolenic acids, they can metabolise them by further desaturation and elongation. Linoleic acid can ultimately be converted to arachidonic acid (20:4*n*-6). Using the same series of enzymes, α-linolenic acid can be converted to EPA (20:5*n*-3) and on to DHA (22:6*n*-3). Fatty acids that are important in intravenous nutrition and their typical sources for this purpose are listed in Table 1.

Roles for lipids in parenteral nutrition

Lipids used in intravenous nutrition should provide a source of energy as an alternative to glucose; fatty acids that can be used in the biosynthesis of phospholipids for membrane synthesis, since patients requiring parenteral nutrition will typically be undergoing processes involving cell replication and tissue repair; and essential fatty acids so that deficiency symptoms are avoided. Soyabean oil provides fatty acids as energy sources, provides several fatty acids that are components of membrane phospholipids and is a good source of the two essential fatty acids. Fatty acids found in medium-chain TAG are equally good energy sources as those in soyabean oil; in fact they may offer metabolic advantages since medium-chain fatty acids are more easily transferred into mitochondria and therefore seem to be more easily oxidised than longer-chain fatty acids[4,5]. However, medium-chain fatty acids are not components of cell membrane phospholipids and medium-chain TAG are not a source of essential fatty acids. With new understandings of the roles of fatty acids, especially PUFA, in membrane structure and function, cell signalling, regulation of gene expression and as precursors of important lipid mediators[10–14], the concept that the lipid used in parenteral nutrition should provide a more optimal fatty acid balance has developed, although the precise definition of this balance is still lacking. One way to view this is that the lipid component should provide fatty acids with desirable biological activities and should not provide an excess of fatty acids with undesirable biological properties. In this way, the lipid component of parenteral nutrition would not exacerbate inappropriate cellular responses and would, at best, modulate these in a way that would improve patient outcome. It is this thinking that has led to the development of lipid emulsions that include fish oil and/or olive oil.

Use of soyabean oil in parenteral nutrition

Soyabean oil is rich in linoleic acid, which consists of about 50% of fatty acids present, and contains about 7% α-linolenic acid. Soyabean oil-based lipid emulsions include Intralipid® (Fresenius-Kabi), Lipovenos® (Fresenius-Kabi) and Lipofundin® (B. Braun) and these are widely used. A study in patients following major gastrointestinal surgery identified that the amount of *n*-6 PUFA (i.e. linoleic acid) infused was one of two predictors of the length of hospital stay (increased by 1·6 d/100 g *n*-6 PUFA infused), the other being the delay in the onset of initiating nutritional support[15]. However, clinical trials with soyabean oil-based lipid emulsions, mainly in undernourished patients undergoing major gastrointestinal surgery, provide conflicting evidence, some showing selective immunosuppressive effects[16–18], perhaps linked to poorer patient outcomes[17], and other studies not showing such effects on the immune system[19–21] or on clinical outcomes[22]. These studies have been described and discussed previously[6,8]. The study of Furukawa *et al.*[18] provides some insight into why different studies might produce different findings. Patients received standard glucose-containing parenteral nutrition with no lipid or including soyabean oil from 7 d before gastrointestinal surgery until 14 d later. Patients were classified as moderately or severely stressed based upon the nature of the surgical procedure. In the moderately stressed group there were no differences in the post-surgical plasma IL-6 response or T-lymphocyte function between patients receiving no lipid or soyabean oil. In contrast, severely stressed patients receiving soyabean oil showed an exaggerated IL-6 response and an impairment of T-lymphocyte function

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compared with those not receiving lipid. Thus, it would seem that in more-stressed patients soyabean oil can exaggerate the inflammation and immune impairment seen post-surgery, while there is no such effect in less-stressed patients. Despite the inconsistencies of the outcomes of the studies with soyabean-based lipid emulsions, a view has developed that the use of lipid emulsions based solely upon soyabean oil may not be optimal or may even be harmful, the concern being that *n*-6 PUFA might be pro-inflammatory, immunosuppressive and pro-coagulatory. It is important to note however that, despite these concerns, soyabean oil remains widely used as the sole lipid provided in parenteral nutrition regimens.

Use of medium-chain TAG in parenteral nutrition

Emulsions containing medium-chain TAG mixed with soyabean oil are well established, having been introduced in the 1980s[4,5]. Lipovenos® medium-chain TAG (Fresenius-Kabi) and Lipofundin® medium-chain TAG/long-chain TAG (B. Braun) are 50 : 50 (v/v) mixtures of soyabean oil and medium-chain TAG. Medium-chain fatty acids are more soluble than longer-chain fatty acids and are readily cleared from the circulation; are easily oxidised and not stored in adipose tissue as TAG; may be protein sparing because they are ketogenic; do not impair liver function and do not interfere with pulmonary hydrodynamics or gas exchange; and are resistant to peroxidation[4,5]. Studies have directly compared the influence of soyabean oil and a mixture of medium-chain TAG and soyabean oil on immune function[20,21]. In critically ill patients there was no difference in numbers of various immune cells in the bloodstream but the ratio of $CD4^+$ to $CD8^+$ cells was maintained in the medium-chain TAG plus soyabean oil group whereas it declined in the soyabean oil group[20]; this finding is indicative of better maintenance of immune function in the former group. In patients following gastrointestinal surgery there were no differences in lymphocyte proliferation or IL-2 production between soyabean oil and medium-chain TAG plus soyabean oil[21]. However, natural killer cell activity was increased in the medium-chain TAG plus soyabean oil group. Again, this finding is suggestive of better immune function in this group. Thus, there may be metabolic and functional advantages of the mixture of medium-chain TAG and soyabean oil compared with soyabean oil alone.

Use of olive oil in parenteral nutrition

Olive oil is found in two lipid emulsions, ClinOleic® (Baxter Healthcare) and SMOFLipid® (Fresenius-Kabi). Since SMOFLipid® also contains fish oil, studies with this emulsion will be described in the section on fish oil (see later). ClinOleic® is an 80 : 20 (v/v) mixture of olive oil and soyabean oil. Olive oil is an important component of the Mediterranean diet and is generally considered to be healthy[23]. Oleic acid, a major constituent of olive oil, has little impact on immune function, is fairly resistant to peroxidation and may have some mild anti-inflammatory actions[24]. The effect of olive oil was examined in a murine model of endotoxaemia[25]. Mice fed on diets rich in linoleic acid, including a diet with soyabean oil as the fat source, showed a strong inflammatory response to endotoxin and had 100% mortality within 72 h. In contrast, mice fed on a diet that included olive oil as the fat source had a blunted inflammatory response and showed 60% survival at 168 h.

Trials of ClinOleic® in hospitalised adult patients are summarised in Table 2; in each of these trials a group of patients receiving ClinOleic® was compared with a control group who received either soyabean oil or a 50 : 50 (v/v) mixture of medium-chain TAG and soyabean oil. A comparison has been made of a parenteral regimen of high glucose in combination with medium-chain TAG plus soyabean oil and low glucose in combination with ClinOleic® in patients with severe trauma in the intensive care unit (ICU)[26]. The low glucose-ClinOleic® group had lower blood glucose and less requirement for insulin, as would be expected, and also showed shorter duration of mechanical ventilation, fewer infections, better immune function and shorter length of ICU stay. These findings were interpreted as being a result of the use of ClinOleic®, but the study design does not permit this conclusion since the findings may be the result of the different amount of glucose provided to the two groups. A study of soyabean oil as control *v.* ClinOleic® in critically ill patients (mainly post-surgery patients in the ICU) showed no differences between groups in inflammatory markers, infections, ICU stay, hospital stay or mortality[27]. Similarly, in patients with severe burns in the ICU, no difference was found between medium-chain TAG plus soyabean oil as control and ClinOleic® in relation to inflammatory markers, number of infections, organ (including liver) dysfunction, duration of ICU stay, duration of hospital stay or mortality[28]. Most recently, there was no difference in inflammatory markers, number of infections, duration of ICU stay, duration of hospital stay or mortality between medical–surgical patients in the ICU receiving either soyabean oil as control or ClinOleic®[29]. Thus, studies with ClinOleic® have now been performed in medical–surgical ICU, trauma, critically ill and burned patients. These studies show that ClinOleic® is safe and without adverse effects, but that it seems to be little different from soyabean oil or a mixture of soyabean oil plus medium-chain TAG with regard to laboratory and clinical outcomes.

Use of fish oil in parenteral nutrition

Fish oil contains the very long chain *n*-3 PUFA, EPA and DHA. There is strong evidence for health benefits of these fatty acids especially with regard to CVD[30–33]. They act to modify tissue and blood lipid metabolism, blood lipid concentrations, blood coagulation, immune function, inflammation and endothelial function[34–38]. EPA and DHA are readily incorporated into cells and tissues and act to modify membrane properties, eicosanoid profiles, signal transduction processes and gene expression[10–14]. Through these mechanisms they result in altered cell and tissue function. Animal feeding studies have demonstrated that fish oil decreases inflammation in endotoxaemia[39–41] and

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Table 2. Summary of clinical trials of intravenous ClinOleic® (an 80 : 20 (v/v) mixture of olive and soyabean oils) in hospitalised adults

Reference	Patient type	Comparison made	Duration	Outcomes reported	Effect seen in the ClinOleic® group compared with control
Huschak *et al.*[26]	Trauma	Low glucose + ClinOleic® (*n* 18) *v.* high glucose + soyabean oil (*n* 15)	>6 d (enteral feeding introduced from day 1)	Metabolic profile (blood glucose etc.)	Improved
				Insulin requirement	Lower
				Immune function (monocyte HLA-DR)	Higher
				Infections	Fewer
				Duration of mechanical ventilation	Shorter (13 *v.* 20 d; $P = 0{\cdot}01$)
				Length of ICU stay	Shorter (18 *v.* 25 d; $P = 0{\cdot}04$)
Mateu de Antonio *et al.*[27]	Critically ill (mainly post-surgery ICU)	ClinOleic® (*n* 16) *v.* soyabean oil (*n* 23)	>5 d	Inflammatory markers	None
				Number and type of infections	None
				Length of ICU stay	None
				Length of hospital stay	None
				Mortality	None
Garcia de Lorenzo *et al.*[28]	Severely burned	ClinOleic® (*n* 11) *v.* MCT-soyabean oil (*n* 11)	5–7 d	Inflammatory markers	None
				Organ dysfunction	None
				Ventilation requirement	None
				Number of infections	None
				Length of ICU stay	None
				Length of hospital stay	None
				Mortality	None
Umpierrez *et al.*[29]	Medical–surgical ICU	ClinOleic® (*n* 51) *v.* soyabean oil (*n* 49)	Mean 13 d	Inflammatory markers	None
				Number of infections	None
				Length of ICU stay	None
				Length of hospital stay	None
				Mortality	None

HLA-DR, human leucocyte antigen-DR; ICU, intensive care unit; MCT, medium-chain TAG.

sepsis[42–44] and that this is associated with a decreased metabolic response[45–48], improved organ function[40,49–54] and improved survival [42–44,55–57].

Using fish oil to partly replace soyabean oil in parenteral nutrition offers the possibility to both decrease the amount of linoleic acid present and to increase the amount of biologically active *n*-3 PUFA[58–61]. Three lipid emulsions that include fish oil as a component are currently available. Omegaven® (Fresenius Kabi) is a pure fish oil emulsion (100 g lipid/l) that will typically contain about 3 g EPA plus DHA/100 ml. It is recommended that Omegaven® is used in combination with other emulsions (e.g. those based on soyabean oil) such that Omegaven® contributes 10–20 % of infused emulsion. Lipoplus® (also known as Lipidem®; B. Braun) is an emulsion (200 g lipid/l) with the lipid being a 50 : 40 : 10 (by vol.) mix of medium-chain TAG, soyabean oil and fish oil. Since fish oil used to produce Lipoplus® is concentrated in EPA and DHA, each 100 ml Lipoplus® will typically contain about 1·2 g EPA plus DHA. SMOFLipid® (Fresenius Kabi) is an emulsion (200 g lipid/l) with the lipid being a 30 : 30 : 25 : 15 (by vol.) mix of soyabean oil, medium-chain TAG, olive oil and fish oil. Each 100 ml SMOFLipid® will typically contain about 1 g EPA plus DHA.

Fish oil compared with soyabean oil or with a mixture of soyabean oil and medium-chain TAG in surgical patients

Trials of fish oil containing lipid emulsions in surgical patients and reporting clinical outcomes are summarised in Table 3; in most of these studies patients receiving a fish oil containing lipid emulsion have been compared with patients receiving either soyabean oil or a 50 : 50 (v/v) mixture of medium-chain TAG and soyabean oil as control. Intravenous infusion of lipid emulsions containing fish oil into patients following gastrointestinal surgery altered the fatty acid composition of plasma[62,63,74,75], platelets[76], leucocytes[64] and erythrocytes[77], typically with an increase in EPA content. A change in EPA content of leucocytes and platelets would be expected to affect the profile of eicosanoids produced from arachidonic acid and EPA. Indeed, several studies have demonstrated that, compared with what is seen with soyabean oil or a mixture of medium-chain TAG and soyabean oil, intravenous infusion of lipid emulsions containing fish oil into patients who had undergone major gastrointestinal surgery results in lower production of arachidonic acid-derived eicosanoids and higher production of EPA-derived eicosanoids by blood leucocytes stimulated *ex vivo*[62,64,74,77]. Plasma TNF concentrations were lower at day 6 post-surgery while plasma IL-6 concentrations were lower at day 10 post-surgery in patients who had undergone major gastrointestinal surgery and then received a 50 : 30 : 20 (by vol.) mixture of medium-chain TAG, soyabean oil and fish oil (this was a prototype version of Lipoplus®) for 5 d post-surgery compared with the control group who received a mixture of soyabean oil and medium-chain TAG[64]. The study found no differences between the two groups for infectious complications or length of ICU or hospital stay, although some trends were seen for better outcomes in patients receiving fish oil (Table 3). Another study infused Omegaven®, providing 10 g fish oil/d, on the day before abdominal surgery and on days 1–5 following abdominal surgery[65]. On days 4 and 5 the patients also received standard total parenteral nutrition, which included 50 g fat/d as soyabean oil. TNF production by endotoxin-stimulated whole blood tended to be lower at post-operative day 5 in the fish oil group, but this was not significant. Serum IL-6 concentrations were significantly lower at days 0, 1 and 3 in the fish oil group than in the control group. Monocyte expression of human leucocyte antigen-DR, an indication of the ability to present antigen and hence to mount an immune response, was preserved in the fish oil group, but declined at post-surgery days 3 and 5 in the control group. No differences between the two groups in infection rates or mortality were observed, but post-operative stay in ICU tended to be shorter in the fish oil group as did total hospital stay (Table 3). Post-operative stay in medical wards was shorter in the fish oil group ($P<0·05$). Another study compared the effects of lipid-free total parenteral nutrition or parenteral nutrition including soyabean oil or an 84 : 16 (v/v) mix of soyabean oil and Omegaven® for 5 d after large bowel surgery[78]. There were no differences between the groups with respect to the number of circulating lymphocytes, B lymphocytes, helper T lymphocytes, cytotoxic T lymphocytes or natural killer cells before surgery or at days 3 and 6 post-surgery, although these were affected by the surgery itself. There were no differences between groups with respect to T lymphocyte proliferation, but IL-2 production was increased in the fish oil group and the post-surgery decline in interferon-γ production was prevented by fish oil. Liang *et al.*[66] compared soyabean oil (as control) with a mixture of soyabean oil and Omegaven® (84 : 16, v/v) over 7 d in patients who had undergone radical colorectal cancer resection. The decline in serum IL-6 concentration between post-operative day 1 and day 8 was greater in the group receiving fish oil, while the increase in the ratio of $CD4^+$ to $CD8^+$ cells in the bloodstream, believed to be a marker of the cell-mediated immune response, was greater in that group. Length of hospital stay was slightly, but not significantly shorter in the fish oil group and there were few infections and no mortality in either group (Table 3). Wichmann *et al.*[63] reported shorter length of hospital stay in post-gastrointestinal surgery patients receiving Lipoplus® compared with a control group who received soyabean oil (Table 3). In another study in post-surgical patients, SMOFLipid® for 6 d resulted in significantly shorter hospital stay than seen with soyabean oil[62]. Taken together, these studies indicate that inclusion of fish oil in parenteral nutrition regimens for gastrointestinal surgical patients modulates generation of inflammatory eicosanoids[62,64,74,77] and cytokines[64–66] and may help to counter the surgery-induced decline in antigen presenting cell activity[65] and T-lymphocyte cytokine production[78]. More importantly, these studies do not reveal any deleterious effects of fish oil infusion in these patients. Furthermore, the studies that have examined the hard endpoint of length of hospital stay suggest a real clinical benefit from fish oil infusion in these patients[62–64,66]. Another report

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Table 3. Summary of clinical trials of intravenous fish oil in adult surgical patients reporting clinical outcomes

Reference	Type of surgery	Comparison made	Duration	Outcomes reported	Effect seen in fish oil group compared with control
Koch and Heller[15]	GI cancer	Used Omegaven® but not a controlled trial	>3 d	Antibiotic use Complications Length of ICU stay Length of hospital stay Mortality	Decreased by about 25% ($P<0{\cdot}0005$)* Decreased by about 20% ($P<0{\cdot}0005$)* Shorter by about 10% ($P=0{\cdot}05$)* Shorter by about 25% ($P<0{\cdot}0005$)* None
Grimm *et al.*[62]	GI; mainly cancer	Soyabean oil *v.* SMOFLipid®	Days 1–5 post-surgery	Length of hospital stay	Shorter (13·4 *v.* 20·4 d; $P<0{\cdot}05$)
Wichmann *et al.*[63]	Mainly GI cancer	Soyabean oil *v.* Lipoplus®	Days 1–5 post-surgery	Infections Length of ICU stay Length of hospital stay Mortality	Fewer but NS Shorter (4·1 *v.* 6·3 d) but NS Shorter (17·2 *v.* 21·9 d; $P=0{\cdot}006$) None
Wachtler *et al.*[64]	GI cancer	MCT-soyabean oil *v.* 50% MCT + 30% Soyabean oil + 20% fish oil	Days 1–5 post-surgery	Infections Length of ICU stay Length of hospital stay	Fewer but NS Shorter (0·9 *v.* 2 d) but NS None
Weiss *et al.*[65]	GI cancer	Soyabean oil *v.* Omegaven®	Day 1 pre-surgery to day 5 post-surgery	Infections Length of ICU stay Length of hospital stay Mortality	None Shorter (4·1 *v.* 9·1 d) but NS Shorter (17·8 *v.* 23·5 d) but NS None
Liang *et al.*[66]	GI cancer	Soyabean oil *v.* 84% Soyabean oil + 16% Omegaven®	Days 1–7 post-surgery	Infections Length of hospital stay Mortality	There was only one case of infection Shorter (17·5 *v.* 19·6 d) but NS There was no mortality in either group
Tsekos *et al.*[67]	Mainly GI cancer	Retrospective comparison of MCT-soyabean oil *v.* MCT-soyabean oil + Omegaven® (maximum 33% Omegaven®)	Mean 6 d	Need for mechanical ventilation Infections Length of ICU stay Readmission to the ICU Length of hospital stay Mortality	None Fewer (6 *v.* 11%) but NS None Decreased (5 *v.* 17%; $P<0{\cdot}05$) Shorter (25 *v.* 29 d) but NS None
Heller *et al.*[68]	GI cancer	Soyabean oil *v.* 80% Soyabean oil + 20% Omegaven®	Days 1–5 post-surgery	Liver and pancreatic function Length of ICU stay Length of hospital stay	Normalised more quickly None None
Berger *et al.*[69]	Aorta aneurysm repair	MCT-soyabean oil *v.* Lipoplus®	Days 1–4 post-surgery	Length of ICU stay Length of hospital stay Mortality	Shorter (1·6 *v.* 2·3 d) but NS Shorter (9·9 *v.* 11·3 d) but NS There was no mortality in either group
Heidt *et al.*[70]	Coronary artery bypass graft	Soyabean oil *v.* Omegaven®	Until transfer to ward	Atrial fibrillation Length of ICU stay	Lower (17·3 *v.* 30·6%; $P<0{\cdot}05$) Stated to be shorter but no details given
Piper *et al.*[71]	GI and other	ClinOleic® *v.* SMOFLipid®	Days 1–4 post-surgery	Liver function	Better preserved
Badia-Tahull *et al.*[72]	GI cancer	ClinOleic *v.* 84% ClinOleic + 16% Omegaven®	>5 d post-surgery	Liver function Infections Development of sepsis Length of hospital stay Mortality	None Fewer (23 *v.* 79%; $P=0{\cdot}007$) Less (8 *v.* 36%) but NS ($P=0{\cdot}098$) None Less (8 *v.* 14%) but NS
Wang *et al.*[73]	Mainly GI cancer	MCT-soyabean oil *v.* Lipoplus®	Days 1–6 post-surgery	Infections Progression to SIRS	None None

GI, gastrointestinal; ICU, intensive care unit; MCT, medium-chain TAG; NS, not significant; SIRS, systemic inflammatory response syndrome.
*Comparison between highest and lowest doses of fish oil.

from a cohort of patients receiving parenteral nutrition post-surgery also indicates benefits of inclusion of fish oil in the regimen[67]. There were no differences between a control group (receiving a mixture of soyabean oil and medium-chain TAG) and patients receiving fish oil (a mix of Omegaven® with a 50 : 50 soyabean oil-medium-chain TAG mix where a maximum of one-third of the mix was as fish oil) with respect to the proportion of patients who developed wound infections or who died, or in the length of hospital stay (Table 3). However, the proportion of patients in the fish oil group who were readmitted to ICU was significantly lower than in the control group (Table 3). A group of patients also received the fish oil containing emulsion for 2 d preoperatively. This group showed a decreased need for mechanical ventilation (17% *v.* 31% in the control group; $P<0{\cdot}05$), a shorter length of hospital stay (22 *v.* 29 d; $P<0{\cdot}05$), less need for readmission to the ICU (5 *v.* 17%; $P<0{\cdot}05$) and lower mortality (3% *v.* 15%; $P<0{\cdot}05$)[67]. Another study revealed that intravenous infusion of a lipid emulsion containing 80% soyabean oil and 20% Omegaven® into patients for 5 d following major gastrointestinal surgery accelerated normalisation of liver and pancreatic function compared with soyabean oil alone[68]. Overall, there was no difference between the groups with respect to length of stay in the ICU or in hospital. However, in a subgroup of patients at risk of sepsis, there was reduced ICU stay in patients receiving fish oil (4·0 *v.* 5·3 d in the control group; $P=0{\cdot}01$)[68]. In another study, a mixed group of over 650 patients including about 230 post-surgical patients received parenteral nutrition including Omegaven® for at least 3 d (mean 8·7 d); there was a significantly lower rate of infections, fewer complications and shorter length of hospital stay in post-surgery patients receiving fish oil compared with those who received a traditional emulsion[15]. However, this was not a properly controlled trial. These authors identified that infusion of about 0·15 g fish oil/kg per d decreased mean ICU stay from 8·7 to 5·3 d and hospital stay from 27·4 to 25·5 d. Thus, findings available from published studies in gastrointestinal surgical patients fairly clearly demonstrate clinical benefit from the inclusion of *n*-3 PUFA in the form of fish oil in parenteral nutrition regimens[15,62,63,65–68]. The study of Tsekos *et al.*[67] demonstrates a greater benefit if these fatty acids are additionally provided pre-surgery, which, of course, is only possible in elective surgery. The greater benefit of preoperative infusion of *n*-3 PUFA most likely relates to better incorporation of fatty acids into leucocytes and other tissues.

Although most of these studies have focused on gastrointestinal surgery, two studies have examined the role of intravenous fish oil following other types of surgery. One of these studies compared a mixture of soyabean oil and medium-chain TAG, as control, with Lipoplus® in patients who had undergone abdominal aorta aneurysm repair surgery[69]. There were no differences in glucose metabolism or in inflammatory markers. Clinical outcomes were not affected either, but there was a trend towards shorter ICU stay and shorter hospital stay (Table 3). In another study, patients destined to undergo coronary artery bypass grafting received soyabean oil, as control, or Omegaven® soon after hospital admission until post-surgery transfer to a normal ward[70]. Post-operative atrial fibrillation was lower in the Omegaven® group (Table 3).The paper comments that ICU stay was shorter in the Omegaven® group, but the data for this outcome are not presented and no indication of statistical significance is given.

Thus, all three available fish oil containing lipid emulsions have been used in adult post-surgery (mainly gastrointestinal) patients where the comparator lipid emulsion has been soyabean oil or a mixture of soyabean oil and medium-chain TAG. No adverse effects of the use of fish oil have been reported, indicating that it is safe to use in such patients. The use of fish oil is associated with altered patterns of inflammatory eicosanoids and cytokines in post-gastrointestinal surgery patients, and immune function may be better maintained by fish oil in these patients. Studies have reported reductions in lengths of ICU or hospital stay or trends towards such reductions. The lack of significance in studies that report favourable trends may be due to the small sample size of those studies. Perioperative administration of fish oil may be superior to post-operative[67], and this should be explored further. Taken together the studies in post-surgery patients present a fairly consistent and positive view of the efficacy of intravenous fish oil administration post-surgery. However, in these studies patients who would not normally require parenteral nutrition have frequently been included. Furthermore, the lengths of ICU and hospital stay reported in both control and fish oil groups are frequently much longer than typically seen in many clinical settings. Thus, although the data presently available are highly supportive of the use of intravenous fish oil, translation of the findings to the real clinical situation requires further studies designed to mimic current clinical practice; clearly such studies need to be properly designed and adequately powered.

Fish oil compared with a mixture of soyabean and olive oils in surgical patients

Although the comparator for most studies of fish oil containing lipid emulsions has been soyabean oil or a mixture of soyabean oil and medium-chain TAG (Table 3) two studies have compared a fish oil containing lipid emulsion with ClinOleic® (Table 3). Piper *et al.*[71] reported that post-operative liver function was preserved in a better manner if patients received SMOFLipid® compared with ClinOlec® for 5 d after gastrointestinal surgery. Badia-Tahull *et al.*[72] compared the effect of ClinOlec® and an 84 : 16 (v/v) mixture of ClinOleic® and Omegaven® in post-gastrointestinal surgery patients. They found no differences in inflammatory markers, liver function tests, hospital stay or mortality between the groups but there was a lower rate of infections in the group that received some fish oil and there was a strong trend towards reduced development of sepsis (Table 3). These two studies suggest a superiority of fish oil containing lipid emulsions over ClinOleic® in this patient group, but clearly more studies are needed.

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Fish oil compared with soyabean oil or a mixture of soyabean oil and medium-chain TAG in critically ill patients

Trials of fish oil containing lipid emulsions in critically ill patients and reporting clinical outcomes are summarised in Table 4; in most of these studies patients receiving a fish oil containing lipid emulsion have been compared with patients receiving either soyabean oil or a 50 : 50 (v/v) mixture of medium-chain TAG and soyabean oil as control. However, one study listed in Table 4[86] used a group not receiving lipid as the comparator, while another study[81] was not controlled. Septic patients who were intolerant of enteral nutrition received a standard soyabean oil-based emulsion as control or Omegaven® for 5[79] or 10[80] d. Blood leucocyte counts and serum C-reactive protein concentration tended to be lower and production of EPA-derived leucotriene B_5 by stimulated neutrophils was significantly higher in patients receiving fish oil[79]. Production of TNF, IL-1β, IL-6, IL-8 and IL-10 by endotoxin-stimulated mononuclear cells did not increase during infusion of the fish oil-containing emulsion whereas production of the four pro-inflammatory cytokines was markedly elevated during the first 2 d of soyabean oil infusion[80]. These studies establish that infusion of *n*-3 PUFA into patients with sepsis can modulate inflammatory mediator production and related inflammatory processes, although this did not translate into significant clinical benefits (Table 4). Heller *et al.*[81] included patients with abdominal sepsis, multiple trauma and severe head injury in their study of Omegaven® infusion. They found a significantly lower rate of infection and shorter lengths of ICU and hospital stay in patients receiving more than 0·05 g fish oil/kg per d than in those receiving less than this (Table 4). Mortality was significantly decreased in those patients who received more than 0·1 g fish oil/kg per d (Table 4). The survival advantage was greater in some patient groups than others (severe head injury>multiple trauma>abdominal sepsis>non-abdominal sepsis>post-surgery), but small numbers of patients in some groups make interpretation of these data difficult. Furthermore, this study was not controlled or blinded. Nevertheless, these data are strongly suggestive of genuine clinical benefit from inclusion of fish oil in parenteral nutrition regimens given to critically ill patients. This conclusion is in part supported by a study in patients with severe acute pancreatitis[82]. The patients received soyabean oil as control or a 80 : 20 (v/v) mixture of soyabean oil and Omegaven® for 5 d. Although there were no differences between the groups with regard to inflammatory markers, number of infections, or lengths of ICU and hospital stay, there was better gas exchange and a reduced requirement for continuous renal replacement therapy in those patients receiving fish oil (Table 4). Barbosa *et al.*[83] compared a mixture of soyabean oil and medium-chain TAG as control with Lipoplus® given for 5 d soon after ICU admission in septic patients. The decrease in IL-6 concentration over time was greater in the Lipoplus® group and there was better gas exchange at day 6 in that group. ICU stay did not differ between groups but length of hospital stay was shorter with Lipoplus® (Table 4). In contrast with the positive findings from the above studies, Friesecke *et al.*[84] reported no differences between a mixture of soyabean oil and medium-chain TAG as control and a mixture of soyabean oil, medium-chain TAG and Omegaven® given over 7 d in medical ICU patients with regard to several outcomes including immune markers, inflammatory markers, bleeding, ventilation requirement, number of infections, length of ICU stay and mortality (Table 4). A short infusion of Lipoplus® in patients with acute respiratory distress syndrome reduced inflammation[87] but had little clinical impact[85].

Thus, of the three available fish oil containing lipid emulsions, Omegaven® has been used alone or as a mixture with standard lipid emulsions in a small number of studies in critically ill adults[79–82,84]; Lipoplus® has been used in one study in septic patients[83] and one study in patients with acute respiratory distress syndrome[85,87]. No adverse effects of the use of fish oil have been reported in these studies, indicating that it is safe to use in such patients. Fish oil may reduce inflammation in critically ill patients, although this is not a consistent finding and effects on immune function are not yet well explored. The impact of fish oil on clinical endpoints like infections, length of ICU and hospital stay and mortality is not clear, since there are too few studies and those that are available report contradictory findings or do not have a satisfactory design. An improvement in gas exchange is reported in two studies[82,83]. One important factor, highlighted by the study of Heller *et al.*[70] is the dose of fish oil required to influence clinical outcomes. Overall, the data available are suggestive of some clinical benefit from the inclusion of long chain *n*-3 PUFA in parenteral nutrition regimens given to critically ill patients. However, only limited studies have been published and the inconsistency of the findings limits translation. Thus, further studies are required; clearly such studies need to be properly designed and adequately powered.

Meta-analyses of intravenous fish oil in hospitalised adult patients

The trials of intravenous fish oil in hospitalised adults were subject to two meta-analyses published in 2010[88,89]. Recently, two further meta-analyses were published on this topic[90,91]. Table 5 describes the main findings of these analyses. Wei *et al.*[88] and Chen *et al.*[89] both included studies of surgical patients, mainly those undergoing surgery for gastrointestinal cancer removal, although the study of Berger *et al.*[69] in patients who had undergone aortic aneurysm repair surgery was included in both meta-analyses. Wei *et al.*[88] included one study in patients who had developed post-operative abdominal sepsis. Both these analyses combined studies where patients were transferred into an ICU unit with those who were not. Although these two meta-analyses searched the same literature base and covered an almost identical period of time there are only three studies common to both. Chen *et al.*[89] excluded studies published in abstract form only, while three of the six studies included by Wei *et al.*[88] had been published as abstracts only. Despite the relatively small overlap in the included studies, these two meta-analyses produced very

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Table 4. Summary of clinical trials of intravenous fish oil in critically ill adults reporting clinical outcomes

Reference	Patient type	Comparison made	Duration	Outcomes reported	Effect seen in fish oil group compared with control
Mayer *et al.*[79]	Septic	Soyabean oil *v.* Omegaven®	5 d	Requirement for mechanical ventilation Mortality at 14 d	None None
Mayer *et al.*[80]	Septic	Soyabean oil *v.* Omegaven®	10 d	Duration of mechanical ventilation Mortality at 10 d	Shorter but NS ($P = 0{\cdot}07$) There was no mortality in either group
Heller *et al.*[81]	Mixed: surgical, septic, trauma, severe head injury	Used Omegaven® but not a controlled trial	>3 d (mean 8·7 d)	Antibiotic use Length of ICU stay Length of hospital stay Mortality	Decreased from 93 to 70% ($P<0{\cdot}05$)* Shorter (8 *v.* 23 d; $P<0{\cdot}001$)* Shorter (26 *v.* 40 d; $P<0{\cdot}001$)* Decreased (10 *v.* 20%; $P<0{\cdot}05$)*
Wang *et al.*[82]	Severe acute pancreatitis	Soyabean oil *v.* 80% Soyabean oil + 20% Omegaven®	5 d	Gas exchange Infections Days of renal replacement therapy Length of ICU stay Length of hospital stay Mortality	Improved at day 5 Fewer but NS Fewer (18 *v.* 26 d; $P<0{\cdot}05$) Shorter (21 *v.* 27 d) but NS Shorter (65 *v.* 71 d) but NS None
Barbosa *et al.*[83]	Septic	MCT-soyabean oil *v.* Lipoplus®	5 d	Gas exchange Duration of mechanical ventilation Length of ICU stay Length of hospital stay Mortality at 5 and 28 d	Improved at day 6 None None Shorter (28 *v.* 82 d†; $P = 0{\cdot}044$) None
Friesecke *et al.*[84]	Critically ill medical	MCT-soyabean oil *v.* 83% MCT-soyabean oil + 17% Omegaven®	7 d	Infections Duration of mechanical ventilation Length of ICU stay Mortality at 28 d	None None None None
Sabater *et al.*[85]	ARDS	Soyabean oil *v.* Lipoplus®	12 h	Gas exchange ICU mortality Mortality during ICU stay	None None None
Khor *et al.*[86]	Septic	No lipid *v.* Omegaven®	7 d	Length of ICU stay Length of hospital stay	None None

ARDS, acute respiratory distress syndrome; ICU, intensive care unit; MCT, medium-chain TAG; NS, not significant.
*Comparison between highest and lowest doses of fish oil.
†Excluding patients who died.

Table 5. Summary of the meta-analyses of intravenous fish oil in hospitalised adult patients

Meta analysis	Studies included (*n*)	Years of publication of the included studies	Patient group	Outcomes reported (number of studies)	Effect of fish oil *v.* control
Wei *et al.*[88]	6	2002–2008	Surgical (one study in post-surgical patients with abdominal sepsis)	Mortality (5) Infections (4) ICU stay (3) Hospital stay (4)	None Reduced (RR = 0·49; $P = 0·03$) Shorter (− 2·07 d; $P = 0·004$) Shorter (− 3·06 d; not significant); Shorter (− 1·61 d; $P = 0·02$) when the study in patients with abdominal sepsis was excluded
Chen *et al.*[89]	13	1996–2008	Surgical	Mortality (3) Infections (7) ICU stay (5) Hospital stay (7)	None Reduced (RR = 0·56; $P = 0·04$) Shorter (− 1·80 d; $P = 0·004$) Shorter (− 2·98 d; $P < 0·001$)
Pradelli *et al.*[90]	23	1996–2011	Surgical and not admitted to ICU (10 studies) or ICU (13 studies; includes surgical, sepsis, critical illness)	Mortality (10; 3 in non-ICU and 7 in ICU) Infections (11; 6 in non-ICU and 5 in ICU) ICU stay (8) Hospital stay (15; 7 in non-ICU and 8 in ICU)	None Reduced (RR = 0·61; $P = 0·002$); Reduced in non-ICU patients (RR = 0·53; $P = 0·004$) but not ICU patients (RR = 0·71; $P = 0·14$) Shorter (− 1·92 d; $P = 0·005$) Shorter (− 3·29 d; $P < 0·001$); Shorter in both ICU patients (− 5·17 d; $P = 0·001$) and non-ICU patients (− 1·86 d; $P = 0·004$)
Palmer *et al.*[91]	8	2003–2010	Critical illness	Mortality (8) Infections (5) ICU stay (6) Hospital stay (3)	None None (RR = 0·78) None (− 0·57 d) Shorter (− 9·49 d; $P = 0·008$)

ICU, intensive care unit; RR, relative risk.

similar findings: including fish oil in parenteral nutrition reduced infections by about 50%, length of ICU stay by about 2 d and length of hospital stay by about 3 d (Table 5). There was no effect on mortality, but rate of mortality was typically very low in these studies anyway. The recent meta-analysis of Pradelli *et al.*[90] included a combination of surgical patients who were not admitted to the ICU and patients in the ICU, irrespective of their origin (i.e. surgical, sepsis and critical illness); they also conducted analyses in these two groups separately. The ICU group of Pradelli *et al.* included three of the studies included in Wei *et al.*[88] and six of the studies included in Chen *et al.*[89]. Furthermore, the surgical, non-ICU group of Pradelli *et al.* included six of the studies included in Chen *et al.* Consequently, only one study from Chen *et al.* was not included in the analysis of Pradelli *et al.*, although the latter included twenty studies not included by Wei *et al.* and eleven studies not included by Chen *et al.* Across all studies combined, Pradelli *et al.*[90] identified that inclusion of fish oil reduced infection by about 40%, length of ICU stay by about 2 d and length of hospital stay by about 3 d (Table 5). Among the non-ICU patients (all gastrointestinal cancer surgery patients) fish oil reduced infections by about 50% and length of hospital stay by about 2 d (Table 5), consistent with the two earlier meta-analyses in this patient group. The 30% reduction in infections in ICU patients was not significant, but fish oil shortened hospital stay by about 5 d in this group (Table 5). The similarity of the findings of these three meta-analyses, despite the limited overlap in the studies included and the different combinations of patient groups, gives some confidence to the robustness of the findings in favour of improved outcome with inclusion of fish oil in parenteral nutrition. Most recently, Palmer *et al.*[91] performed a meta-analysis of studies with parenteral fish oil restricted to critically ill patients, the first meta-analysis of fish oil in this group. Eight studies were included, three of which had been published in abstract form only. There was an overlap of only one study with Wei *et al.*[88], no overlap with Chen *et al.*[89] and an overlap of three studies with the ICU group of Pradelli *et al.*[90]. The reduction of infections of about 20% and of ICU stay by about half a day seen with fish oil were not significant (Table 5). There was a significantly shorter length of hospital stay by about 9 d in critically ill patients receiving parenteral fish oil (Table 5).

The combined findings of these meta-analyses suggest that if gastrointestinal cancer surgery patients are placed on 3–6 d or so of total parenteral nutrition from post-operative day one they suffer fewer complications, get better more

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quickly and go home sooner if the lipid component includes fish oil compared with if it does not. If these patients happen to be admitted to an ICU they stay for a shorter time. However, such a long duration of total parenteral nutrition in this type of patient is not normal clinical practice in many places. Therefore, although the findings certainly support the hypothesis that intravenous fish oil can bring about clinical benefit, the application of the findings to routine clinical care of this patient group in most places is fairly limited. On the other hand, pre-elective surgery provision of marine *n*-3 fatty acids, either orally or intravenously may offer a strategy to improve patient outcome and allows for a prolonged period of administration of these biologically active substances prior to an operation. Three meta-analyses identified that length of ICU stay is shortened by about 2 d with inclusion of fish oil in the parenteral regimen[88–90]. However, the one meta-analysis restricted to critically ill patients did not find a significant effect of fish oil on ICU stay, although there was an effect on length of hospital stay[91].

Summary and conclusions

Lipids traditionally used in parenteral nutrition are based on *n*-6 PUFA-rich vegetable oils like soyabean oil. This may not be optimal because it may present an excessive supply of linoleic acid. Alternatives to use of soyabean oil include its partial replacement by medium-chain TAG, olive oil or fish oil, either alone or in combination. Lipid emulsions containing medium-chain TAG, olive oil or fish oil are well tolerated without adverse effects in a wide range of adult patients. Lipid emulsions that include fish oil have been used in parenteral nutrition in adult patients, post-surgery (mainly gastrointestinal). This has been associated with alterations in patterns of inflammatory mediators and in immune function and, in some studies, a reduction in length of ICU and hospital stay. These benefits are brought out by recent meta-analyses. Perioperative administration of fish oil may be superior to post-operative, but this requires greater exploration. Parenteral fish oil has been used in critically ill adults. Here, the influence on inflammatory processes, immune function and clinical endpoints is not clear, since there are too few studies and those that are available report contradictory findings. However, some studies report reduced inflammation, improved gas exchange and shorter length of hospital stay in this patient group if they receive fish oil. Making a firm conclusion on the usefulness of intravenous fish oil (or olive oil) in critically ill patients is impeded by a lack of sufficiently large and well-designed studies. It seems likely that more studies will be performed to help address this important question. A variety of lipid emulsions presenting soyabean oil, medium-chain TAG, olive oil and fish oil in various combinations is currently available, providing multiple choice of options. Until the outcome of new, bigger and better studies is known, it is not possible to absolutely support the use of intravenous fish oil in patient groups that require parenteral nutrition, although the evidence that is currently available is generally favourable.

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