SUCCESSFUL COMPLETION OF THE QUESTIONS AT THE END OF THIS PAPER HAS BEEN APPROVED FOR CONTINUING EDUCATION BY THE BDDT-N; 1.0 CREDIT PARENTERAL THERAPY AND BY THE CNPBC; ONE CE HOUR.

Intravenous Therapies

Fish oil based lipid emulsions (FOBLE)

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Fish oil based lipid emulsions (FOBLE) have an excellent record of safe and effective use, objectively evaluated in over 55 human intervention trials. Critical care hospital settings remain the most thoroughly evaluated areas of their application, however interest in management of flares of chronic inflammatory disorders such as arthritis and psoriasis has begun to emerge. By showcasing the clinical utility of this safe and effective intravenous treatment strategy, it is hoped, progress can be made in adding fish oil to the armament of intravenous therapies at the disposal of integrated healthcare providers.

Introduction

Fish derived omega-3 (n-3) fatty acids, specifically eicosapentanoic acid (EPA) and docosahexanoic acid (DHA) are well recognized for their anti-inflammatory effects (Rangel-Huerta 2012). Upon incorporation into the cell membrane, EPA and DHA competitively inhibit production of pro-inflammatory cytokines from arachidonic acid (AA), such as prostaglandin E2 (PGE2), and serve as a substrate for production of less active prostaglandin E3 (PGE3, anti-inflammatory) (Mayer 2006). In addition, EPA and DHA are precursors for the inflammation-resolving mediators appropriately known as resolvins (Calder 2010). The uses of intravenously (IV) administered fish oils, or *fish oil based lipid emulsions* (FOBLE), are lesser known. Nonetheless, there is a well-developed body of research demonstrating impressive clinical benefits associated with use of IV fish oils. The most supported application of IV fish oils is in the critical care setting, however other areas of application have also been investigated. Figure 1 shows the effect of EPA on generation of inflammatory cytokines.

A Pubmed search for "intravenous omega-3" on 10 August 2012 yielded 57 clinical trials. Not all of these are included here since some pertain to highly specialized applications, such as liver disease in premature infants, total parenteral (TPN) –related liver disease, end-stage renal disease, or biomarker studies such as those investigating effects on antioxidant status. This article includes 18 clinical trials of intravenous omega-3 fatty acids related to the following areas: 1) critical care (n=13); 2) rheumatoid arthritis (n=2); and 3) psoriasis and inflammatory skin diseases (n=3).

Pharmacology

The most widely used and well-researched parenteral lipid emulsion featuring omega-3 fatty acids is *Omegaven* (Fresenius-Kabi, Germany). Omegaven is a 10% fish oil emulsion meaning that it contains 10g refined fish oil per 100mL, including between 1-3g each EPA and DHA (Calder 2010, Fresenius Kabi 2010). Other fish oil based formulations include *SMOFLipid* 20% (Fresenius-Kabi), which contains 30g total fish oils per 1000mL in combination with soybean oil, medium chain triglycerides, and olive oil (AusPAR 2010, Calder 2010); and *Lipoplus* (B. Braun, Germany), which contains 20g total fish oil per 1000mL in combination with soybean oil and medium chain triglycerides (B. Braun un-dated product information).

Intravenous delivery of n-3 PUFAs has been shown to circumvent the slower n-3 incorporation into phospholipid membranes following oral administration (Carpentier 2010, Roulet 1997, Simeons 2008). Incorporation of EPA into leukocyte and platelet membranes after IV administration occurs within 60 minutes (Carpentier 2010). Similarly, Madsen found that IV administration of 4.1g n-3 PUFAs (polyunsaturated fatty acids) resulted in an increase of levels present in platelet phospholipids at 4 hours, and increased levels in plasma phospholipids at 48 hours, while there was no change in the placebo group (2011).

A study by Roulet conducted among 10 post-operative patients found that a lipid emulsion with 10% fish oil added resulted in a greater than two-fold increase in the EPA content of platelet phospholipids, and decreased maximal platelet reaction speed ($p < 0.02$) while increasing latency ($p < 0.002$), indicating a less heightened immune response (1997). Importantly, no toxicities, including no increase in postoperative bleeding and no abnormalities in hepatic and renal function, were observed during the fish oil infusion (Roulet 1997). Pradier et al investigated the safety of a bolus IV injection of a medium-chain triglyceride:fish oil emulsion (8:2 ratio) on hemostatic parameters in 12 healthy subjects (2008). No adverse effect was found on 1) occlusion time in response to the ADP (adenosine diphosphate, a platelet activator) or the epinephrine test; 2) levels of certain markers of coagulability, such as fibrinogen, PAC-1, and others, in response to ADP, collagen or thrombin receptor analog peptide six when examined ex vivo. Authors concluded that these results support the hemostatic safety of the IV fish oil emulsion (Pradier 2008).

Clinical trials

Critical Care: Sepsis and Systemic Inflammatory Response Syndrome (SIRS)

In the critical care setting, intravenous supplementation with fish oil is being studied for its powerful immunologic effects (Mayer 2006). In particular, IV fish oil has been shown to decrease the length of hospitalization in patients undergoing abdominal surgery (Jiang 2010), decrease levels of inflammation in patients with sepsis or SIRS (Sungertekin 2011), and decrease complications in post-operative patients (Heller 2006). For years, the standard lipid based emulsion used in patients requiring total or partial parenteral nutrition (TPN, PN) has consisted of soybean oil rich in omega-6 fatty acids (Mayer 2006). It was subsequently found however that high amounts of omega-6 fatty acids may in fact harmfully suppress immune function, resulting in increased rates of infection (Calder 2010, Nordenström 1979, Snydman 1982). Conversely, newer emulsions such as Omegaven containing 10% (w/v) fish oil have been shown to beneficially impact immune function in healthy (Pittet 2010, Pluess 2007) and hospitalized patients (Wei 2010).

In healthy patients, Omegaven has been shown to blunt the immune response to the endotoxin lipopolysaccharide (LPS) (Pittet 2010, Pluess 2007). Since bacterial-derived LPS acts as a trigger eliciting many of the harmful symptoms of infection and/ or sepsis essentially effected by the immune system, such as fever, systemic inflammation, and shock, reducing this reaction is considered beneficial in these patients. In addition, Pluess et al found that Omegaven blunted the effects of LPS on fever and the neuroendocrine response to infection (2007).

Figure 1. How EPA Impacts Synthesis of Inflammatory Cyotkines (adapted from Mayer 2006).

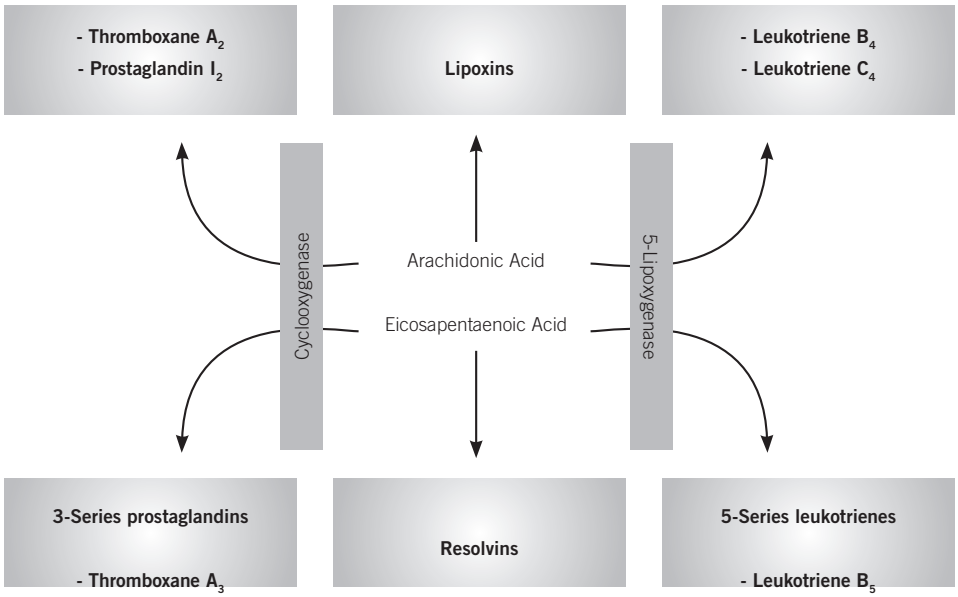

Table 1. Critical Care: Uses in Sepsis, Systemic Inflammatory Response Syndrome (SIRS),& Post-operative Patients

Reference	Design	Intervention	Outcome
Han 2012	RCT; N=38 patients in SICU after major surgery receiving PN	FOBLE (Omegaven 0.2g/kg daily) OR same PN without fish oil n-3's x7d post-op	in IL-1, IL-8, and IFN- on post-op day 4 (p<0.05), and IL-1, IL-8, IFN- , IL-6, and TNF- on post-op day 7 (p<0.05) in n-3 group. NS in post-op liver dysfunction (control 50% vs n-3 33.3%) and infection rate (41.7% vs 27.8%).
Sungertekin 2011	RPCT; N=20 sepsis + 20 SIRS patients receiving PN	FOBLE (Omegaven 0.6g/kg) OR PN with MCT/LCT but not fish oils x 7d	Sepsis groups who did not receive n-3s had grades of liver steatosis on ultrasound at days 7 and 10 (P<0.05) compared to the n-3 group. TNF- and IL-6 levels were higher in control patients compared to the n-3 group on day 7.
Khor 2011	RDBPCT; N=28 patients with severe sepsis	10% FOBLE (Omegaven) OR saline infusion placebo	APACHE II score on days 3, 5 & 7 (p<0.05 for all); APACHE III (p = 0.028) and Simplified Acute Physiology Score II (p = 0.019) on day 7. No significant difference in length of hospital stay.

Jiang 2010	RCT; N=206 patients completed surgery for gastrointestinal or colonic cancer	10% FOBLE (Omegaven 0.2g/kg) OR isocaloricisonitrogenous infusion based on soybean oil only over 20-24h daily x7d	The n-3 group had:
			infectious complications (4 vs 12; P= 0.066);
			incidence of SIRS (4 vs 13; P = 0.039);
			hospital stay (mean 15vs 17 days; P = 0.041).
			No severe adverse events.

Xiong 2009	RCT; N= 60 patients with severe acute pancreatitis	10% FOBLE (Omegaven 0.2g/kg) x7d plus conventional therapy OR conventional therapy only	In the n-3 group: APACHE-II scores compared to controls (P<0.05); fluid equilibrium time (5.1+/-2.2 days vs 8.4+/-2.3 days); SIRS scores and the SIRS state resolved after the 4th day; TNF-alpha (P<0.05).
Liang 2008	RDBPCT; N= 42 patients undergoing radical colorectal cancer resection on TPN	10% FOBLE (Omegaven 0.2g/kg) OR standard soybean oil based TPN x 7d	The n-3 group had: Greater reduction in IL-6 and TNF-alpha (p<0.05). CD4+/CD8+ (P = 0.035). Shorter postoperative hospital stay (17.45 +/- 4.80 d vs 19.62 +/- 5.59 d, P = 0.19).
Wichmann 2007	RDBPCT; N= 256 patients undergoing major abdominal surgery receiving PN	2% FOBLE (Lipoplus) OR emulsion without fish oil (Intralipid) x5d post-op	In the n-3 group, plasma levels of EPA, leukotriene B5, and antioxidant content were significantly increased, and length of hospital stay of was 21% shorter (17.2 vs. 21.9 days; p = .0061).
Tappy 2006	RCT; N= 24 SICU patients on PN	10% FOBLE (Omegaven) OR a standard soybean oil emulsion	Total energy expenditure was significantly lower in patients receiving n-3 fatty acids (0.015+/-0.001 vs. 0.019+/-0.001 kcal/kg/min, P<0.05).
Mertes 2006	RDBPCT; N= 199 postoperative patients on TPN (abdominal or thoracic surgery)	20% FOBLE (SMOFlipid, 30g fish oil/L) or standard soybean oil emulsion (Lipovenoes 20%) (1.5g/kg/d x5d)	Trend towards a reduced length of hospital stay with SMOFlipid (15.7 +/- 6.3 vs. 17.8 +/- 13.2 days).

Grimm 2006	RDBPCT; N=33 post-op patients on TPN (major abdominal surgery)	20% FOBLE (SMOFlipid, 30g fish oil/L) or standard soybean oil emulsion (Lipovenoes 20%) (1.5g/kg/d x5d)	Phospholipid ratio of EPA/AA with SMOFLipid but not the control emulsion. Length of hospital stay with SMOFlipid (13.4 +/- 2.0 vs. 20.4 +/- 10.0 days, $p < 0.05$).
Antebi 2004	RDBPCT; N= 20 stressed ICU patients on TPN	FOBLE (SMOF, 15% fish oil) OR standard soybean oil-based emulsion (LIPOVEN) daily x 5d	liver enzymes and phospholipids/apo A1 ratio in both groups, however, the increases were lower in the SMOF group, and was non-significant for the CRP level and the ALT activity.
Mayer 2003A	RCT; N=21 critical care patients with sepsis requiring PN	10% FOBLE (Omegaven), OR conventional soybean oil based emulsion (Lipoven) x 5d	Before lipid infusion therapy, AA was greatly increased. Within 2 days of fish oil infusion, free n-3 fatty acids increased, and the n-3/n-6 ratio was reversed. Generation of proinflammatory cytokines was markedly amplified during n-6 and suppressed during n-3 lipid application.
Mayer 2003B	Open label RCT; N=10 patients with sepsis requiring PN + 8 healthy controls	10% FOBLE (Omegaven), OR conventional soybean oil based emulsion (Lipoven) x10d	At baseline levels of plasma free fatty acids including AA were elevated. Neutrophils isolated from septic patients showed reduced responsiveness to ex vivo stimulation. With the omega-6 lipid infusion,these abnormalities persisted or worsened. In response to n-3's a shift occurred in the n-3/ n-6 ratio, and neutrophil function improved.

Key: APACHE Acute Physiology and Chronic Health Evaluation score; ICU intensive care unit; IL interleukin; LCT long chain triglyceride; MCT medium chain triglyceride; NS non significant; PN parenteral nutrition; SICU surgical intensive care unit; TPN total parenteral nutrition.

Table 1 presents a summary of 13 human trials investigating use of IV fish oil in critical care patients for outcomes related to sepsis, systemic inflammatory response syndrome (SIRS, syndrome secondary to severe infection), hospitalization, and mortality. These studies show that use of FOBLE may: improve post-operative liver function and rates of infection (Han 2012); improve Acute Physiology and Chronic Health Evaluation (APACHE) scores, a disease severity scoring system used in ICU settings, in patients with severe sepsis (Khor 2011) and pancreatitis (Xiong 2009); prevent infectious complications and incidence of SIRS, and reduce hospital stays in cancer patients undergoing major abdominal surgery (Jiang 2008, Liang 2008).

In addition, a 2010 meta analysis reviewed six RCTs conducted in Europe and Asia that compared parenteral nutrition with or without fish oil emulsion in post-operative patients (Wei 2010). Although in this study there was no significant impact on mortality, use of fish oil was associated with a significant reduction in infectious complications (relative risk RR 0.49, 95% confidence interval 0.26-0.93, P=0.03). The length of hospital stay was non-significantly decreased by over 3 days, with a decrease in 2.07 days in the intensive care unit (Wei 2010).

A prospective study of Omegaven among 661 patients with major abdominal surgery, abdominal sepsis, non-abdominal sepsis, serious trauma, or other diagnoses, and receiving TPN for three days or more, in 82 German hospitals, found that use of FOBLE resulted in: favorable effects on survival, infection rates, and length of stay, when administered in doses between 0.1 and 0.2 g/kg/day (Heller 2006). At doses of 0.15-0.2 g/kg/day, antibiotic requirements were 26% lower when compared with doses of <0.05 g/kg/day. After peritonitis and abdominal sepsis, the fish oil dose for minimizing length of intensive care unit stay was 0.23 g/kg/day (Heller 2006).

Rheumatoid Arthritis

Table 2 summarizes two human trials investigating IV fish oil emulsions in the treatment of active rheumatoid arthritis (RA) (Bahadori 2010, Leeb 2006). In a randomized, double blind, placebo controlled trial, Bahadori administered IV fish oil 0.2g/kg daily for 14 days in patients with moderate to severe RA, followed by oral fish oil for 20 weeks, and found that after only one week, as well as after two weeks, swollen joint count was significantly lower in the fish oil group (2010). This effect persisted to the end of 20 weeks/ end of oral

Table 2. Trials of Intravenous Fish Oil in Rheumatoid Arthritis

Reference	Design	Intervention	Outcome
Bahadori 2010	RDBPCT; N= 23 patients with moderate to severe RA	10% FOBLE (Omegaven, 0.2g/kg) OR 0.9% saline infusion daily x14d, followed by 0.05g fish oil/kg or placebo taken orally x20wk	Swollen joint count was significantly lower in the n-3 group compared with the placebo group after 1 and 2 weeks (P<.05). Tender joint count was NS lower in the n-3 group. At the end of oral treatment (20wk), both swollen and tender joint counts were significantly lower in the omega-3 FA group.
Leeb 2006	Open pilot study; N=34 patients with severe active RA (DAS28 score ≥4) (Fransen2009)	10% FOBLE (Omegaven, 0.1–0.2 g/kg) daily x7d	There was no change in DAS28 over the 7day treatment period, however there was a significant reduction thereafter from week 1 to ~1month (P< .001). 56% of patients achieved a reduction of the DAS28 > 0.6 (predefined endpoint) after 7days; 27% had improvement >1.2. Response to treatment, defined as 20 and 50% responses by the ACR criteria, were seen in 29 and 12% of patients, respectively after 1wk.

Key: ACR American College of Rheumatology (ACR) response criteria; DAS28 Disease activity score including a 28 joint count;

supplementation as well. Leeb conducted an open pilot trial in patients with severe RA, administering 0.1-0.2g/kg fish oil daily for seven days; there was a significant reduction in disease severity ratings over time ($p<0.001$) and tolerability was rated as "excellent" (Leeb 2006). Intravenous fish oil may represent a safe and rapidly acting strategy to control severe acute RA.

Dermatology: Psoriasis and Atopic Dermatitis

Table 3 summarizes three human trials investigating IV fish oil emulsions for the treatment of psoriasis or atopic dermatitis (Grimminger 1993, Mayser 2002, Mayser 1998). In patients with moderate to severe atopic dermatitis, IV fish oil for 10 days resulted in significant improvement in disease severity (visible by day 6) ($p<0.05$) compared to placebo (Mayser 2002). An earlier study by the same team examined patients hospitalized for chronic plaque type psoriasis (Mayser 1998). Treatment with Omegaven for 14 days resulted in significant reduction in the Psoriasis Activity Severity Index (PASI) ($p=0.048$) in the fish oil group compared to controls. A total of 16 of 43 patients (37%) in the fish oil group experienced a clinical response, defined as a reduction in PASI of 50% or greater, compared to 23% in the control group. Finally, Grimminger found that IV fish oil improved disease severity between 45-76% depending on the scoring measure ($p<0.05$ for all) in hospitalized patients with psoriasis involving 10% or more of their body surface area (1993). Remarkably, the treatment effect was evident within four to seven days of daily IV fish oil administration.

Finally, IV fish oils have been shown to reduce cardiac arrhythmias (Heidt 2009) and improve PN-associated liver disease (Le 2010), however these applications are beyond the scope of this paper.

Conclusion

Intravenously administered fish-derived omega-3 fatty acids have been studied for a number of indications including the treatment and prevention of serious infection and SIRS in hospitalized patients; treatment of acute rheumatoid arthritis; inflammatory skin conditions including psoriasis and atopic dermatitis; as well as the prevention of arrhythmias and liver disease. In these populations, IV fish oil has been demonstrated to improve immune function, shorten hospitalization, reduce mortality, and significantly decrease disease activity. In some cases, the rate of disease improvement is rapid, occurring within the first week of treatment. Although parenteral fish oil emulsions are not currently available to NDs, we hope that access to this safe and efficacious agent will be broadened in the future. ■

Table 3. Psoriasis and Atopic Dermatitis

Reference	Design	Intervention	Outcome
Mayser 2002	RDBPCT; N=22 patients hospitalized for moderate-to-severe atopic dermatitis	10% FOBLE (Omegaven, 100 mL 2x/d as 120minute peripheral infusion) OR conventional soybean oil based lipid emulsion x10d. Emollients only were allowed topically.	Marked improvement from baseline was seen in both groups but was more pronounced ($p < .05$) in the n-3 group. With response defined as a in disease severity score of ≥50%, 63.6% receiving n-3 and 11.1% receiving n-6 experienced a response. This was significant on days 9 to 11 ($p <0.05$) but not in the post-treatment phase. Authors describe relapse in some patients apparently treated subsequently with n-3 and psoralene-ultraviolet A (PUVA) infusion, but this is very poorly described.
Mayser 1998	RDBPCT; N= 83 patients hospitalized for chronic plaque-type psoriasis with severity score ≥15 on PASI	FOBLE (Omegavenous; 200 ml/d with 4.2g EPA+DHA) OR a conventional soybean oil based emulsion (Lipovenous; EPA+DHA <0.1g/100 ml) x14d	Total PASI score by 11.2 +/- 9.8 in the n-3 group and by 7.5 +/- 8.8 in the n-6 group ($p = 0.048$). Response (decrease in PASI ≥50%) was seen in 37% of patients receiving n-3 and 23% of those receiving n-6.
Grimminger 1993	RDBPCT; N=20 patients hospitalized for acute guttate psoriasis with ≥10% body surface area involvement	FOBLE (Omegavenous; 50mL 2x daily with 2.1g EPA+ 21g DHA) OR a conventional soybean oil based emulsion (Lipovenous; EPA+DHA <0.1 g/100 ml) x10d	The n-6 group had a 16-25% improvement from baseline within 10 days. In contrast, disease severity by 45% and 76% within 10 days ($P < 0.05$ for each variable) in the n-3 group.

Key: PASI Psoriasis Area and Severity Index; RCT randomized controlled trial; RDBPCT randomized double blind placebo controlled trial;

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Questions

1. Fish oil based lipid emulsion, aka FOBLE, has been evaluated in RCTs for which of the following areas of application:
a) rheumatoid arthritis
b) infection
c) post abdominal surgery
d) all of the above

2. The most widely researched parenteral lipid emulsion featuring omega-3 fatty acids is SMOFLipid 20%
a) true
b) false

3. Which of the following is true about FOBLE pharmacology?
a) IV delivery circumvents the slower n-3 incorporation rate into phospholipid membranes following oral administration
b) Incorporation of EPA into leukocyte and platelet membranes after IV administration occurs within 30 minutes
c) FOBLE has been shown to increase risk of bleeding post-operatively
d) All of the above

4. In the critical care setting, FOBLE has been shown to:
a) decrease levels of inflammation in patients with sepsis or SIRS
b) decrease complications including infection rates in post-operative patients
c) decrease the length of hospitalization in patients undergoing abdominal surgery
d) all of the above

5. FOBLE has been shown to reduce the immune response to LPS, which may increase risk of serious infections.
a) true
b) false

6. According to a 2010 meta analysis including six RCTs conducted in Europe and Asia and parenteral nutrition with omega-3 oils was associated with:
a) significant 50% reduction in mortality, RR 0.50.
b) significant reduction in infectious complications, RR 0.49
c) highly significant reduction in the length of hospital stay, with a decrease of over 3 days overall, and a decrease in 2.07 days in the intensive care unit.
d) all of the above

7. A German prospective study of Omegaven found that in patients hospitalized for major abdominal surgery, sepsis, or serious trauma, FOBLE doses of 0.15-0.2 g/kg/day, Omegaven reduced antibiotic requirements 26%, compared with lower doses of <0.05 g/kg/day.
a) true
b) false

8. The same study found that after peritonitis and abdominal sepsis, FOBLE reduced the length of intensive care unit stay when given at doses of 0.23 g/kg/day.
a) true
b) false

9. FOBLE has been shown to benefit moderate to severe rheumatoid arthritis. The length of time required to obtain an effect appears to be:
a) approximately ≥1 week
b) approximately ≥2 weeks
c) approximately 1 month
d) none of the above

10. FOBLE has been demonstrated to improve which of the following chronic inflammatory skin condition?
a) psoriasis
b) vitiligo
c) eczema
d) a and c
e) b and c

FAX OR EMAIL ANSWERS TO: 416.703.6392 or philip@ihpmagazine.com

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