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# Parenteral Fish Oil Lipid Emulsions in the Critically Ill: A Systematic Review and Meta-Analysis

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## Abstract

*Introduction*: ω-3 Polyunsaturated fatty acids contained in fish oils (FO) possess major anti-inflammatory, antioxidant, and immunologic properties that could be beneficial during critical illness. We hypothesized that parenteral FO-containing emulsions may improve clinical outcomes in the critically ill. *Methods*: We searched computerized databases from 1980–2012. We included randomized controlled trials (RCTs) conducted in critically ill adult patients that evaluated FO-containing emulsions, either in the context of parenteral nutrition (PN) or enteral nutrition (EN). *Results*: A total of 6 RCTs (n = 390 patients) were included; the mean methodological score of all trials was 10 (range, 6–13). When the results of these studies were aggregated, FO-containing emulsions were associated with a trend toward a reduction in mortality (risk ratio [RR], 0.71; 95% confidence interval [CI], 0.49–1.04; $P$ = .08; heterogeneity $I^2$ = 0%) and a reduction in the duration of mechanical ventilation (weighted mean difference in days [WMD], −1.41; 95% CI, −3.43 to 0.61; $P$ = .17). However, this strategy had no effect on infections (RR, 0.76; 95% CI, 0.42–1.36; $P$ = .35) and intensive care unit length of stay (WMD, −0.46; 95% CI, −4.87 to 3.95; $P$ = .84, heterogeneity $I^2$ = 75%). *Conclusion*: FO-containing lipid emulsions may be able to decrease mortality and ventilation days in the critically ill. However, because of the paucity of clinical data, there is inadequate evidence to recommend the routine use of parenteral FO. Large, rigorously designed RCTs are required to elucidate the efficacy of parenteral FO in the critically ill. (*JPEN J Parenter Enteral Nutr*. 2014;38:20-28)

## Keywords

fish oils; lipid emulsions; critically ill; meta-analyses

Parenteral lipid emulsions (LEs) are a dense source of energy and a source of essential fatty acids. As such, they lend themselves to strategic inclusion in parenteral nutrition (PN) formulations to avoid metabolic complications of glucose overfeeding.[1] Furthermore, the fatty acids composing LEs are active, with complex immunologic properties influencing biochemical pathways and signal transduction, which is of particular significance during critical illness.[2,3] LEs commonly used in critically ill patients are typically rich in long-chain triglycerides (LCTs), especially linoleic acid (ω-6 polyunsaturated fatty acids [PUFAs], 18:2 ω-6).[4] Nonetheless, over the past decade, different alternative oil-based LEs or "soybean-sparing" strategies, including fish oil (FO), olive oil, and medium-chain triglycerides (MCTs), have been developed.[5]

The current literature suggests that intravenous (IV) soybean oil may adversely affect systemic inflammation, immune status, and clinical outcomes.[6] In severe sepsis and trauma, parenteral LCTs, derived from soybean oil, might promote production of proinflammatory eicosanoids and increase oxidative stress.[7,8] In 1998, a meta-analysis of PN suggested that inclusion of soybean oil–based lipid emulsions might be detrimental, at least in the most seriously ill patients.[9] Immunomodulation with the ω-3 PUFAs, eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), is recognized for the ability to modify leukocyte activity; downregulate expression of nuclear factor–κB (NF-κB), peroxisome proliferator-activated receptor γ, intracellular adhesion molecule 1, and E-selectin; and decrease cytokine production.[10] In fact, IV infusion of FO leads to a rapid incorporation of ω-3 fatty acids in leukocyte cell membrane phospholipids, increasing the ratio of ω-3 to

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ω-6 fatty acids in different cell types[11] and displacing ω-6 fatty acids from the cell membranes of immune cells, which is a major cause of modulating systemic inflammation.[12]

However, clinical trials using parenteral FO have provided controversial results.[13] Because available research provides conflicting data on the effects of parenteral FO in critically ill patients, their influence on inflammatory processes and clinical outcomes remains unclear. In 2009, the Canadian guidelines[14] concluded that there were insufficient data to make a recommendation about FO-containing emulsions. Nevertheless, the European Society of Parenteral and Enteral Nutrition[15] suggests that the optimal PN regimen should include FO and concludes that FO-enriched LEs probably decrease length of stay in critically ill patients (Grade B).[15]

Over the past few years, several trials have been published of parenteral FO-containing LEs in the critically ill. Some of these trials have been included in prior meta-analyses, but these meta-analyses have included trials of both elective surgical patients and critically ill patients,[16,17] and a more recent meta-analysis also has included trials that reported only biochemical and immunologic outcomes.[18] To inform clinical recommendations pertinent to the critically ill, studies of elective surgery and critically ill patients should not be combined as the treatment effects of the nutrition strategies may differ.[19]

The purpose of the current study was to provide an up-to-date systematic review and meta-analysis of all randomized controlled trials (RCTs) of FO-containing LEs on relevant clinical outcomes in the critically ill.

## Methods

### *Study Identification*

We conducted a systematic review of the published literature to identify all relevant clinical trials using keywords or MeSH headings containing *randomized, blind, clinical trial, nutritional support, parenteral nutrition, omega-3 fatty acids, fish oils, lipid emulsions, critical illness*, and *critically ill*. To locate these articles, we performed computerized searches on MEDLINE, EMBASE, CINAHL, the Cochrane Controlled Trials Register, and the Cochrane Database of Systematic Reviews from 1980 to May 2012. We also searched our personal files, and comprehensive review articles were searched for additional original studies. No language restrictions were placed on the searches. Abstracts from scientific meetings had been accepted for inclusion into this systematic review if a copy of the manuscript was available to complete the data abstraction.

### *Study Selection Criteria*

We included original studies only if they met the following inclusion criteria: (1) study design: randomized clinical, parallel group, controlled trials (RCTs); (2) population: critically ill adult patients (>18 years of age); (3) intervention: parenteral FO LE vs placebo (enteral, parenteral, or both); and (4) study outcomes: prespecified outcomes included one of the following: mortality, intensive care unit (ICU) and hospital length of stay (LOS), infectious complications, and other clinically important complications. We excluded the clinical studies that reported only biochemical, metabolic, immunologic, or nutrition outcomes. Furthermore, we excluded those trials performed in elective surgery patients even if cared for in an ICU. Critically ill patients were defined as patients admitted to an ICU who had an urgent or life-threatening complication (high baseline mortality rate ≥5%) to distinguish them from patients with elective surgery who are also cared for in some ICUs but have a low baseline mortality rate (<5%), a low requirement for mechanical ventilation, and a low incidence of infections, including ICU-acquired pneumonia.

All original studies were abstracted in duplicate, independently by 2 reviewers, using a data abstraction form with a scoring system, which has been used previously. Disagreement on the individual scores of each of the categories was resolved by consensus between both reviewers. We attempted to contact the authors of included studies and requested additional information not contained in published articles. We scored the methodological quality of individual trials considering the following key features of high-quality studies: (1) extent to which randomization was concealed, (2) blinding, (3) analysis based on the intention-to-treat (ITT) principle, (4) comparability of groups at baseline, (5) extent of follow-up, (6) description of treatment protocol and cointerventions, and (7) definition of clinical outcomes. Each individual study was scored from 0–14. We designated a study as level 1 if all of the following criteria were fulfilled: concealed randomization, blinded outcome adjudication, and an ITT analysis. Meanwhile, a study was considered level 2 if any one of the above characteristics was unfulfilled.

### *Data Synthesis*

The primary outcome of the systematic review was overall mortality. From all studies, we combined hospital mortality where reported (specified or assumed to be hospital if not specified). If hospital mortality was not reported, we used ICU mortality, or if ICU mortality not reported, we used 28-day mortality. Secondary outcomes included infections and ICU and hospital LOS (when reported). We included RCTs conducted in critically ill adult patients that evaluated parenteral FO-containing emulsions, in the context of patients receiving PN or enteral nutrition (EN). Given that PN-based strategies contained a non–fish oil–based emulsion and the EN-based strategies did not, we did a sensitivity analysis excluding the studies of EN-based strategies.

We used definitions of infections as defined by the authors in their original articles. If studies had more than 1 experimental intervention, these were each considered separately. We combined data from all trials to estimate the pooled risk ratio

**Table 1.** Details and Clinical Outcomes of Included Trials on Fish Oil–Containing Emulsions in PN-Fed Patients.

| Fish Oil–Containing Emulsions in PN-Fed Patients vs LCT or LCT + MCT | | | | | |
|---|---|---|---|---|---|
| Study | Population | Methods (Score) | Intervention | Mortality | Infections |
| Grecu et al,[59] 2003 | Patients with abdominal sepsis (n = 54) (15/54 in ICU) | CR: yes<br>ITT: yes<br>Blinding: double (12) | PN + FO–based LE (10% FO) plus LCTs vs PN with LCT | FO-based LE + LCT: ICU, 2/28 (7%)<br>LCT: ICU, 3/26 (12%) | FO-based LE: VAP, 0/8<br>LCT: VAP, 1/7 (14%) |
| Friesecke et al,[60] 2008 | Medical ICU patients (n = 166) | CR: yes<br>ITT: yes<br>Blinding: double (10) | PN + Lipofundin MCT (50% LCT + 50% MCT) + FO-based LE (10% FO) vs Lipofundin MCT (50% LCT + 50% MCT) | LCT + MCT + FO: 28 days, 18/83 (22%)<br>LCT + MCT: 28 days, 22/82 (27%) | LCT+ MCT+ FO: 10/83 (12%)<br>LCT + MCT: 11/82 (13%) |
| Wang et al,[61] 2009 | Severe acute pancreatitis patients in ICU (n = 56) | CR: no<br>ITT: yes<br>Blinding: double (11) | PN + FO–based LE (10% FO) plus Lipovenos (LCTs, soybean oil) (ω-3:ω-6 ratio was 1:4) vs PN with Lipovenos (LCTs, soybean oil). Both received same amounts of lipids (1 g/kg/d) | FO-based LE: ICU, 0/28<br>LCT: ICU, 2/28 (7%) | FO-based LE: 6/28 (21%)<br>LCT: 9/28 (32%) |
| Barbosa et al,[63] 2010 | ICU patients with SIRS or sepsis requiring PN (n = 25) | CR: yes<br>ITT: yes<br>Blinding: single (10) | PN + Lipoplus (50% MCT, 40% LCT soybean oil, 10% fish oil) vs Nutriflex LipidSpecial (50% MCT, 50% LCT, soybean oil). Both received same amounts of lipids (~1 g/kg/d) | MCT + LCT + FO: 5 days, 2/13 (15%); 28 days, 4/13 (31%)<br>MCT + LCT: 5 days, 1/10 (10%); 28 days, 4/10 (40%) | MCT + LCT + FO: NA<br>MCT + LCT: NA |

CR, concealed randomization; FO, fish oil; ICU, intensive care unit; ITT, intention to treat; LCT, long-chain triglycerides; LE, lipid emulsion; MCT, medium-chain triglycerides; NA, nonattributable; PN, parenteral nutrition; SIRS, systemic inflammatory response syndrome; VAP, ventilator-associated pneumonia.

(RR) with 95% confidence intervals (CIs) for death and infectious complications and overall weighted mean difference (WMD) with 95% confidence intervals for LOS data. All analyses, except the test for asymmetry, were conducted using RevMan 5.1 (Cochrane IMS, Oxford, UK). Pooled RRs were calculated using the Mantel-Haenszel estimator, and WMDs were estimated by the inverse variance approach. The random effects model of DerSimonian and Laird[20] was used to estimate variances for the Mantel-Haenszel and inverse variance estimators.[21] RRs were undefined and excluded for studies with no event in either arm. When possible, studies were aggregated on an ITT basis. The presence of heterogeneity was tested by a weighted Mantel-Haenszel $\chi^2$ test and quantified by the $I^2$ statistic as implemented in RevMan. The possibility of publication bias was assessed by generating funnel plots and testing asymmetry of outcomes using methods proposed by Rucker and colleagues.[22] We considered $P < .05$ to be statistically significant and $P < .20$ as an indicator of trend.

## Results

### *Study Identification and Selection*

A total of 44 relevant citations were identified from the search of computerized bibliographic databases and a review of reference lists from related articles. Of these, we excluded 38 due to the following reasons: 22 trials[23-44] did not include ICU patients (mostly elective surgery and cancer patients), 10 trials[45-54] did not evaluate clinically important outcomes, 2 trials[55,56] were published as abstracts and we were unable to obtain the data from the author to complete our data abstraction process, 1 trial[57] was conducted in a pediatric population, 1 trial[4] had a short duration of intervention (12 hours of LE infusion during the first day), 1 trial included patients with poisoning and was not representative of ICU patients,[58] and 1 article was a systematic review.[16] In the end, 6 RCTs[59-64] enrolling a total of 390 patients met the inclusion criteria and were included in this systematic review (see Tables 1–4). Among these trials, we found 5 level 1 studies[59,60,62-64] and 1 level 2 study.[61] Furthermore, among RCTs in PN-fed patients, 1 trial compared the LCT + MCT + FO emulsion with an MCT + LCT emulsion,[63] and 3 trials compared an FO-containing emulsion mixed with LCT or LCT/MCT with an LCT or LCT + MCT mixture.[59-61] Among the 2 RCTs evaluating EN-fed patients, 1 trial compared supplementation with IV FO with normal saline,[62] and the other trial compared supplementation of EN with an FO-containing emulsion with standard EN alone.[64]

The authors reached 100% agreement for inclusion of relevant trials in this review. The mean methodological score of all trials was 10 (range, 9-12). Randomization was concealed in 5 of 6 (83%) trials, ITT analysis was performed in 6 of 6 (100%) trials, and 5 of 6 (83%) trials were double blinded.

**Table 2.** Details and Clinical Outcomes of Included Trials on Fish Oil–Containing Emulsions in EN-Fed Patients.

| Fish Oil–Containing Emulsions in EN-Fed Patients vs None | | | | | |
|---|---|---|---|---|---|
| Study | Population | Methods (Score) | Intervention | Mortality | Infections |
| Gupta et al,[64] 2011 | ICU patients with suspected ARDS (n = 61) | CR: yes<br>ITT: yes<br>Blinding: double (9) | EN (standard diet) + FO-based LE 10% (ω-3:ω-6 ratio was 1:4) vs EN (standard diet) | FO-based LE: ICU, 7/31 (23%); hospital, 9/31 (29%)<br>Standard EN: ICU, 13/30 (43%); hospital, 14/30 (47%) | FO-based LE: NA<br>Standard EN: NA |
| Khor et al,[62] 2011 | ICU patients with severe sepsis/ septic shock (n = 28) | CR: yes<br>ITT: yes<br>Blinding: double (9) | Supplementation with 100 mL 10% FO-based LE (10 g refined fish oil, EPA 12.5–28.2 g/L, DHA 14.4–30.9 g/L) vs 100 mL 0.9% normal saline | Omegaven: NA<br>Saline: NA | FO-based LE: NA<br>Saline: NA |

ARDS, acute respiratory distress syndrome; CR, concealed randomization; DHA, docosahexaenoic acid; EN, enteral nutrition; EPA, eicosapentaenoic acid; FO, fish oil; ICU, intensive care unit; ITT, intention to treat; LE, lipid emulsion; NA, nonattributable.

**Table 3.** Outcomes of Included Trials on Fish Oil–Containing Emulsions in PN-Fed Patients.

| Fish Oil–Containing Emulsions in PN-Fed Patients vs LCT or LCT + MCT | | | |
|---|---|---|---|
| Study | LOS Days | Ventilation Days | Other |
| Grecu et al,[59] 2003* | FO-based LE 10%: ICU, 3.32 ± 1.48 (8); hospital, 11.68 ± 2.04 (28)<br>LCT: ICU, 9.28 ± 3.08 (7); hospital, 20.46 ± 3.27 (26) | FO-based LE: 2.83 ± 1.62 (8)<br>LCT: 5.23 ± 2.80 (7) | Patients undergoing reoperation for septic episode: FO-based LE, 2/28 (7%); LCT, 8/26 (31%) |
| Friesecke et al,[60] 2008 | FO: ICU, 28 ± 25 (83)<br>LCT: ICU, 23 ± 20 (82) | LCT + MCT + FO: 22.8 ± 22.9 (83)<br>LCT + MCT: 20.5 ± 19.0 (82) | Urinary tract infections: LCT + MCT + FO, 6/83 (7%); LCT + MCT, 4/82 (5%)<br>Catheter-related infections: LCT + MCT + FO, 1/83 (1%); LCT + MCT, 3/83 (4%)<br>Total EN energy intake (kcal/kg): LCT + MCT + FO, 22.2 ± 5.5; LCT + MCT, 21.6 ± 5.6 |
| Wang et al,[61] 2009 | NA | NA | Surgery of infected pancreatic necrosis: FO-based LE, 3/28 (11%); LCT, 6/28 (21%) |
| Barbosa et al,[63] 2010 | MCT + LCT + FO: ICU, 12 ± 14.4[a] (13); hospital, 22 ± 25.2[a] (13)<br>MCT + LCT: ICU, 13 ± 12.6[a] (10); hospital, 55 ± 50.6[a] (10) | MCT + LCT + FO: 10 ± 14.4 (13)<br>MCT + LCT: 11 ± 12.64 (10) | MCT + LCT + FO: 2057 ± 418 kcal<br>MCT + LCT: 1857 ± 255 kcal |

FO, fish oil; ICU, intensive care unit; LCT, long-chain triglycerides; LE, lipid emulsion; LOS, length of stay; MCT, medium-chain triglycerides; NA, nonattributable; PN, parenteral nutrition. The numbers in parentheses represent the number of patients.
*Data obtained from the author. Eight out of 28 in the FO group and 7 out of 26 in the LCT group were in the ICU.
[a]Converted standard error mean (SEM) to standard deviation (SD).

## *Meta-Analyses of Primary Outcome*

*Overall effect on mortality.* When the results of 5 RCTs[59-61,63,64] that evaluated mortality as one of the outcomes were statistically aggregated, FO-containing lipid emulsions were associated with a trend toward a reduction in mortality (RR, 0.71; 95% CI, 0.49–1.04; $P = .08$; see Figure 1). The test for heterogeneity was not significant ($P = .89$, $I^2 = 0\%$). When a sensitivity analysis was done without the Gupta et al[64] study, a similar point estimate was observed, but the 95% CI was considerably wider (RR, 0.76; 95% CI, 0.48–1.21; $P = .25$; heterogeneity $I^2 = 0\%$).

## *Secondary Outcomes*

*Overall effect on infectious complications.* When the data from 3 RCTs[59-61] of FO emulsions in PN-fed patients that reported overall infections were aggregated, FO-containing emulsion strategies had no effect in reducing infectious complications (RR, 0.76; 95% CI, 0.42–1.36; $P = .35$; heterogeneity $I^2 = 0\%$) (Figure 2).

*Overall effect on ICU length of stay.* When the data from the 5 RCTs[59,60,62-64] that reported on this outcome were aggregated (including the studies of EN-fed patients), no effect on ICU

**Table 4.** Outcomes of Included Trials on Fish Oil–Containing Emulsions in EN-Fed Patients.

| Fish Oil–Containing Emulsions in EN-Fed Patients vs None | | | |
|---|---|---|---|
| Study | LOS Days | Ventilation Days | Other |
| Gupta et al,[64] 2011 | FO-based LE: ICU, 15.96 ± 7.57 (31); hospital, 21.5 ± 13.49 (31)<br>Standard EN: ICU, 15.88 ± 6.47 (30); hospital, 26.63 ± 18.22 (30) | FO-based LE: 11.78 ± 10.63 (31)<br>Standard EN: 10.71 ± 14.55 (30) | FO-based LE: NA Standard EN: NA |
| Khor et al,[62] 2011 | FO-based LE: ICU, 10.3 ± 8.4 (14); hospital, 19.6 ± 7.4 (14)<br>Saline: ICU, 8.4 ± 6.5 (13); hospital, 17.5 ± 6.0 (13) | FO-based LE: 13.0 ± 10.1 (9)<br>Saline: 11.6 ± 9.5 (5) | FO based LE: NA<br>Saline: NA |

EN, enteral nutrition; FO, fish oil; ICU, intensive care unit; LE, lipid emulsion; LOS, length of stay; NA, nonattributable. The numbers in parentheses represent the number of patients.

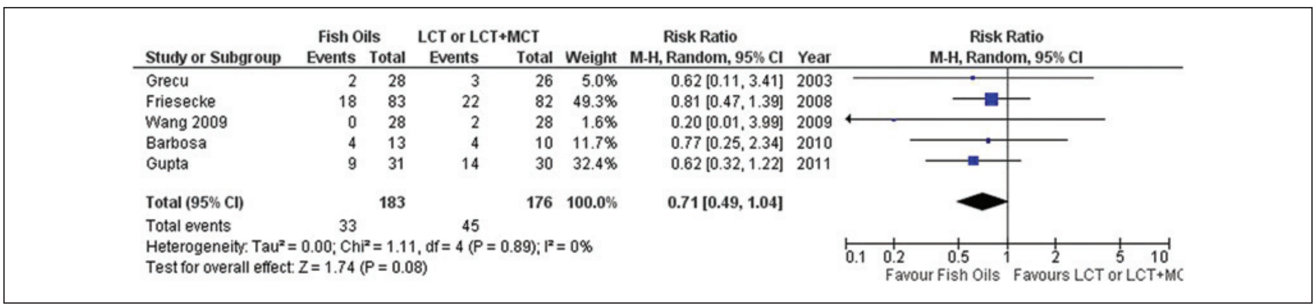


**Figure 1.** Effects of fish oil lipid emulsion strategies on mortality (n = 5). CI, confidence interval; LCT, long-chain triglyceride; MCT, medium-chain triglyceride.

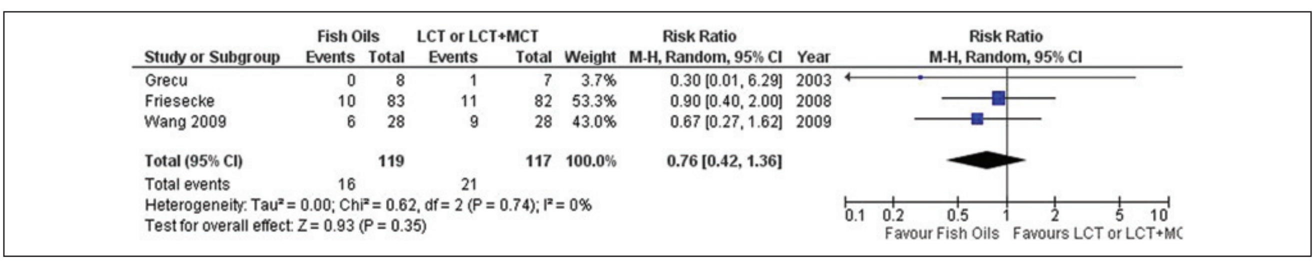


**Figure 2.** Effects of parenteral fish oil lipid emulsions on infections (n = 3). CI, confidence interval; LCT, long-chain triglyceride; MCT, medium-chain triglyceride.

LOS was observed (WMD, −0.46; 95% CI, −4.87 to 3.95; $P$ = .84; heterogeneity $I^2$ = 75%). Similarly, when a sensitivity analysis was done excluding the studies of EN-fed patients,[62,64] no effect on ICU LOS was observed (WMD, −1.13; 95% CI, −8.96 to 6.69; $P$ = .78; heterogeneity $I^2$ = 78%).

*Overall effect on ventilator days.* When the 5 RCTs[59,60,62-64] reporting ventilator days were aggregated, FO-containing emulsions showed a trend toward reduction in the duration of mechanical ventilation days (WMD, −1.41; 95% CI, −3.43 to 0.61; $P$ = .17); heterogeneity was not significant ($P$ = .59; $I^2$ = 0%) (Figure 3). When a sensitivity analysis excluding the 2 EN-fed trials[62,64] was done, there was still a trend toward a reduction in the duration of mechanical ventilation (WMD, −1.81; 95% CI, −3.98 to 0.36; $P$ = .10; heterogeneity $I^2$ = 0%).

*Risk of publication bias in included trials.* There was no indication that publication bias influenced the observed aggregated results. Funnel plots were created for each study outcome (data not shown), and the tests of asymmetry were not significant for any outcome measure (mortality, $P$ = .55; infections, $P$ = .39; ICU LOS, $P$ = .30; and mechanical ventilation days, $P$ = .28).

| Study or Subgroup | Fish Oils Mean | Fish Oils SD | Fish Oils Total | Non Fish Oils Mean | Non Fish Oils SD | Non Fish Oils Total | Weight | Mean Difference IV, Random, 95% CI | Year |
|---|---|---|---|---|---|---|---|---|---|
| Grecu | 2.83 | 1.62 | 8 | 5.23 | 2.8 | 7 | 73.3% | -2.40 [-4.76, -0.04] | 2003 |
| Friesecke | 22.8 | 22.9 | 83 | 20.5 | 19 | 82 | 9.9% | 2.30 [-4.12, 8.72] | 2008 |
| Barbosa | 10 | 14.4 | 13 | 11 | 12.64 | 10 | 3.3% | -1.00 [-12.07, 10.07] | 2010 |
| Khor | 13 | 10.1 | 9 | 11.6 | 9.5 | 5 | 3.6% | 1.40 [-9.22, 12.02] | 2011 |
| Gupta | 11.78 | 10.63 | 31 | 10.71 | 14.55 | 30 | 9.9% | 1.07 [-5.34, 7.48] | 2011 |
| **Total (95% CI)** | | | **144** | | | **134** | **100.0%** | **-1.41 [-3.43, 0.61]** | |

Heterogeneity: Tau² = 0.00; Chi² = 2.81, df = 4 (P = 0.59); I² = 0%
Test for overall effect: Z = 1.37 (P = 0.17)

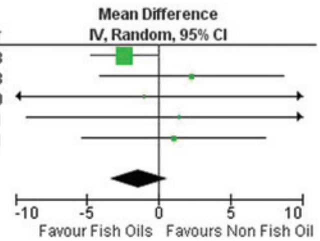


**Figure 3.** Effects of parenteral fish oil lipid emulsions on ventilation days (n = 5). CI, confidence interval.

## Discussion

Critical illness is characterized by hyperinflammation, immune dysfunction, and multiple organ failure. In this context, anti-inflammatory and immunomodulatory effects of FO-containing LEs may represent an important therapeutic option for critically ill patients with systemic inflammatory response syndrome (SIRS). Nonetheless, according to current evidence, FO administration in the critically ill is still a subject of debate. Therefore, we have systematically reviewed 6 eligible RCTs[59-64] in ICU patients for evaluating the effects of parenteral FO-based strategies in the context of PN- or EN-fed patients. In this meta-analysis, we found that FO-containing emulsions may be associated with a tendency to reduce mortality and ventilation days in the critically ill. At the same time, we did not observe any effect on infectious complications or the duration of ICU LOS. Although no major benefit can be confirmed by our analysis, we observe no harm conferred by FO-containing emulsions, and given that the upper end of the confidence limit on the effect on mortality is 1.04, the probability of increased mortality is extremely small.

Our systematic review is the most updated and pertinent to critically ill patients as it contains only RCTs evaluating relevant clinical outcomes in the critically ill. Unfortunately, with the exception of 1 trial,[60] most trials included in this systematic review were relatively small studies with fewer than 100 patients and thus inadequate to detect a clinically important treatment effect of FO-containing emulsions on mortality. However, the advantage of meta-analytic techniques is that they can combine across studies to gain a more precise effect of treatment effect. Furthermore, since the mortality effect seems to be greater than the effect on infectious complications, it is plausible that the mortality effect could be mediated by different mechanisms other than by reducing infection, although this is only a postulate and not supported by our data. According to our analysis, there is no indication of publication bias. However, the sample size was small because 3–5 RCTs were included in the analyses for each outcome; therefore, we should interpret these results with caution because big *P* values may be due to lack of power.

Van der Meij et al[16] published the results of a systematic review of FO in cancer, surgery, and critical care on clinical effects, incorporation, and washout of oral or enteral compared with parenteral supplementation. In their report of critically ill patients, when the authors evaluated the effects of 4 RCTs supplementing FO-containing emulsions in PN, they concluded that ω-3 PUFAs did not demonstrate any beneficial effects on clinical outcomes. However, our systematic review is not comparable with the study by van der Meij et al insofar as they included RCTs that we excluded due to a short duration of intervention (12 hours) as well as another trial performed in elective surgical patients.

In another meta-analysis including RCTs performed with elective surgery and critically ill patients, Pradelli et al[17] demonstrated that parenteral FO-enriched LEs were associated with a statistically and clinically significant reduction in infections (RR, 0.61; 95% CI, 0.45–0.84) and LOS, both in the ICU (−1.92; −3.27 to −0.58) and in the hospital (−3.29; −5.13 to −1.45).[17] Notwithstanding, these results cannot be compared with our findings because our meta-analysis is the first and more pertinent to critically ill patients, as it contains only trials evaluating relevant clinical outcomes for intensive care.

More recently, Palmer et al,[18] in another meta-analysis of the role of ω-3 fatty acid–supplemented PN in critically ill adults, concluded that parenteral FO does not improve mortality, infectious complications, and ICU LOS in comparison with standard PN. These results are slightly different from our findings. We found a trend toward a reduction in mortality, and our other major finding was a tendency toward a reduction in mechanical ventilation days. Furthermore, we believe that these differences were largely due to the difference in the studies included in the different reviews. In fact, Palmer et al[18] included trials that did not evaluate relevant clinical outcomes in the critically ill.[50] In addition, they included both studies published by Wang et al in 2008[37] and 2009.[61] However, we decided to include the study published in 2009 and exclude the previous study because it did not include ICU patients and did not report on relevant clinical outcomes. In addition, we excluded 2 unpublished studies by Leiderman et al[55] and Ignatenko et al,[56] as both are published as abstracts and we have not had any response from the investigators, which was needed to complete our data abstraction form. Finally, we included 2 trials[62,64] on parenteral FO-based emulsions performed in enterally fed patients that were excluded in the systematic review by Palmer et al.

Nonetheless, although studies included in both systematic reviews are different, current evidence derived from both meta-analyses provides similar conclusions that there is insufficient evidence to recommend the supplementation of PN in critically ill adult patients with ω-3 fatty acids.

The parenteral route may be a more reliable strategy to provide FO than the enteral route due to better bioavailability, but the optimal dose and timing are still unknown. Most trials supplementing parenteral FO have used between 0.1 and 0.2 g/kg/d FO, and lipids were started within the first 24–48 hours after admission to the ICU. A daily dose of 0.1 and 0.2 g/kg/d has been supported by the analysis of a database in 661 critically ill patients,[65] including patients with severe sepsis, where best outcome data were found in this dose range. Furthermore, this dose would be able to decrease available arachidonic acid (derived from ω-6 fatty acids) and produce balanced pro-/anti-inflammatory effects influencing physiological end points.[66]

The anti-inflammatory properties of FO have been described and exhaustively studied in many experimental and clinical studies.[67] The involved mechanisms include the following: (1) inhibition of the ω-3 PUFAs on the Toll-like receptor–NF-κB axis, controlling gene expression and thus downregulating the synthesis of proinflammatory cytokines[68]; (2) synthesis of DHA-derived lipid mediators such as Resolvin D1 and Protectin D1, which are able to attenuate neutrophil migration[69]; and (3) modulation of vagal tone–restoring parasympathetic activity, which has demonstrated potential anti-inflammatory effects.[70]

Clinical trials included in our systematic review have evaluated mechanistic effects of parenteral FO. In fact, Barbosa et al[63] demonstrated a significant reduction in plasma interleukin (IL)–6 and IL-10 levels in the FO group ($P < .001$). Similarly, Wang et al[61] demonstrated an increase in the IL-10 levels and human leukocyte antigen DR (HLA-DR) expression, as well as concomitantly a significant reduction in C-reactive protein levels, in patients with severe acute pancreatitis. In contrast, Friesecke et al[60] reported that administration of a mixed MCT/LCT/FO LE in critically ill patients with SIRS had no effect on inflammatory markers such as IL-6 and monocyte HLA-DR expression.

Meanwhile, in 2 randomized, open-label studies in patients with sepsis, Mayer et al[48,50] reported a significant reduction in tumor necrosis factor–α, IL-1β, IL-6, IL-8, and IL-10 production by cultured monocytes in patients with sepsis receiving a soybean oil–FO mix compared with those receiving soybean oil alone. Unfortunately, both trials did not report any relevant clinical outcomes, and therefore they were not included in our review.

Unfortunately, the current evidence from RCTs[59-64] and our systematic review and meta-analysis is too weak and sparse to make definitive and conclusive recommendations about the role of FO-containing emulsions in the treatment of critically ill adult patients. Currently, the superiority of FO to MCT/LCT for ICU patients cannot be asserted. Undoubtedly, more research is needed to clarify the role of FO-containing emulsions in the critically ill population. As a first step in a prospective study, it would be needed to determine the optimal dose able to optimize the effects on underlying inflammatory, immunologic, and metabolic processes that is at the same time safe and well tolerated by patients with SIRS. Recently, the position paper by the American Society for Parenteral and Enteral Nutrition about the clinical role for alternative intravenous LEs[5] suggests that dosing studies on the FO-containing emulsions need to be conducted to further define the optimal dose range to obtain the desired effects and avoid undesirable side effects.[5] Currently, the Fish OIL optimal dosE Determination study (FOILED; ClinicalTrials.gov NCT01146821)[71] is evaluating the safety and efficacy of parenteral FO doses of 0.20 g/kg and 0.50 g/kg, compared with a control group, in critically ill patients with sepsis.

The strength of our meta-analysis is based on the fact that we have used several methods to reduce bias (comprehensive literature search, duplicate data abstraction, specific criteria for searching and analysis) and have focused on clinically important primary outcomes for ICU patients. Nevertheless, we are aware that our meta-analysis has several limitations, including the small number of trials included to evaluate different outcomes and the heterogeneity of the included ICU study populations, which may limit the reliability of the analysis and the strength of our conclusions.

## Conclusion

In this meta-analysis, we have demonstrated that FO-containing LEs may be able to decrease mortality and ventilation days in the critically ill. However, because of the paucity of clinical data, there is inadequate evidence to recommend the routine use of FO-containing emulsions in PN and/or as a therapeutic strategy in an EN-fed patient population. Large, rigorously designed RCTs that can elucidate the efficacy of parenteral FO in this patient population are clearly warranted.

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