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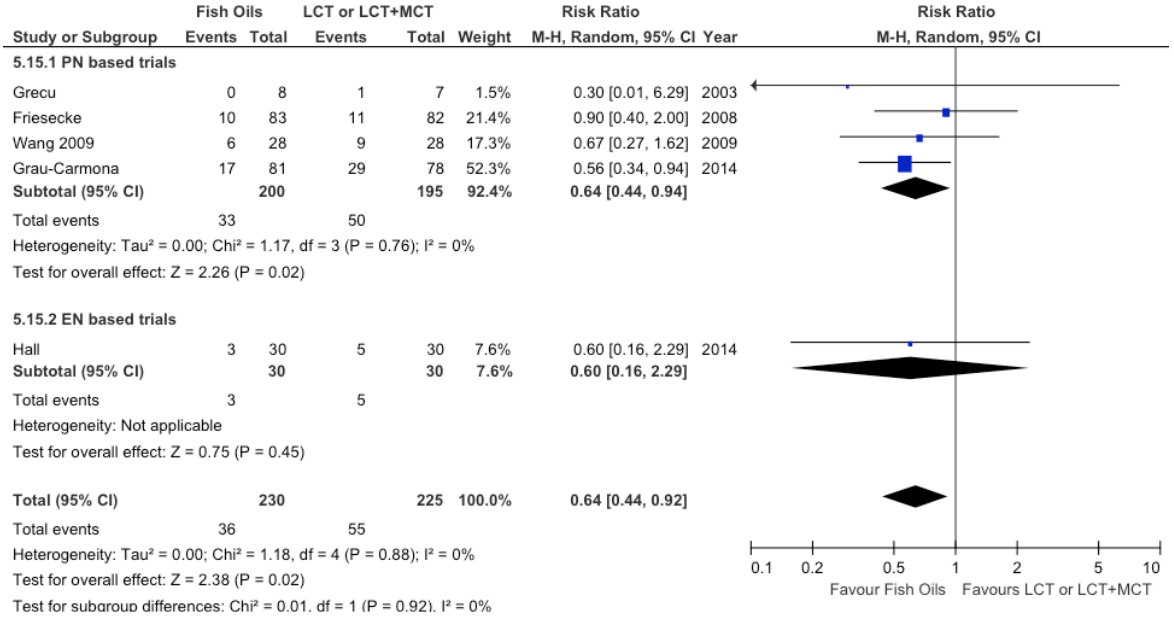
Fish Oil Containing Emulsions: When Fat Seems to Improve Clinical Outcomes in the Critically Ill

Third generation lipid emulsions were developed as a soybean oil sparing strategy with the aim to provide ω-3 polyunsaturated fatty acids (ω-3-PUFAs) derived from fish oil (FO), such as eicosapentanoic acid (EPA) and decosahexanoic acid (DHA), and reduce the amount of ω-6 polyunsaturated fatty acids (ω-6-PUFAs), which have been associated with negative effects on immune function and inflammatory response [1,2]. Over the last decade, several relatively small phase II randomized controlled trials (RCTs) have evaluated clinical and mechanistic effects of intravenous (I.V.) FO containing emulsions in intensive care unit (ICU) patients.

In 2013, we demonstrated that FO containing emulsions were associated with a tendency to decrease mortality and could reduce the duration of mechanical ventilation in the critically ill [3]. Nonetheless, this signal only emerged after aggregating those small RCTs, which are inadequate to detect clinically important treatment effects of parenteral FO containing emulsions on clinically important outcomes. Over the last two years, four new RCTs [4-7] evaluating clinical effects of FO containing emulsions as compared to other lipid emulsions in ICU patients receiving parenteral nutrition (PN) and/or enteral nutrition (EN)-based strategies have been published. In an updated meta-analysis [8], which was recently published, after statistically aggregating ten RCTs evaluating the effects of parenteral FO containing emulsions on relevant clinical outcomes in a heterogeneous ICU patient population, we demonstrated a significant reduction in infections (relative risk, RR 0.64; 95% CI 0.44-0.92; P=0.02; heterogeneity I^2 =0%; Figure 1), as well as a tendency to reduce ventilation days (weighted mean difference, WMD,−1.14; 95% CI, −2.67, 0.38, P=0.14, heterogeneity I^2 =0%) and hospital length of stay (WMD-3.71; 95% CI,−9.31, 1.88, P=0.19; heterogeneity I^2 = 87%, P < 0.00001) [8]. Another interesting finding in the subgroup analysis was that predominantly EN based trials showed a tendency towards a reduction in mortality (RR 0.69; 95% CI 0.40-1.18; P=0.18; heterogeneity I^2=35%) [8].

Despite these auspicious and positive results, the optimal approach of I.V. lipid emulsions in the critically ill is still controversial. In 2015, the Canadian Clinical Practice Guidelines Committee [9] developed updated recommendations for nutritional support in the critically ill. Regarding the type of IV lipids, the recommendation has not been modified. In fact, the committee noted that the previous trend for a reduction in mortality was not evident with the inclusion of the four new RCTs using FO containing emulsions in parenterally or enterally fed ICU patients included in our updated meta-analysis. Furthermore, the trend for a reduction in hospital length of stay was still associated with significant statistical heterogeneity, which weakens this signal. Therefore, the committee concluded that *until more data are available, when parenteral nutrition with intravenous lipids is indicated, alternative lipid emulsions that reduce the load of ω-6-PUFAs/soybean oil should be considered.* However, *there are insufficient data to make a recommendation on the type of soybean oil reducing strategy to be used in critically ill patients receiving PN* [9].

Figure 1. Effects of parenteral fish oil containing emulsions on infections



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Which Patient Population May Benefit Most from Fish Oil Containing Emulsions?

At this time, many questions have arisen and just a few answers are available about pharmacokinetics and pharmacodynamics of I.V. FO strategies in the critically ill. Moreover, it is necessary to define the patient population in the ICU setting in which I.V. FO exhibits the major benefits. According to the RCTs included in our recent systematic review and meta-analysis, I.V. FO containing emulsions have demonstrated to be beneficial in ICU patients with sepsis/severe sepsis, severe acute pancreatitis, and acute respiratory distress syndrome (ARDS). In addition, there is an interesting body of evidence indicating that ω-3-PUFAs exert potent effects on the cardiovascular system that may ultimately reduce risk of cardiac death after myocardial infarction and decrease risk of arrhythmia lowering the incidence of perioperative atrial fibrillation in cardiac surgery, although *current data in this field remains inconclusive* [10].

So far, results from small phase II clinical trials on FO containing emulsions in cardiac surgery have demonstrated that perioperative FO infusion is a promising strategy to modulate the biological and clinical response in cardiac surgery with cardiopulmonary by-pass (CPB) [11]. As a testimony of this, FO containing emulsions have been shown to decrease inflammatory biomarkers and have been associated with an early metabolic recovery and improvement in myocardial protection during the postoperative period. More research is encouraged and needed to clarify the role of I.V. FO containing emulsions in high-risk patients undergoing open-heart surgery [10,11]. A first step in this research agenda in this particular patient population should be to identify the optimal dose of FO which is able to safely optimize the effects on underlying inflammatory, immunologic, and metabolic processes. Recently, the position paper by the *American Society for Parenteral and Enteral Nutrition* (A.S.P.E.N) about the clinical role for alternative LEs [1] suggests that dosing studies on FO-containing emulsions need to be conducted to further define the optimal dose range aimed to obtain clinical benefits and avoid undesirable side effects. Therefore, a dose-escalating study aimed to define the optimum and safe dose seems to be mandatory before giving definitive recommendation on the dosage of I.V. FO. In this regard we are proposing to explore up to 0.5 g/kg/day in the perioperative period in open-heart surgery patients with CPB.

Up to now, positive treatment effects with FO containing emulsions mostly derive from small, single centre trials in heterogeneous ICU patient populations. Therefore, in the near future large scale adequately powered and well conducted multicenter clinical trials on parenteral FO strategies, which should aim to consolidate potential positive treatment effects, are needed and warranted.

Key messages

- Our recent results suggest that I.V. FO containing emulsions may reduce infections, as well as may reduce ventilation days and hospital length of stay in ICU patients.
- Intravenous FO strategies in enterally fed patients may be associated with a reduction in mortality, although this preliminary and weak signal must be explored in future trials.
- Phase II dosing studies in specific ICU patients population with systemic inflammation such as open heart surgery exposed to CPB are necessary to define the optimum dose of intravenous FO.
- Until more data are available, alternative lipid emulsions that reduce the load of ω-6-PUFAs should be considered in parenterally fed critically ill patients. However, there are insufficient data to make a final recommendation on the type of soybean oil reducing strategy to be used in the critically ill.

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