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Meta-analyses

Omega-3 polyunsaturated fatty acids in cardiac surgery patients: An updated systematic review and meta-analysis

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SUMMARY

Background: Omega-3 polyunsaturated fatty acids (ω-3 PUFA) supplementation is an attractive therapeutic option for patients undergoing open-heart surgery due to their anti-inflammatory and anti-arrhythmic properties. Several randomized controlled trials (RCT) have found contradictory results for perioperative ω-3 PUFA administration. Therefore, we conducted an updated systematic review and meta-analysis evaluating the effects of perioperative ω-3 PUFA on some clinically important outcomes for cardiac surgery.

Methods: A systematic literature search was conducted to find RCT evaluating clinical outcomes after ω-3 PUFA therapy in adult patients undergoing cardiac surgery. Intensive care unit (ICU) length of stay (LOS) was the primary outcome; secondary outcomes were hospital LOS, postoperative atrial fibrillation (POAF), mortality and duration of mechanical ventilation (MV). Predefined subgroup analysis and sensibility analysis were performed.

Results: A total of 19 RCT including 4335 patients met inclusion criteria. No effect of ω-3 PUFA on ICU LOS was found (*weighted mean difference* WMD −2.95, 95% *confidence interval*, CI −10.28 to 4.39, P = 0.43). However, ω-3 PUFA reduced hospital LOS (WMD −1.37, 95% CI −2.41, −0.33; P = 0-010) and POAF incidence (*Odds Ratio* OR = 0.78, 0.68, 0.90; P = 0.004). No effects were found on mortality or MV duration. Heterogeneity remained in subgroup analysis and we found a significant POAF reduction when ω-3 PUFA doses exceeded 1 g per day or when administered to patients exposed to extra-corporeal circulation. Oral/enteral administration seemed to further reduce POAF.

Conclusions: In patients undergoing cardiac surgery, ω-3 PUFA supplementation by oral/enteral and parenteral route reduces hospital LOS and POAF. Nonetheless considerable clinical and statistical heterogeneity weaken our findings.

1. Introduction

Omega-3 polyunsaturated fatty acids (ω-3-PUFA), such as eicosapentanoic acid (EPA) and docosahexaenoic acid (DHA) exhibit anti-inflammatory and immunomodulatory effects [1]. Currently, there is evidence showing that ω-3-PUFA exert potent effects on the cardiovascular system that may improve morbidity and ultimately reduce risk of cardiac death [2].

Furthermore, ω-3-PUFA have demonstrated positive effects on cardiac electrocardiographic parameters, decreasing the incidence of perioperative atrial fibrillation, which is considered a major risk factor for morbidity and mortality in open-heart surgery patients [3]. According to current knowledge, patients undergoing cardiac surgery with cardiopulmonary bypass (CPB) exhibit marked systemic inflammation due to the exposure of blood to non-endothelial surfaces, ischemia–reperfusion, and oxidative stress. In this context, ω-3-PUFA may be able to reduce systemic inflammatory response and multiple organ dysfunction [4,5], as well as the incidence of postoperative atrial fibrillation (POAF). Nonetheless, available data in this field are contradictory and the role of ω-3-PUFA in patients undergoing open-heart surgery still remains inconclusive. Indeed, over the last two decades several

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randomized controlled trials (RCT) of oral/enteral and parenteral ω-3-PUFA have evaluated the role of this strategy in the surgical setting. These studies have demonstrated contradictory results, although some of them have found that preoperative ω-3-PUFA could be a promising strategy to modulate the biological and clinical response to cardiac surgery and CPB. Earlier systematic reviews and meta-analyses so far have mostly evaluated the effect of ω-3-PUFA on the incidence of POAF [6–9]. However, these reviews have failed to provide a definitive answer about the effects of ω-3-PUFA on clinical outcomes in cardiac surgery. Moreover, since the last systematic review and meta-analysis published in 2014, several new trials have been published.

Therefore, with the aim of further elucidating the overall efficacy of oral/enteral or parenteral ω-3-PUFA, alone or as combination therapy compared to placebo on some relevant clinical outcomes in adult patients undergoing cardiac surgery, we performed an updated systematic review and meta-analysis of the literature.

2. Methods

2.1. Eligibility criteria

Trials were included if they met the following characteristics:

1. Type of study: RCT with a parallel control group.
2. Population: adult patients (≥18 years of age) scheduled for elective or emergency heart surgery, including coronary artery bypass graft (CABG) and/or valve surgery
3. Intervention: Fish oil (FO)-containing intravenous (IV) lipid emulsions (IVLE) as part of parenteral nutrition (PN) or FO-containing oral/enteral nutrition (EN). Oral FO-containing capsules and oral/EN/IV FO, associated with antioxidant micronutrients in antioxidant cocktails were also eligible.
4. Control: PN with soybean oil (SO)-based IVLE or a non-FO-based IVLE, as well as saline solution. Non-FO IVLE and saline solutions were defined as non-FO lipids or non-FO strategies. Oral/EN with non-FO-based capsules or without capsules in the control group.
5. Outcomes: Intensive care unit (ICU) length of stay (LOS) was the primary outcome for this meta-analysis. Secondary outcomes were hospital LOS, postoperative atrial fibrillation (POAF) incidence, mortality and mechanical ventilation (MV) days. We excluded those trials that reported only nutrition, biochemical, metabolic or immunologic outcomes.

2.2. Search strategy and study identification

A systematic review of the literature was conducted to identify in MEDLINE, Embase, CINAHL, the Cochrane Central Register of Controlled Trials and the Cochrane Database of Systematic Reviews all relevant RCT published between 1980 and January 2016. We used the following keywords or medical subject headings: "randomized," "clinical trial," "nutrition support," "omega-3 fatty acids," "pharmaconutrition," "fish oils," "lipid emulsions," "cardiac surgery," "heart surgery" and "coronary artery bypass graft." Our search was not restricted to articles written only in English. We attempted to contact study authors when additional data were needed.

2.3. Data synthesis

As previously published meta-analysis [1], the included trials were evaluated for methodological quality by two independent reviewers using a standardized form with a scoring system from 0 to 14 according to the following criteria:

a. Concealed randomization
b. Extent of blinding
c. Intention-to-treat (ITT) analysis
d. Baseline comparability of the different groups
e. Loss of patients to follow up
f. Quality of the protocol description
g. Cointerventions
h. Well-defined clinical outcomes

Both reviewers reached consensus on the individual scores of each category. When needed the authors of included studies were contacted to obtain additional information not included in the published article. Studies were considered as level I of methodological score if the concealed randomization was actually concealed, the study was double blinded and an ITT analysis was conducted. If any of these three criteria were not fulfilled, it was considered a level II study.

The primary outcome of the systematic review was ICU LOS. ICU LOS and MV duration were expressed in hours and converted when expressed in days, while hospital LOS was expressed in days. POAF was arbitrarily defined by the authors of each individual trial. When more than one POAF event was reported, we used the POAF incidence for the complete hospitalization or longest period in hospital reported. We analyzed data using RevMan 5.3 (Cochrane IMS, Oxford, UK) with a random effects model. We aggregated data from all included trials to estimate the overall weighted mean difference (WMD) with 95% confidence intervals for LOS data the pooled risk ratio (RR) with 95% confidence intervals (CIs) for the incidence of atrial fibrillation, mortality and infections. Inverse variance approach was used to evaluate WMDs and Mantel–Haenszel estimator was used to pool RRs. The random effects model of DerSimonian and Laird was used for variances estimation in the inverse variance estimators and the Mantel–Haenszel [10]. RRs were undefined and these data were excluded when no event was reported in either arm of the study. Weighted Mantel–Haenszel χ^2 test was used to evaluate heterogeneity and it was quantified by the I^2 statistic as implemented in RevMan. Subgroup analysis for statistical differences used the test of subgroup differences described by Deeks et al., and the results were expressed with P-values [11]. The possibility of publication bias was assessed by generating funnel plots and testing asymmetry of outcomes using methods proposed by Egger et al. [12]. We considered $P < 0.05$ to be statistically significant and $P < 0.20$ as an indicator of trend.

2.4. Subgroup and sensibility analysis

We performed a predefined subgroup analysis to assess a number of possible influences of ω-3 PUFA administration on clinical outcomes. We first examined the effect of intravenous versus enteral administration of FO. As the trial quality can influence clinical findings, we postulated that trials with lower quality (defined as level II studies) may demonstrate a greater treatment effect than those trials with higher quality (level I studies), which were previously defined. Similarly, level 1 and level 2 trials were grouped for analysis. In addition, the dose effect of FO IVLE was evaluated by separating the trials into two subgroups: 2 g or less of EPA + DHA per day and more than 2 g per day. To avoid attributing positive results to ω-PUFA administration when it could be attributed to another nutritional supplement, a sensibility analysis was conducted after removing all trials in which antioxidants other than ω-PUFA were used. Finally, following the hypothesis that extracorporeal circulation (ECC) is responsible for ischemia

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