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Meta-analyses

Does intravenous fish oil benefit patients post-surgery? A meta-analysis of randomised controlled trials

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SUMMARY

Background and aims: Supplementation of fish oil (FO) containing lipid emulsions has been associated with a reduction in the length of hospital stay, infections and liver dysfunction in patients undergoing major surgery. We carried out a meta-analysis and subgroup analysis to examine randomised clinical trial (RCT)-based evidence of the aforementioned effects.

Methods: Four databases, reference lists and the WHO ICTRP were systematically searched for RCTs to access the clinical efficacy of fish oil-enriched total parenteral nutrition in post-surgery patients. Methodological quality assessment was based on the Cochrane Handbook and GRADE.

Results: Twenty-one RCTs were enrolled for meta-analysis. FO was associated with a significant reduction in the length of hospital stay (mean = −2.14 d, 95% CI = −3.02 to −1.27), infections (OR = 0.53, 95% CI = 0.35–0.81), ALT (mean = −6.35 U/L, 95% CI = −11.75 to −0.94), GGT (mean = −11.01 U/L, 95% CI = −20.77 to −1.25) and total bilirubin (mean = −2.06 μmol/L, 95% CI = −3.6 to −0.52), as well as a non-significant change in mortality and postoperative medical cost. The quality of evidence of each clinical outcome was accessed as high.

Conclusion: FO-enriched lipid emulsions are likely to reduce infections, the length of hospital stay and liver dysfunction without influencing mortality and may be a safe and preferable choice in post-surgery patients. Further well-designed trials should be performed to determine whether FO lipid emulsions reduce mortality in patients undergoing hepatic surgery, especially liver transplantation, and the cost effectiveness of such treatment.

1. Introduction

Lipid emulsions have been used as a critical component of parenteral nutrition and are frequently used in the postoperative period to provide energy and essential fatty acids.[1,2] In addition to supplying energy, fatty acids may be involved in immune response and inflammation by influencing biochemical pathways, signal transduction and gene expression.[3] Possible adverse effects of conventional soybean (SO)-based lipid emulsions have been attributed to excess n-6 polyunsaturated fatty acids (PUFAs) and reduced amounts of n-3 PUFAs.[4] N-6 PUFAs have been implicated in the depression of cell-mediated immunity and can promote inflammation, which may worsen the clinical outcome of patients that have undergone major surgery, who are already at high risk of mortality, infections and organ damage due to a compromised immune status and excess activation of the inflammatory process, among other reasons[5,6].

N-3 PUFAs, which are considered immunomodulators, exert anti-inflammatory effects, in contrast to n-6 PUFAs. Lipid emulsions enriched with n-3 PUFAs from fish oil (FO), which is primarily composed of eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), have been introduced into clinical practice since the 1990s.[6] The brand names of FO-enriched lipid emulsions are Lipoplus, SMOFlipid and Omegaven. Namely, Intralipid/Lipoven/Lipovenoes are standard SO lipid emulsions, and Lipofundin is a standard SO-MCT (medium-chain triacylglycerol) lipid emulsion. The capacity of n-3 PUFAs may mitigate inflammatory processes by modulating the synthesis of eicosanoids, activating nuclear receptors and nuclear transcription factors and producing resolvins.[3] Moreover, several studies have reported the reversal of severe cholestasis in infants when FO lipid emulsions were used.[7,8] Various reports have demonstrated a lower rate of infection, shorter hospital stay and improved liver function in patients administered n-3 PUFAs postoperatively. However, most of these studies were limited by a small sample size or imperfect design,

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Table 1
Inclusion and exclusion criteria in the review.

	Inclusion criteria	Exclusion criteria
Population	Adult Undergo major surgery	Children Animal data Healthy volunteers Severe infection or trauma
Study type	Randomized controlled trials	Reviews/editorials/case reports Cohort/cross-over/non-randomized studies Published as an abstract
Intervention	FO/n-3/EPA/DHA enriched lipid emulsion vs. standard (SO/ML)lipid emulsion Administered postoperatively TPN	Arginine Glutamine RNA Peri/pre-operatively TPN + EN/EN/oral feeding
Outcomes of interest	At least one of the following outcomes: Mortality Length of hospital stay Postoperative infection rate Hepatic function Immune status Costs of postoperative period	

and some of their results were inconsistent. Two previous similar systematic reviews[9,10] paid little attention to organ function and inflammatory response in surgical patients, and the sources of heterogeneity were not well explained. Furthermore, the Jadad scale, which is not recommended, was used in the methodological quality evaluation.[11] Additionally, further trials have been performed since the last database search. Thus, we aimed to conduct a comprehensive meta-analysis of RCTs to evaluate the effects of FO containing lipid emulsions compared to standard SO/SO-MCT-based emulsions on infections, length of hospital stay, liver function and markers of inflammation in post-surgery patients. We also aimed to access the quality of evidence of each study and outcome and to explore potential sources of heterogeneity across studies for a better understanding of the present literature.

2. Materials and methods

2.1. Literature search strategy

Methods and eligibility criteria were prespecified and documented in a protocol. The Cochrane Central Register of Controlled Trials, MEDLINE, EMBASE and Web of Science were searched up to September of 2012 using the search terms fish oil, eicosapentaen*, EPA, docosahexaen*, DHA, omega-3, PUFA or polyunsaturated fatty acid combined with the terms emulsion, lipids, parenteral nutrition, TPN, total parenteral nutrition, PN, SMOF, Lipoplus or Omegaven. The publication type was restricted to RCTs. The WHO International Clinical Trials Registry Platform (ICTRP) search portal (www.who.int/trialsearch) was searched for additional trials. In addition, a few journals (Clinical Nutrition, Nutrition and Journal of Parenteral and Enteral Nutrition) and the references of eligible studies were manually searched.

2.2. Selection of studies

After removing duplicate records, all titles and abstracts were screened independently by two reviewers. The inclusion criteria are presented in Table 1. Multiple reports of the same study published in several articles were linked together. The results were compared, and discrepancies were resolved by consensus to produce the final study inclusion.

2.3. Data extraction

Data extraction was performed independently by two reviewers using standardised tables to document the following data: (1) source: first author, journal, and publication year; (2) methods: study design, sequence generation, allocation concealment, blinding, and other concerns about bias; (3) characteristics of participants: setting, country, age, sex, weight, nutritional status, surgical sites, and duration of surgery; (4) interventions: number of participants, content of fish oil, and duration of intervention; (5) time points of collection and unit of measurement; and (6) outcomes of interest: missing participants and summary data for each group (standard deviations were calculated from the standard error, CI, t or P value and inter-quartile range, while the median was extracted when the mean was not available. Only the final values of biochemical outcomes were extracted for the meta-analysis because the baselines were comparable. Most of the final values were measured on postoperative day 6 (POD 6), and a few were measured on POD 8)[12]; (7) key conclusions: any discrepancies between the two reviewers were overcome by consensus.

2.4. Assessment of methodological quality

Risk of bias in individual studies was accessed as recommended in the Cochrane Handbook,[11] instead of using composite scoring systems.[13] Six specific domains were addressed, including the sequence generation, allocation concealment, blinding, incomplete outcome data, selective outcome reporting and other issues. The quality of evidence of each outcome was determined according to the Grades of Recommendation Assessment Development and Evaluation (GRADE) Working Group.[14] The quality of randomised trials was downgraded due to (1) risk of bias, (2) inconsistency, (3) indirectness, (4) imprecision, and (5) publication bias. Finally, the quality of evidence was categorised as high, moderate, low and very low. Publication bias was assessed using a funnel plot.[15]

2.5. Statistical analysis

Review Manager Version 5.1 was used to conduct the meta-analysis. A table providing a summary of the findings was created using the GRADE system.[16] The mean difference (MD) was used when continuous data could be converted into the same units, such as the length of hospital stay and liver function, while the standardised mean difference (SMD) was used when the data could not be converted. The odds ratio (OR) was chosen for dichotomous data (mortality and infection rate). Infection rate was equal to the number of infections/(number of participants × number of types of infectious diseases). For dichotomous data, an analysis of the total number of randomised participants and outcomes of missing participants was used (intention to treat analysis) to address incomplete outcome data. For continuous data, only known results were included. A P value $\geq$0.10 and an I^2 value $\leq$50% indicated that the data did not present significant heterogeneity. If the heterogeneity could not be explained or when the number of studies was limited, a random-effects model was applied.[17] Results that were not amenable to presentation in forest plots are described in the text.

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