

Parenteral Nutrition Enriched with Fish Oil after Gastrointestinal Surgery: A Systematic Review and Meta-Analysis of Randomized Controlled Trials

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Abstract

Objective: We performed a systematic review and meta-analysis to assess the effects of parenteral nutrition enriched with fish oil versus without fish oil after gastrointestinal surgery.

Methods: A search was conducted on Medline, Embase and the Cochrane Library electronic databases.

Results: After the review of 17 trials, parenteral nutrition enriched with fish oil improved the infection complications rate (risk ratio (RR) = 0.43; 95% CI: 0.28 to 0.67), length of hospital stay (mean difference (MD) = -1.69; 95% CI: -2.72 to -0.66) and length of intensive care unit stay (MD = -0.33; 95% CI: -0.51 to -0.14). Other beneficial effects included improvement of liver function AST (MD = -18.25; 95% CI: -30.10 to -6.41), immune function CD⁴⁺/CD⁸⁺ (MD = 0.16; 95% CI: 0.01 to 0.31), reduction of inflammation markers IL-6 (MD = -7.03; 95% CI: -11.10 to -2.97) and TNF- α (MD = -1.18; 95% CI: -1.71 to -0.66), and increased concentrations of EPA (standard mean difference (SMD) = 5.41; 95% CI: 2.47 to 8.34) and DHA (SMD = 3.20; 95% CI: 1.27 to 5.14).

Conclusion: Through these results, we conclude that parenteral nutrition enriched with fish oil is safe and effective. However, further studies in larger patient populations with more extensive investigation are needed to reassess the role of FO.

Abbreviations

FO: Fish Oil, HLOS: Length of Hospital Stay, ICULOS: Length of Intensive Care Unit Stay, LCT: Long-chain Triglycerides, MCT: Medium-chain Triglycerides, OO: Olive Oil, PN: Parenteral Nutrition, PUFAs: Polyunsaturated Fatty Acids, SO: Soybean Oil

Introduction

Patients who have undergone a major surgery have a compromised immune system and overactive inflammatory process that increases the risk of infection [1]. This problem has led to the development of parenteral regimens, such as nutritional support enriched with fatty acids to modulate the responses of cells of the immune and inflammatory systems [2]. However, the immune and inflammatory response in patients receiving parenteral nutrition (PN) may be modulated by the type of fatty acid used, which may influence clinical outcomes [3].

There are two principal families of polyunsaturated fatty acids (PUFAs), the n-6 and n-3 PUFAs [4]. Soybean oil is characterized by a high content of linoleic acid (18:2 n-6), a n-6 PUFAs that serve as precursors for inflammatory mediators resulting in increased eicosanoids levels which may contribute to an increased susceptibility to infection and a poorer clinical outcome [5-7]. In contrast, fish oil (FO) is rich in α -linolenic acid (18:3 n-3), a n-3 PUFAs that decreases the eicosanoids synthesis resulting in modulate inflammatory cytokine production and immune system function after trauma or surgery [8,9].

FO favorably modulates lipid mediator patterns [10-12] and the inflammatory response in surgical patients [12,13], reducing the hospital stay [13-15] when compared with Long-Chain Triglycerides (LCT) or Long-Chain Triglycerides/Medium-Chain Triglycerides (LCT/MCT). However, there are studies demonstrating that administration of FO (0.2 g/kg per day) after surgical stress is not immunosuppressive, but increases production of IFN- γ , TNF- α , and IL-2 [16]. Previous meta-analysis demonstrated that parenteral nutrition enriched with FO have proven to be well tolerated, in terms of clinical and metabolic outcomes [17-19]. However, the studies included in these meta-analyses are very heterogeneous in

their interventions and subjects. In our review, we selected studies that of their sole difference being the inclusion of FO between experimental and control groups. Thus, the objective of this meta-analysis was to evaluate the treatment benefits of PN enriched with FO compared to treatment without FO in patients undergoing gastrointestinal surgery.

Methods

Literature search

We performed searches on Medline, Embase and Cochrane Central Register of Controlled Trials (until July 6, 2015). The detailed search strategy for each data base is presented in Table 1. The search was limited to English language. Additionally, we conducted a manual search from bibliographies of relevant journals.

Study selection

The selection of studies was performed using 'EndNote X6' software produced by Thomson Reuters. The studies were selected for review if they fulfilled the following inclusion criteria: (1) study design: randomized controlled trials (RCTs); (2) population: adult (age ≥ 18 years) who received FO after gastrointestinal surgery; (3) intervention: FO enriched parenteral regimen was the only difference between experimental and control groups; (4) outcomes: infection

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complications rate, length of hospital stay (HLOS), length of intensive care unit (ICU) stay, and laboratory values.

Database	Search strategy
Medline	((<i>"Fat Emulsions, Intravenous"</i> [Mesh]) OR <i>"Parenteral Nutrition"</i> [Mesh]) AND <i>"Fatty Acids, Omega-3"</i> [Mesh] AND <i>"Randomized Controlled Trial"</i> [Publication Type]
Embase	<i>'fat emulsions intravenous'/exp</i> OR <i>'fat emulsions intravenous'</i> OR <i>'parenteral nutrition'/exp</i> OR <i>'parenteral nutrition'</i> OR <i>'total parenteral nutrition'/exp</i> OR <i>'total parenteral nutrition'</i> OR <i>'lipid emulsion'/exp</i> OR <i>'lipid emulsion'</i> AND <i>'omega 3 fatty acid'/exp</i> OR <i>'omega 3 fatty acid'</i> OR <i>'fish oil'/exp</i> OR <i>'fish oil'</i> AND <i>'randomized controlled trial (topic)'</i> AND <i>'human'</i>
Cochrane	MeSH descriptor: (<i>[Fat Emulsions, Intravenous]</i> OR <i>[Parenteral Nutrition]</i> AND <i>[Fish Oils]</i> OR <i>[Fatty Acids, Omega-3]</i>) explode all trees.

Table 1: Database and search strategy.

Exclusion criteria were (1) non-RCTs, abstracts, case series, cross-over studies, reviews; (2) pediatric patients, critically ill patients were not related with gastrointestinal surgery, liver transplantation surgery (3) patients that received lipid emulsion in preoperative; (4) there are different types of brand of FO, but SMOF was not included. For example, when intervention group LCT/MCT/FO was compared with control group LCT/MCT, this study was included. But in case of intervention group LCT/MCT/OO/FO (SMOF) was compared with control group LCT, this study was excluded, because was not included MCT/OO in the control group. In order to decrease the heterogeneity between studies.

Data extraction

Titles and abstracts of studies were identified in the primary search and all articles deemed potentially eligible for inclusion were retrieved in full-text format in the secondary search by two reviewers (VK and SAC). Extraction of necessary data including: author, publication year, country, study design, patient type, number of patients (treatment/control), dose of FO and duration of intervention, type of intervention and outcome measures performed independently by investigators. When studies did not report adequate information to determine the above-mentioned assessment criteria, we tried to obtain additional data directly from the authors. Discrepancies between the two investigators were resolved by discussion and consensus with senior investigator (WGS).

Quality assessment

The methodological quality and risk of bias in individual studies were assessed with the components recommended by the Cochrane Collaboration [20]. The assessment tools included sequence generation of the allocation; allocation concealment; blinding participants, personnel, and outcome assessors; incomplete outcome data; selective outcome reporting, and other sources of bias. Publication bias was assessed using a funnel plot.

Statistical analysis

Data were extracted from the text and tables of the original published articles. The mean and standard deviation difference was collected for the analysis. The change found in the intervention and control groups was calculated by subtracting the after treatment values from the baseline values, and it was used to calculate the difference in means [21]. When the data were not reported in the original studies,

the difference between means was calculated on the P value or it was obtained from the previous meta-analysis using similar statistical protocol. Data were synthesized using Review Manager Version 5.2 software provided by the Cochrane Collaboration (RevMan; The Cochrane Collaboration, The Nordic Cochrane Centre, Copenhagen, Denmark). Dichotomous data were expressed as risk ratio (RR) and continuous outcomes as weighted mean difference (WMD), both with their 95% confidence intervals (CI). Heterogeneity was examined using I^2 statistic, where I^2 values of 70% or more represented an indicator of substantial heterogeneity. In the absence of significant heterogeneity, we pooled data using a fixed-effect model ($I^2 < 50\%$); otherwise we used a random effects model ($I^2 > 50\%$) [22]. Results were considered statistically significant at $P < 0.05$. Publication bias was evaluated using a funnel plot.

Results

Selection and characteristics of studies

From the initial literature search, we identified 179 articles using the following databases: Medline (51), Embase (55), and Cochrane (73). Figure 1 shows the process for identifying potentially eligible studies and exclusion criteria. After elaborative screening, 34 articles were assessed by full text and 17 studies with 753 patients [2,10-12,15, 16,23-33] were included for the review. However, three publications [2, 24, 30, 31, 33] are same study that reported different outcomes. The dose of FO varied between 0.04 and 0.28 $\text{g} \cdot \text{kg}^{-1} \cdot \text{d}^{-1}$. The mean treatment period ranged from 1 to 8 days after surgery. The demographic and characteristics of the included studies are summarized in Table 2.

Clinical Outcomes

Infection complications rate. Nine studies reported the occurrence of infectious postoperative complications [11,12,23,26,27,29-32]. The incidence of infection was 8.8% in the intervention group (24/273) and 20.1% in the control group (56/271). The risk ratio of infection in the intervention compared with the control group was 0.43 (95% CI, 0.28 to 0.67, $P = 0.0001$, heterogeneity $I^2 = 0\%$; Figure 2). Heterogeneity was not significant ($I^2 = 0.76$).

Length of hospital stay. Eight studies reported this outcome [11, 12, 15, 23, 24, 26, 27, 32]. The analysis showed a significant decrease in HLOS within the intervention group compared with the control group. The mean difference for HLOS was -1.69 (95% CI, -2.72 to -0.66, $I^2 = 0.001$, heterogeneity $I^2 = 0\%$; Figure 3). Heterogeneity was not significant ($P = 0.86$).

Length of ICU stay. Three studies reported this outcome [11, 15, 24]. The analysis showed a significant decrease in length of ICU stay within the intervention group compared with the control group. The mean difference for length of ICU stay was -0.33 (95% CI, -0.51 to -0.14, $I^2 = 0.0005$, heterogeneity $I^2 = 0\%$; Figure 4). Heterogeneity was not significant ($P = 0.66$).

Laboratory outcomes

Liver function. The analysis of two studies [27, 30] showed a significant improvement in value of aspartate transaminase (AST) within the intervention group compared with the control group. The mean difference for AST was -18.25 (95% CI, -30.10 to -6.41, $P = 0.003$, heterogeneity $I^2 = 0\%$). However, there is no significant difference in the values of alanine aminotransferase (ALT), gamma glutamyl transferase (GGT) and total bilirubin (TBIL) between intervention and control groups (Table 3).

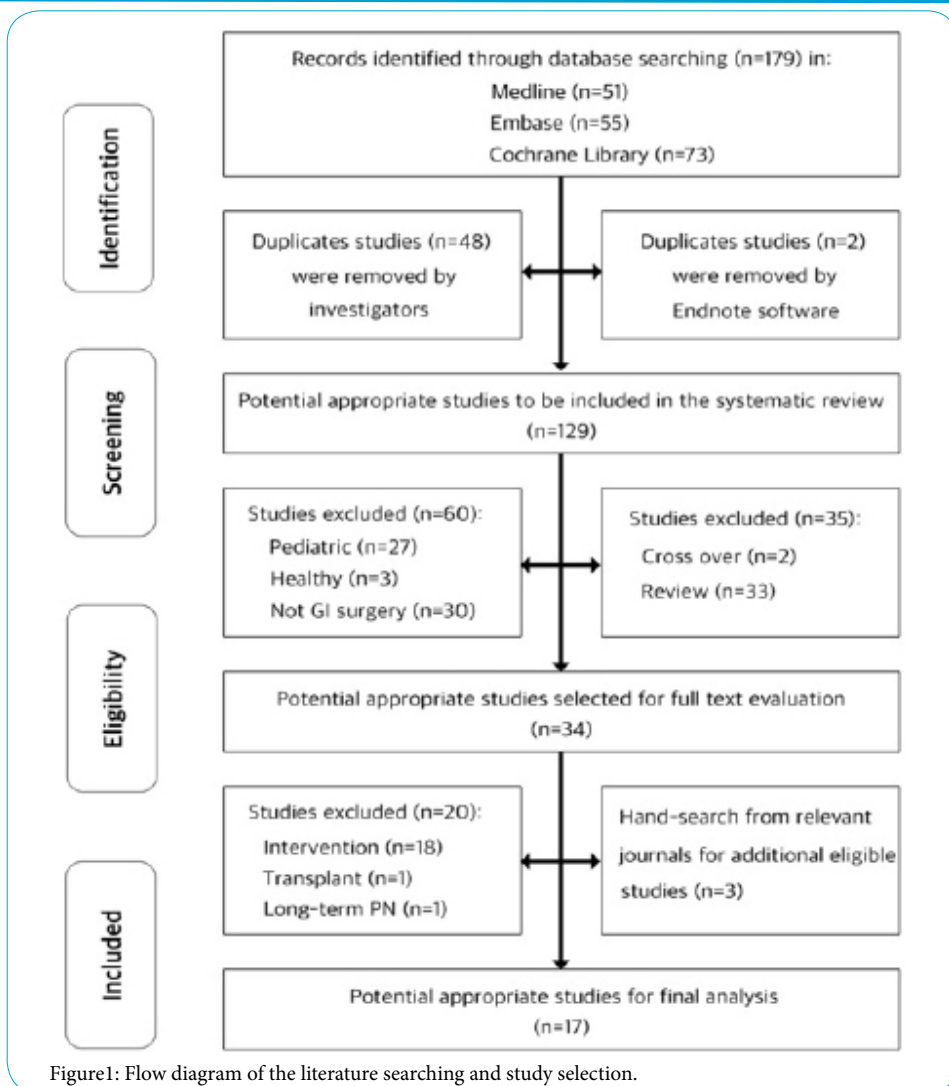


Figure1: Flow diagram of the literature searching and study selection.

Infection rate

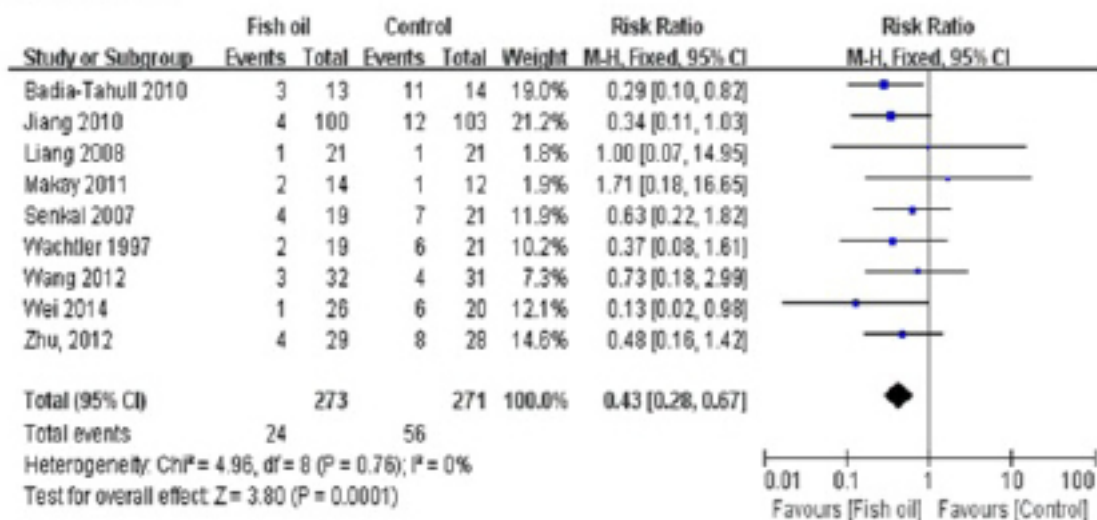


Figure 2: Forest plot of risk ratios for infection complications rate. CI: Confidence interval; M-H: Mantel-Haenszel.

Length of Hospital Stay

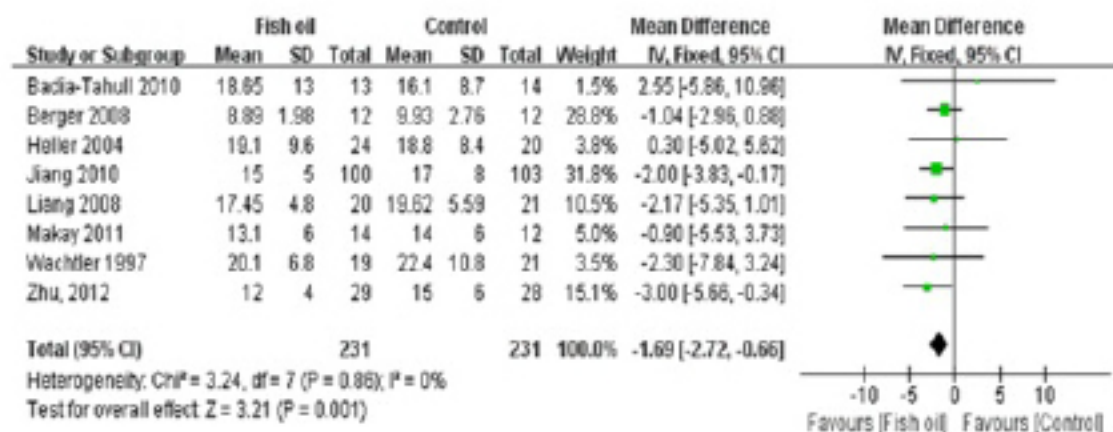


Figure 3: Forest plot of mean difference for length of hospital stay. CI: Confidence interval; IV: Inverse variance; SD: standard deviation.

Length of ICU Stay

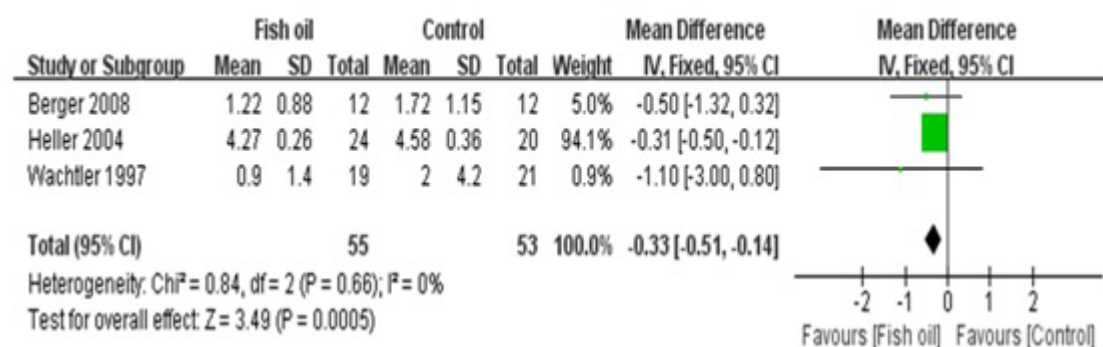


Figure 4: Forest plot of mean difference for length of ICU stay. CI: Confidence interval; IV: Inverse variance; SD: standard deviation.

Lipid profile. The analysis showed that intervention and control groups were not significant in the improvement of lipid profile (Table 3).

Immune function. The analysis of five studies [12, 16, 30-32] showed a significant increase in ratio of $\text{CD}^{4+}/\text{CD}^{8+}$ within the intervention group compared with the control group. The mean difference for $\text{CD}^{4+}/\text{CD}^{8+}$ was 0.16 (95% CI, 0.01 to 0.31, $I^2 = 0.04$, heterogeneity $I^2 = 15\%$). However, there is no significant difference in the values of CD^{4+} and CD^{8+} between intervention and control groups (Table 3).

Inflammatory markers. The analysis of four [12,30-32] and five [12,16,30-32] studies showed a significant reduction in values of pro-inflammatory cytokines IL-6 and TNF- α , respectively, within the intervention group compared with the control group. The mean difference for IL-6 was -7.03 (95% CI, -11.10 to -2.97, $P = 0.0007$, heterogeneity $I^2 = 49\%$) and for TNF- α was -1.18 (95% CI, -1.71 to -0.66, $P < 0.0001$, heterogeneity $I^2 = 9\%$). However, there is no difference in the values of WBC and CRP between intervention and control groups (Table 3).

Coagulation. The analysis showed that intervention and control groups were not significant in the improvement of coagulation parameters (Table 3).

Lipid fatty acid pattern. The analysis of three studies [10,15,29]

showed a significant increase in concentrations of EPA and DHA within the intervention group compared with the control group. The standard mean difference for EPA was 5.41 (95% CI, 2.47 to 8.34, $P = 0.0003$, heterogeneity $I^2 = 88\%$) and DHA was 3.20 (95% CI, 1.27 to 5.14, $P = 0.001$, heterogeneity $I^2 = 87\%$). However, there is no difference in the values of AA (Table 3).

Methodological quality

A summary of the methodological quality of all 17 studies was performed using Review Manager 5.2 [2, 10-12, 15, 16, 23-33]. Among 17 studies, 11 studies [2, 11, 12, 23, 24, 26, 27, 29, 30, 32, 33] used an adequate approach to sequence generation using computer generated random numbers or random-number tables. The adequacy of randomization was unclear in the remaining 6 studies. In 7 studies [2, 11, 12, 23, 24, 30, 33], method of allocation concealment was adequate, but was inadequate in one study [26]. In the remaining 9 studies, the information regarding approaches to allocation concealment could not be determined. In 12 studies, the double-blind methods were used [2, 11, 12, 15, 16, 23, 24, 26, 27, 32, 33]. In the remaining 5 studies, information about blinding was unclear. Twelve studies [2, 10, 12, 15, 16, 24-28, 32, 33] had no loss to follow-up, while three studies [23, 30, 31] recorded numbers lost to follow-up in each treatment group, and in two studies loss to follow-up was unclear (Figure 5).

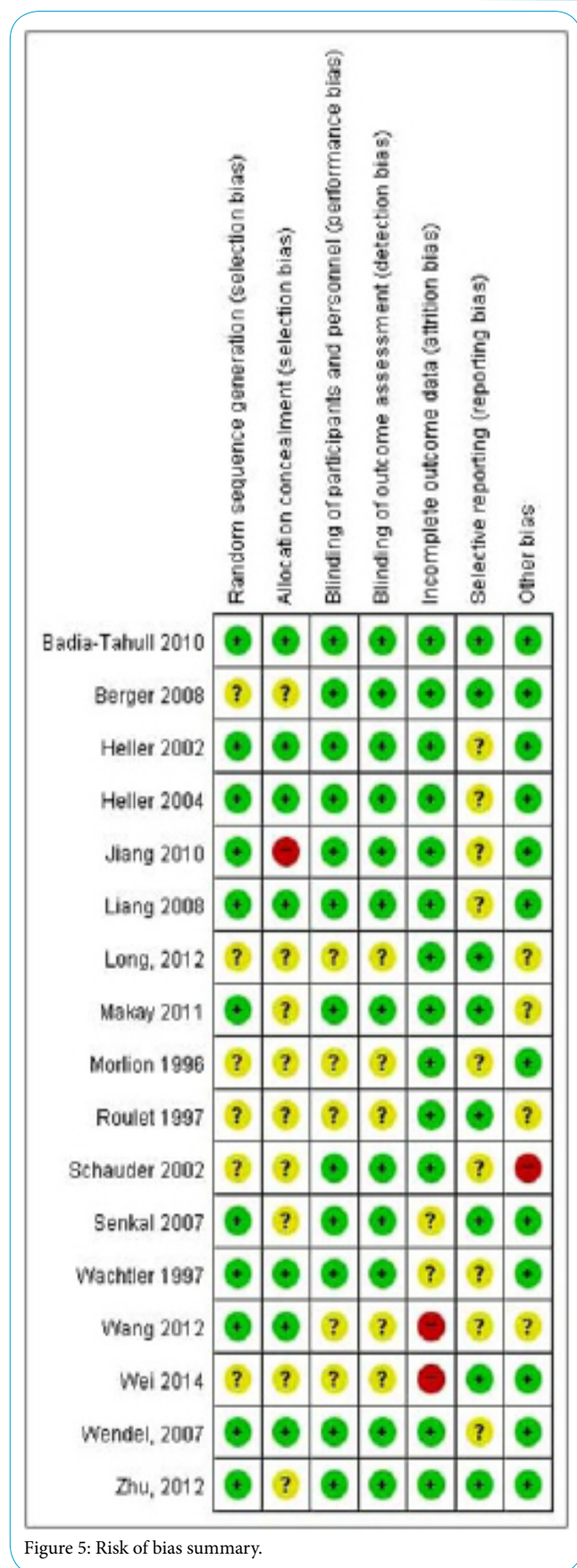


Figure 5: Risk of bias summary.

Publication bias

We used the funnel plot to examine the publication bias in the outcome of meta-analysis with the most RCTs contributing data. The horizontal axis of the plot was the RR effect estimate and the vertical axis of the plot was the standard error (SE) of the log (RR or MD or SMD). The funnel plot of the infection complications rate and HLOS suggests that the quantity distribution of the RCTs is asymmetric, indicating possible publication bias. However, only a small number of studies were included in the review, most of which contained a small sample size. For other parameters, the influence of publication bias is limited to the meta-analysis due to the small number of studies.

Discussion

Surgery elicits a series of reactions including release of stress hormones and inflammatory mediators. This release of mediators to the circulation has a major impact on body homeostasis. For optimal rehabilitation and wound healing, the body needs to be well nourished to mobilise adequate substrates [34]. A positive effect of PN enriched with FO emulsion on clinical outcomes has previously been observed in adult surgical patients [23, 26]. Lipid emulsions represent not only energy supply and essential fatty acids, but they are also necessary for proper biologic function and modulate cell signaling pathways, including immunosuppression and excess inflammation [35]. In this context, the present meta-analysis investigated the effects of parenteral nutrition enriched with FO in patients who have undergone gastrointestinal surgery.

After aggregated our data we found favorable effects of clinical and laboratory outcomes. The current review pooled data from 17 studies and showed like Chen et al. [17] a significant reduction in the infection complications rate, HLOS and ICU stay, liver profile (AST), and lipid fatty acid patterns (increase of EPA and DHA) when PN was enriched with FO. In our study, further improvement was noted in the results of immune function (CD⁴⁺/CD⁸⁺) and inflammatory response (decrease of IL-6 and TNF- α). Nonetheless, our meta-analysis included 6 RCTs among 13 studies included by Chen et al.

Infectious complications were defined in accordance with the definitions of nosocomial surgical-site infections of the US Centers for Disease Control and Prevention [36]. Postoperative complications including wound infections, respiratory tract infections, abdominal infections, urological infections and skin infections. In our meta-analysis, we found a significantly higher chance of postoperative infections in the control group (Figure 2), which suggest that FO can reduce pro-inflammatory markers level after surgery, contributing to lower rates of postoperative infection complications and supporting in the early recovery of patients.

The most important laboratory outcome is the serum concentrations of liver enzymes. Phytosterols found in soybean oil have a deleterious effect on liver function [37]. Phytosterol is absorbed in small amounts and metabolized slowly by the liver [38]. Moreover, long-term use of soybean oil may lead to the accumulation of phytosterol content in cell membranes and plasma lipoproteins, which has been associated with cholestasis in children on long-term PN [39]. Previous studies in infants and adults with severe total parenteral nutrition-associated cholestasis were reversed when FO was used in lipid emulsions [40, 41]. In our study, we found significant reduction in AST concentration for those who received FO compared to those who did not, while no significant difference was observed for ALT, GGT and TBIL between intervention and control groups. The possible explanation for the

lack of a significant difference in ALT, GGT and TBIL between the treatment and control groups may be the short time period between the test and liver cell injury.

There are only a few studies regarding the pathophysiology of the development of hypertriglyceridemia [42]. Hypertriglyceridemia during PN infusion indicates excess triglyceride synthesis, reduced fat clearance, dextrose overfeeding, or excess lipid infusion. Stressed patients such as those having surgery are at a higher risk for hypertriglyceridemia due to increased lipolysis and hepatic fatty acid re-esterification [43]. Nonetheless, our results showed that PN enriched with FO did not significantly improve the lipid profile.

Certain PUFAs (dihomo-gamma-linolenic acid, 20:3 n-6; AA, 20:4 n-6; EPA, 20:5 n-3) serve as precursors in the synthesis of eicosanoids. The n-6 PUFAs arachidonic acid is a precursor of pro-inflammatory mediators (such as leukotrienes of the n-4 series), and of prostaglandins and thromboxanes of the n-2 series, which increase the vascular tone and promote platelet aggregation. In contrast, prostaglandins and thromboxanes of the n-3 series and leukotrienes of the n-5 series, formed from the n-3 PUFAs eicosapentaenoic acid, have many antagonistic effects such as a reduction in platelet aggregation and vascular tone as well as anti-inflammatory effects [44]. Through of these mediators, n-3 PUFAs may play critical role in regulating the inflammatory response in surgical patients. Morlion et al. [10] showed significant alterations the FA composition of leukocytes in that the EPA and LTB5 content were increased 2.5-fold and 1.5-fold, respectively. Moreover, studies have shown that the PN enriched with FO increases the ratio of leukotriene B5/leukotriene B4 [11, 30]. Consistent with these findings, we found statistically significant increases in plasma concentrations of EPA and DHA with n-3 PUFA-enrichment, but not in AA. Consequently, the pro-inflammatory cytokine IL-6 and TNF- α was release at significantly lower levels in the FO group, which may suggest that n-3 PUFAs are involved with improvement of inflammatory effects. On the other hand, the concentration of inflammation markers WBC and CRP were not significant. More studies are needed, however, to fully assess the effects of n-3 PUFAs in leukocytosis.

T cells can be divided into helper and cytotoxic cells. The CD⁴⁺ T lymphocytes are the major helper-inducer T cells of the immune system, where they activate and produce cytokines such as IL-2 that stimulate immune cells such as macrophages, CD⁸⁺ T cells, B cells, and NK cells. CD⁸⁺ T cells are the cytotoxic-suppressor T cells, which are capable of efficiently lysing target cells [45]. In our study, we found that CD⁴⁺/CD⁸⁺ ratio was significantly increased in FO group. Although CD⁴⁺ and CD⁸⁺ were not significant, the values tended to increase for FO group. These findings are in agreement with the clinical outcome of infection rate and suggest that enrichment of FO may restrain inflammatory response and maintain the function of immunocompetent cells.

One of the benefits adding the n-3 long-chain fatty acids to lipid emulsions is that it decreases the risk of postoperative thrombosis and bleeding. Rouletet al. [28] shows that patients received FO modify the platelet composition and some parameters of platelet function in humans. Another study published by Heller et al. [13, 24] showed that no coagulation and platelet abnormalities are evoked by FO enrichment as high as 0.2 g/Kg per day for five days after surgery. Our study showed that PN enriched with FO did not have a significant beneficial effect on improving of coagulation due few studies, but the platelets levels trend to decrease in the group of patients that received

FO. Thus, further studies should be done to determine the amount of FO necessary to be added in lipid emulsions to reduce the risk of thrombosis and bleeding.

There are some limitations in our study that merit consideration when interpreting our results. First, among the seventeen trials included, only one enrolled more than 100 patients. Further large scale randomized clinical trials are needed. Second, there are differences in characteristic of the population and study designs between the included trials. For example, brand, dose and duration of FO use. Finally, bias may have been introduced because of the operative methods performed by different surgeons for different severity of the diseases. Unfortunately, these factors may increase the heterogeneity and affects the interpretation of results.

Conclusion

In conclusion, this meta-analysis demonstrated that parenteral nutrition enriched with FO seems to be safety and efficacious after gastrointestinal surgery. Among the clinical and laboratory outcomes observed in this review were improvements in liver function, improvements in measures of immunologic function and inflammatory response, increased patterns of lipid mediator, reduced risk of infectious complications, and adecreased length of hospitalization. However, further studies in larger patient populations with more extensive investigation are needed to reassess the role of FO.

Competing Interests

The authors declare that they have no competing interests.

Author Contributions

Conception, design, data collection analysis, interpretation: Vera Kim, Soo An Choi

Writing the article, statistical analysis: Vera Kim

Critical revision of the article: Wan Gyoon Shin, Soo An Choi

Final approval: Soo An Choi

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