Original Article

Effects of parenteral ω-3 fatty acid supplementation in postoperative gastrointestinal cancer on immune function and length of hospital stay: a systematic review and meta-analysis

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Background and Objectives: Omega-3 fatty acids are widely used in nutritional support. However, whether parenteral supplementation with ω-3 fatty acids is effective for gastrointestinal cancer patients remains uncertain. This study assessed the effects of this form of parenteral nutrition on immune function and clinical outcomes in postoperative gastrointestinal cancer patients. **Methods and Study Design:** We searched Medline, Embase, Scopus, and the reference lists of selected studies to identify randomized controlled trials that compared ω-3 fatty acids with a control, and that included immune indices, infectious complications, or length of hospital stay in the final outcomes. The odds ratio and weighted mean difference with 95% confidence intervals were calculated and the I^2 statistic was used to assess heterogeneity. **Results:** Seven trials with a total of 457 participants were included in the meta-analysis. Five pooled trials with 373 participants indicated that the incidence of infectious complications was significantly different between the intervention and control groups (odds ratio: 0.36; 95% confidence interval: 0.18, 0.74, $p<0.05$). Five trials involving 385 participants indicated that parenteral ω-3 fatty acid supplementation significantly shortened the length of hospital stay (weighted mean difference: −2.29, 95% confidence interval: −3.64, −0.93; $p<0.05$). Meta-analysis also indicated that ω-3 fatty acids increased the level of $CD4^+$ and $CD4^+/CD8^+$ ratio. **Conclusions:** The results of this study suggest that parenteral ω-3 fatty acid supplementation is beneficial for gastrointestinal cancer patients, and is accompanied by improved postoperative immune function and satisfactory clinical outcomes.

Key Words: ω-3 fatty acid, parenteral nutrition, gastrointestinal cancer, meta-analysis

INTRODUCTION

Omega-3 (ω-3) fatty acids, including docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA), are critical for maintaining the functioning and homeostasis of the human body. The main dietary sources of these fatty acids are several deep-sea fishes and algae. In recent years, increasing evidence has shown that ω-3 fatty acids are potentially potent anti-inflammatory agents, which can dramatically decrease the production of inflammatory eicosanoids and cytokines (prostaglandin E2 and leukotriene B4).[1] Moreover, ω-3 fatty acids have been found to regulate the release of proinflammatory cytokines, modulating immune response and improving immune function.[2,3] As an essential fatty acid, ω-3 fatty acid supplementation in patients has been heavily emphasized.

Gastrointestinal cancers are among the most common types of cancers, and a recent survey indicates that they are responsible for a large proportion of new cancer cases and cancer-related deaths in the United States.[4] Patients with cancer frequently suffer from various infectious complications and lowered immune function after surgery. Cachexia is also common, especially in patients with pancreatic and gastric malignancies.[5] These patients are often characterized by malnutrition and have increased mortality.

Recently, studies have made progress in investigating ω-3 fatty acids and their application in patients with gastrointestinal cancer. A previous article indicated that administering fish oil through enteral nutrition to patients with upper gastrointestinal malignancy can reduce the number of infectious and gastrointestinal complications and enhance renal and liver function.[6] Other recent studies have found that enteral nutrition supplemented with EPA and γ-linolenic acid (GLA) might significantly improve mechanical ventilation, shorten the length of ICU stays, and reduce the occurrence of new organ failures.[7,8]

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In a multiple-center trial, intervention involving ω-3 fatty acids was shown to reduce mortality, the use of antibiotics, and the average length of intensive care unit stay and overall hospital stay.[9] In addition, numerous studies have revealed the positive effects of supplementation with ω-3 fatty acids on nutritional status, immune function, and clinical outcome.[10-13]

The role of parenteral ω-3 fatty acid supplementation in gastrointestinal cancer patients is controversial.[14,15] Makay et al demonstrated that ω-3 fatty acid supplementation had no significant effect on biochemical parameters or clinical outcomes in patients after gastric cancer surgery.[14] Postoperative nutrition supplementation with ω-3 fatty acids may partially improve outcomes in cancer patients. Whether this form of supplementation is effective for improving immune function and clinical outcomes is unknown.

To gain further insight into these potential associations, we conducted a meta-analysis of published data. This study assessed the effect of parenteral supplementation with ω-3 fatty acids on the immune response and clinical outcomes of postoperative gastrointestinal cancer patients.

METHODS

Search strategy

A comprehensive literature search was performed by the Medline, Embase, and Scopus databases, from inception through April 2016. We used the following search terms: ("ω-3 fatty acid" OR "fish oil" OR "EPA" OR "DHA") AND ("cancer" OR "malignancy" OR "carcinoma" OR "neoplasms") AND "parenteral nutrition". Furthermore, reference lists of eligible studies and other relevant review articles were also manually searched. We would contact the author to obtain the complete data if the information was insufficient.

Inclusion and exclusion criteria

The studies were included in our analysis if they met the following criteria: (1) research design: randomized controlled trials; (2) participants: the patients with gastrointestinal cancer; (3) intervention measures: ω-3 fatty acid supplementation through the parenteral nutrition after major cancer surgery; (4) outcomes: immune indices, postoperative infectious complications and length of hospital stay.

Exclusion criteria: (1) The intervention group contains other immunonutritions such as glutamine or arginine; (2) The ω-3 fatty acid supplemented before the operation.

Data extraction and quality assessment

The following data were extracted independently by 2 authors (BH and LZP) from the included studies: name of first author, publication year, country, diagnosis of disease, number of participants, intervention measures, intervention time, and reported outcomes. Any disagreements in the results of data extraction were resolved through discussion with a third author (DQS).

The quality of included studies was assessed using the modified Jadad scale,[16] which addresses 5 main items: randomization, concealment of allocation, double blinding, withdrawals, and dropouts. Quality was assessed on a scale of 0 to 7, and a study with a score of ≥4 points was considered to have high quality. In our meta-analysis, we excluded poor-quality studies with scores of <4 points.

Statistical analysis

All statistical analysis was conducted using Stata (version 11.0; StataCorp LP, College Station, Texas, USA). We calculated the odds ratio (OR) with a 95% confidence interval (CI) to evaluate the data on infectious complications. The mean and standard deviation (SD) were extracted and the pooled weighted mean difference (WMD) was used to represent continuous variables. In the analysis, $p<0.05$ was considered statistically significant. Potential heterogeneity between studies was evaluated using the I^2 statistic.[17] I^2 >50% indicated significant heterogeneity between the studies, and we selected the random effects model for analysis. When $I^2 \leq 50\%$, the fixed effects model was used. If significant heterogeneity was shown, we used subgroup analysis to identify the sources of heterogeneity. If more than 10 studies were included, we evaluated publication bias by using an Egger test with funnel plots.[18]

RESULTS

Study selection

A systematic search yielded 543 citations. After evaluating the titles and abstracts of all articles, 519 studies were excluded. According to the inclusion and exclusion criteria, we assessed full-text articles among the remaining studies. A total of 17 studies were excluded because they involved non-randomized controlled trials, duplicate reports, and irrelevant outcomes. Only one study was considered to be of poor quality, and it did not report sufficient details regarding intervention measures.[19] For another study, we were only able to obtain the abstract.[20] Thus, 7 studies were eventually included in our meta-analysis, all of which were published in English. Figure 1 displays a flow diagram of the literature selection process.

Study characteristics

The characteristics of the included studies are described in Table 1. All studies were published between 1995 and 2014. Seven trials with 457 participants were included in

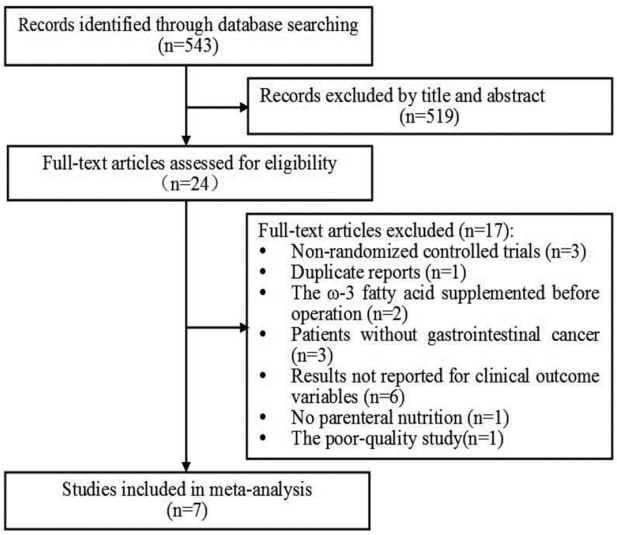

Figure 1. Flow diagram of literature searching and selection.

Table 1. Characteristics of included studies in meta-analysis

First author	year	Country	Diagnosis of patients†	Number of participants (I/C)‡	Intervention measures		Intervention time (d)	Quality scores
					Intervention group	Control group		
Makay[14]	2013	Turkey	GC	14/12	ω-3 and ω-6 fatty acids (Omegaven, 0.2 g/kg/d; Lipovenoes 10%, 0.6 g/kg/d)	ω-6 fatty acid (Lipovenoes 10%, 0.8 g/kg/d)	5	4
Wei[25]	2014	China	GRC	26/20	ω-3 fatty acid (10% Omegaven, 0.2 g/kg/d, ω-3/ω-6 ratio was 1:4)	ω-6 fatty acid (20% Intralipid,1.0 g/kg/d)	6	4
Heller[23]	2004	Germany	GIC	24/20	0.8 g/kg/d soybean oil + 0.2 g/kg/d fish oil (ω-3/ω-6 ratio was 1:4)	1.0 g/kg/d soybean oil	5	6
Jiang[12]	2009	China	GIC	100/103	0.2 g/kg/d fish oil + 1.0 g/kg/d soybean oil (ω-3/ω-6 fatty acid ratio 1:3)	1.2 g/kg/d soybean oil	7	7
Zhu[22]	2012	China	CRC	29/28	0.2 g/kg/d fish oil + 1.0 g/kg/d soybean oil	1.2 g/kg/d soybean oil	7	7
Liang[21]	2008	China	CRC	20/21	0.2 g/kg/d ω-3 PUFA (ω-3/ω-6 ratio was 1:3)	0.8 g/kg/d soybean oil	7	7
Wachtler[24]	1997	Germany	CRC	19/21	MCT:LCT: fish oil, 5:3:2	MCT:LCT, 5:5	5	6

†CRC: colorectal cancer; GC: gastric cancer; GIC: gastrointestinal Cancer.
‡I: intervention Group; C: control group

our analysis. Five trials were double blinded and had allocation concealment.[12,21-24] The 2 other trials were single blinded. Only the study by Jiang was regarded as a multicenter trial.[12] The ages of participants ranged from 18 to 75 years. Three trials evaluated the effect of ω-3 fatty acids on immune function,[21,25,26] including $CD4^+$ and $CD8^+$ expression and the $CD4^+/CD8^+$ ratio. Five studies reported the outcomes of infectious complications,[12,14,21,22,25] and 5 studies reported length of hospital stay.[12,21-24] The study by Makay et al[14] lacked a data set, and our attempts to contact the author were unsuccessful. When the length of hospital stay was presented as the mean and SD, we extracted the data directly. The standard error of the mean (SEM) was transformed into the SD by using the formula SD = SE x $\sqrt{N}$.[27] The durations of interventions were between 5 and 7 days.

Assessment of validity

We applied the modified Jadad scale to assess the quality of the included studies. The quality score was calculated and all studies were classified as high-quality research. The quality scores of the included studies ranged from 4 to 7, with a median of 6.

Effect of parenteral ω-3 fatty acid supplementation on infectious complications

Figure 2 shows the forest plots of pooled results for the effect of ω-3 fatty acid supplementation on infectious complications. The test of homogeneity indicated no statistical significance (I^2=0%; p=0.459). The 5 pooled trials showed that the incidence of infectious complications was significantly different between the intervention and control groups (OR: 0.36; 95% CI: 0.18, 0.74, p=0.005).[12,14,21,22,25] Parenteral ω-3 fatty acid supplementation was effective in reducing the incidence of infectious complications. In this meta-analysis, the tests for funnel plots were not performed, because fewer than 10 studies were included and the power of the tests was insufficient to distinguish chance from real asymmetry.

Effect of parenteral ω-3 fatty acid supplementation on length of hospital stay

The association between parenteral supplementation with ω-3 fatty acids and length of hospital stay in postoperative gastrointestinal cancer patients is shown in Figure 3. A test revealed no heterogeneity between the included studies (I^2=0%; p=0.981). The pooled WMD was −2.29 (95% CI: −3.64, −0.93; p=0.001). The pooled estimates

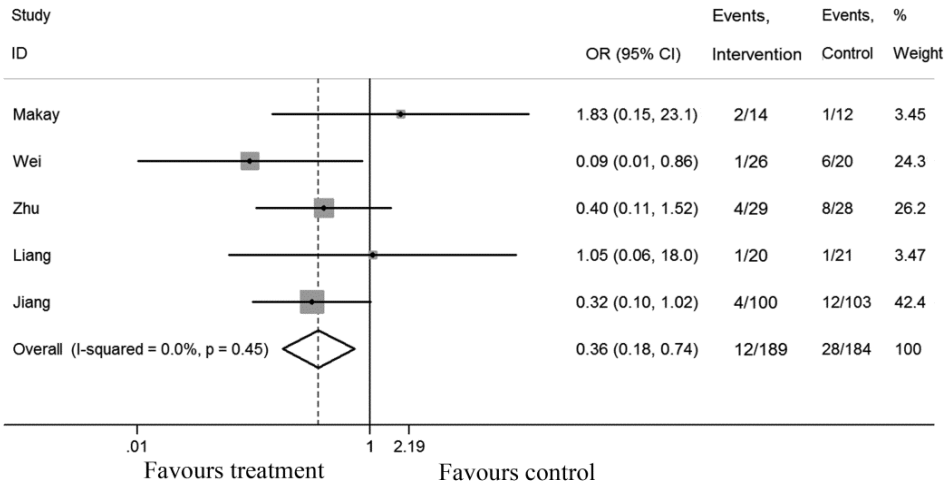

Figure 2. Effect of parenteral ω-3 fatty acid supplementation on infection complications

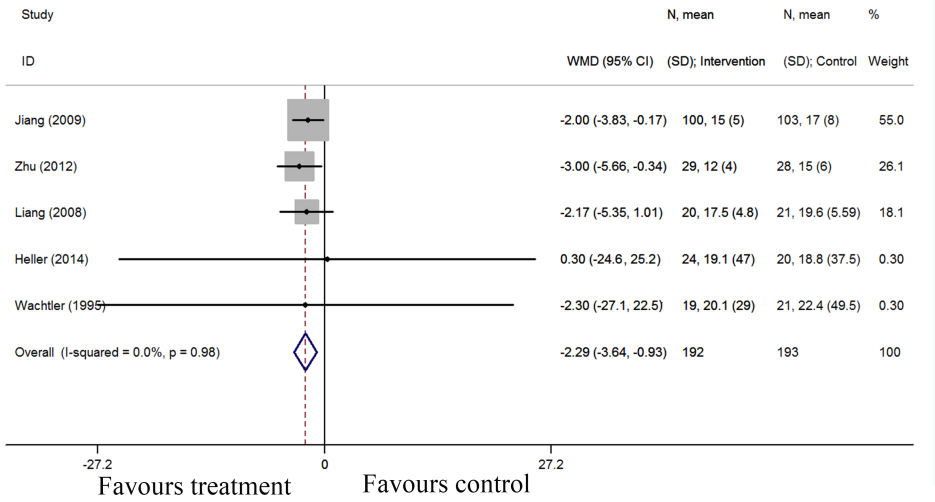

Figure 3. Effect of parenteral ω-3 fatty acid supplementation on length of hospital stay

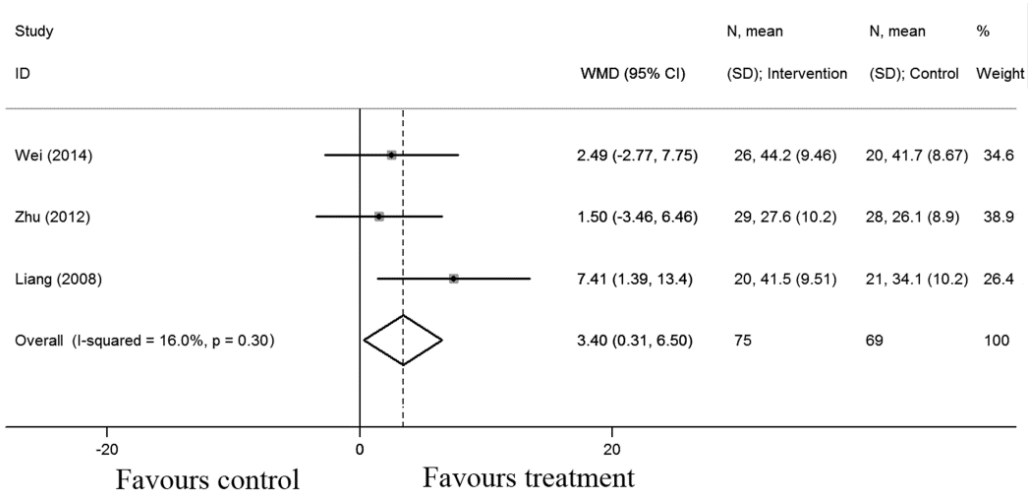

Figure 4. Effect of parenteral ω-3 fatty acid supplementation on $CD4^+$

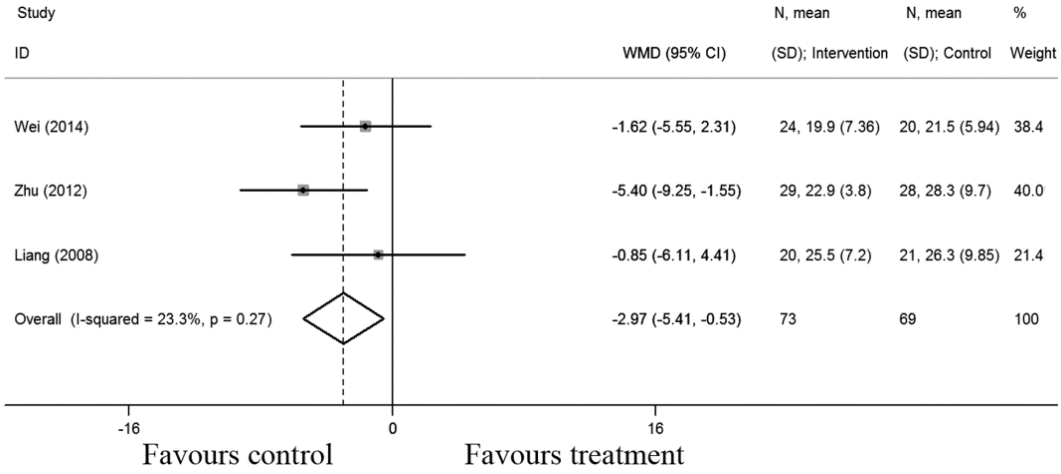

Figure 5. Effect of parenteral ω-3 fatty acid supplementation on $CD8^+$

of 5 trials indicated that ω-3 fatty acid supplementation had a positive effect on length of hospital stay.[12,21-24] The length of hospital stay of patients in the intervention group was shortened by ω-3 fatty acid supplementation compared with that in the control group.

Effect of parenteral ω-3 fatty acid supplementation on immune function

Figures 4, 5, and 6 show the association between parenteral ω-3 fatty acid supplementation and immune function. The pooled data of $CD4^+$ and $CD8^+$ expression and the $CD4^+/CD8^+$ ratio were extracted from 3 trials.[21,22,25] There was a significant difference between the ω-3 fatty acid and control groups at the level of $CD4^+$ (WMD: 3.40; 95% CI: 0.31, 6.50; p=0.031). $CD8^+$ expression was significantly lower in the intervention group compared with the control group (WMD: −2.97; 95% CI: −5.41, −0.53; p=0.017). Meta-analysis indicated that parenteral ω-3 fatty acid supplementation effectively increased the $CD4^+/CD8^+$ ratio (WMD: 0.35; 95% CI: 0.04, 0.66; p=0.028). Overall, there was no significant heterogeneity between the studies.

DISCUSSION

Seven randomized controlled trials with 457 participants were examined in our current meta-analysis. The results indicated an association between parenteral ω-3 fatty acid supplementation and major outcomes in postoperative gastrointestinal cancer participants. This is new evidence that ω-3 fatty acids have a positive effect on clinical outcomes. Infectious complications and length of hospital stay both decreased significantly in the intervention group. This meta-analysis also suggests that parenteral ω-3 fatty acid supplementation is beneficial to immune function, according to summaries of data on $CD4^+$ $CD8^+$ expression and the $CD4^+/CD8^+$ ratio.

To our knowledge, the results of research on perioperative ω-3 fatty acid supplementation have been inconclusive. A recent meta-analysis indicated that parenteral ω-3 fatty acid supplementation shortened the length of hospital stay.[28] Overall, however, the reported results provided insufficient evidence that this form of parenteral nutrition had a significant effect in critically ill patients on mortality, infectious complications, and length of stay in intensive therapy units. Because the trials included in this analysis had insufficient data and a high risk of bias, the results should be interpreted with caution. In 2013, the Canadian Critical Care Nutrition Guidelines suggested that the evidence was insufficient for recommending fish oil supplementation in critically ill patients, and down-

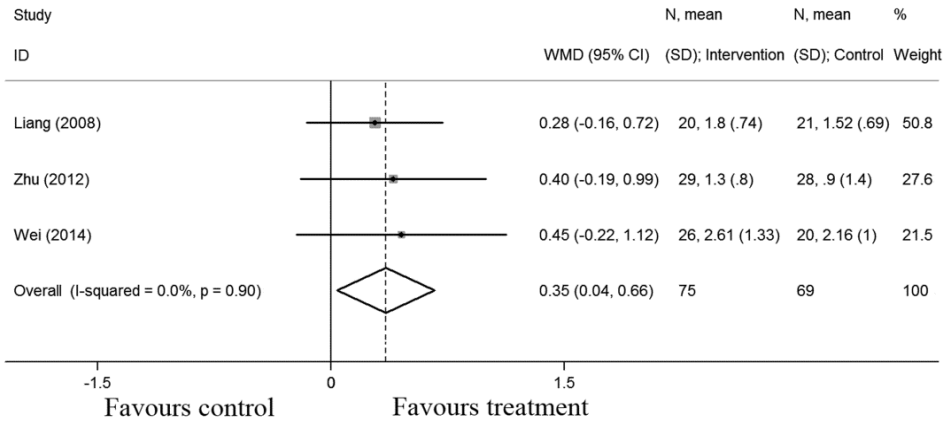

Figure 6. Effect of parenteral ω-3 fatty acid supplementation on CD4+/CD8+ ratio

graded the recommendation for the use of fish oils in patients with acute respiratory distress syndrome.[29] Our study combined the results of previous research and provided positive evidence for the clinical applications of ω-3 fatty acids.

According to most studies included in our meta-analysis, ω-3 fatty acids may also influence the outcomes of the inflammatory response. A potential mechanism is inhibition of leukocyte–endothelial interactions by oxidized ω-3 fatty acids.[30] Additionally, ω-3 fatty acids affect the production of inflammatory mediators and expression of adhesion molecules.[31] However, studies have also shown that ω-3 fatty acids do not significantly affect the levels of interleukin-6, tumor necrosis factor-α, or C-reactive protein in postoperative gastric and colorectal cancer patients receiving parenteral nutrition therapy.[26] In this meta-analysis, we did not assess the association between ω-3 fatty acids and the production of inflammatory mediators, owing to a lack of consistent data. Methods of comparison must be improved to enable such assessment in future studies. According to our findings, the postintervention values of inflammatory mediators and immune indices were directly used to assess the differences between intervention and control groups.[14,22-25] By contrast, Jiang et al reported changes from the baseline in immune status between postoperative days 1 and 8. Similarly, Liang et al reported the mean value difference of 2 sets between postoperative days 1 and 8. Notably, this method may be favorable for eliminating the influence of individual differences, and provides an instructive suggestion for future research.

Our meta-analysis has several strengths. Poor-quality studies were removed from the analysis, which controlled for potential confounding factors and improved the strength of evidence. Additionally, we did not find any heterogeneity between the included studies. However, this study had some limitations that should be considered. First, a systematic search of the literature revealed few trials related to our research topic. Although all the included studies were randomized controlled trials, most of them were single-center trials with small sample sizes. Only one was a multicenter trial with more than 200 participants. Second, only English language studies were included in our analysis, which might have resulted in our missing critical data from non-English language articles. Third, there may be a risk of bias in the meta-analysis. In studies by Heller et al and Wachtler et al,[23,24] length of hospital stay was presented as the mean ± SEM. We emailed the authors in an attempt to obtain the SD data for these studies, but we received no reply. We therefore transformed the SEMs into SDs by using a formula. The forest plots show that the 95% CIs of these 2 studies were wide because of large SDs. Other studies were weighted more heavily, especially that conducted by Jiang. Because the outcomes of length of hospital stay were unstable, the corresponding results must be considered with great caution.

Through conducting this meta-analysis, we found that current nutrition programs do not have an agreed-upon standard for the application of the optimal dose of ω-3 and ω-6 fatty acids and their optimal ratio. In most of the included studies, the ratio of ω-3 to ω-6 fatty acids was 1:3 to 1:4. Arachidonic acid (AA), a type of ω-6 polyunsaturated fatty acid and one of the essential fatty acids in the human body, plays a crucial role in physiology, pharmacology, and health. Metabolites of AA, including prostaglandin and leukotrienes, can induce and modulate the inflammatory response.[31] However, ω-3 fatty acids have been shown to compete with AA. When this occurs, the generation of prostaglandin and leukotrienes decreases, resulting in a decreased inflammatory reaction. This may be a critical factor in the development of cancer.[32]

Another key question is the appropriate time for ω-3 fatty acid intervention in cancer surgery patients. A previous study found that preoperative oral ω-3 fatty acid supplementation could improve perioperative inflammatory and immune responses.[33] Another retrospective study indicated that preoperative parenteral fish oil supplementation resulted in greater clinical benefits in patients after major abdominal surgery than did postoperative fish oil supplementation.[34] However, at present, few studies have been conducted on the relationship between preoperative provision of parenteral fish oil and postoperative outcomes in gastrointestinal cancer patients. Through a search of the literature, we found that short-term preoperative administration of fish oil improves the immune response in patients after gastrointestinal cancer surgery.[15] However, this study did not show a significant difference in the frequency of infectious complications or the lengths of intensive care unit and hospital stay between

preoperative and postoperative administration. Unfortunately, on the basis of the existing data, we could not compare the difference in clinical effectiveness between preoperative ω-3 fatty acid intervention and postoperative supplementation. Future research should focus on solving this problem.

Conclusion

In conclusion, our meta-analysis clearly indicated that parenteral ω-3 fatty acid supplementation is effective in improving the immune function and clinical outcomes of gastrointestinal cancer participants. Our findings may provide support for the clinical application of ω-3 fatty acids. However, these partial results should be treated with caution because of the limitations of and potential risk of bias in the included studies. Large-scale, randomized, prospective trials are warranted to assess the effect of parenteral ω-3 fatty acid supplementation in postoperative gastrointestinal cancer patients.

AUTHOR DISCLOSURES

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