

## Peer Review File

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### First round of peer review

Use of omega-3 fatty acids (O3FA) in parenteral nutrition (PN) has been shown to be of benefit to patients undergoing surgery for colorectal cancer resection. Typically, they improve immunity and reduce inflammation and this is associated with fewer infections and shorter hospital stay. Here the authors report a retrospective analysis of patients with Crohns Disease undergoing surgery some of whom received O3Fa in PN post-surgery and some of whom didn't. O3FA was associated with lower post-op CRP (= less inflammation), fewer complications and shorter hospital stay. The study is novel and sample size is good. The limitation is it isnt a randomised controlled trial. Nevertheless, the data are of interest. The manuscript is generally well written and of interest.

### Major comments:

1. You need to specify when the post-operative blood was collected (e.g., for CRP)

Reply: Thank you for your kind advise. The suggestion you raised is really helpful for us. We added the time when the postoperative blood was collected in the revised manuscript. For example, the postoperative CRP was collected on POD 3, because previous studies have reported that postoperative CRP on POD3 exhibited the best performance in predicting postoperative complications [Ann Surg. 2012 Aug;256(2):245-50] [Dis Colon Rectum. 2017 Mar;60(3):326-334].

Changes in the text: We have modified our text in the revised manuscript and highlighted it (page 4, paragraph 3 of Methods part).

2. The information on the omega-3 intervention is insufficient to a) understand and interpret what was done and b) to repeat the study. The following information needs to be provided:

a) did all patients receive PN

Reply: Thank you for your careful reading. All the patients including in the study received PN after surgery. We described this information in the Methods.

Changes in the text: We highlighted this information in the revised manuscript (page 3, paragraph 1 of Methods part).

b) what was the duration of PN in each group

Reply: Thank you for your careful reading. Patients with the PN used less than 4 days were excluded in this study, in other words, the duration of PN in each group was more than 4 days. We described this information in the Methods.

Changes in the text: We highlighted this information in the revised manuscript (page 3, paragraph 1 of Methods part).

c) what lipid was used in the non-O3FA group

Reply: Thank you for your careful reading. The suggestion you raised is really helpful for us. The medium- and long-chain fat emulsion injection (C6-24, Fresenius Kabi, Bad Homburg, Germany) was supplemented at a dose of 1.0 and 1.2 g/kg/day in groups with and without  $\omega$ -3 PUFAs, which was same as previous studies [JPEN J Parenter Enteral Nutr. 2022 May;46(4):878-886]. In order to make it more accurate, we added this information in the revised manuscript.

Changes in the text: We highlighted this information in the revised manuscript (page 4, paragraph 4 of Methods part).

d) what else was in the PN (and the amounts) - was this the same in both groups

Reply: Thank you for your kind suggestion. Patients receiving PN were divided into two groups according to supplementation or nonsupplementation of  $\omega$ -3 PUFAs. So, the PN was almost the same in both groups, except  $\omega$ -3 PUFAs. We added this information in the revised manuscript.

Changes in the text: We highlighted this information in the revised manuscript (page 4, paragraph 4 of Methods part).

e) how much energy did PN provide (by day) in each group

Reply: Thank you for your kind suggestion. The nonprotein energy was 20-25 kcal/kg/day, and the protein energy was 1.2-1.5 g/kg/day. We added this information in the revised manuscript.

Changes in the text: We highlighted this information in the revised manuscript (page 4, paragraph 4 of Methods part).

f) Was the O3FA PN a commercial source - if so what is it called

Reply: Thank you for your kind advise. The  $\omega$ -3 PUFAs was a commercial source, which was called Omegaven. We added this information in the revised manuscript.

Changes in the text: We highlighted this information in the revised manuscript (page 4, paragraph 4 of Methods part).

g) on line 144 you refer to  $\omega$ -3 PUFAs. By this do you mean EPA+DHA

Reply: Thank you for your kind advise. The  $\omega$ -3 PUFAs include  $\alpha$ -linolenic acid (ALA; 18:3  $\omega$ -3), stearidonic acid (SDA; 18:4  $\omega$ -3), eicosapentaenoic acid (EPA; 20:5  $\omega$ -3), docosapentaenoic acid (DPA; 22:5  $\omega$ -3), and docosahexaenoic acid (DHA; 22:6  $\omega$ -3). So, we mean EPA+DHA.

h) is the dose referred to dose of O3FA or dose of the lipid that contains O3FA (fish oil?)

Reply: Thank you for your kind advise. The medium- and long-chain fat emulsion injection (C6-24, Fresenius Kabi, Bad Homburg, Germany) was supplemented at a dose of 1.0 and 1.2 g/kg/day in groups with and without  $\omega$ -3 PUFAs. The dosage of  $\omega$ -3 PUFAs (Omegaven, Fresenius Kabi, Bad Homburg, Germany) was 0.1-0.2 g/kg/d. In order to make the dose more clearly, we added this information in the revised manuscript.

Changes in the text: We highlighted this information in the revised manuscript (page 4, paragraph 4 of Methods part).

g) were there other lipids/oils in the blend that provided O3FA

Reply: Thank you for your kind suggestion. There were no other lipids/oils in the blend that provided  $\omega$ -3 PUFA.

### **Other comments:**

1. Line 32. incidences -> incidence

Reply: Thank you for your careful reading. We corrected it in the revised manuscript.

Changes in the text: We highlighted this information in the revised manuscript (page 2, Abstract part; page 7, paragraph 2 of Discussion part).

2. Lines 38 and 39, The numbers of patients in the two groups are the wrong way around.

Reply: Thank you for your careful reading. We corrected the numbers of patients in the two groups in the revised manuscript.

Changes in the text: We highlighted this information in the revised manuscript (page 2, Abstract part).

3. Line 43. Need to say when CRP was measured.

Reply: Thank you for your kind suggestion. The suggestion you raised is really helpful for us. We added the time when the postoperative blood was collected in the revised manuscript.

Changes in the text: We highlighted this information in the revised manuscript (page 2, Abstract part).

4. Line 45. reduced incidences of -> fewer

Reply: Thank you for your kind suggestion. We used “fewer” instead of “reduced incidences of” in the revised manuscript.

Changes in the text: We highlighted this information in the revised manuscript (page 2, Abstract part).

5. Line 48-50. In do not understand this. risk factor for what? positive or negative risk factor? Please clarify.

Reply: Thank you for your kind suggestion. We added “the positive or negative risk factor” in the revised manuscript.

Changes in the text: We highlighted this information in the revised manuscript (page 2, Abstract part).

6. Line 66. Delete "considered to be"

Reply: Thank you for your kind suggestion. “considered to be” was deleted in the revised manuscript.

Changes in the text: We highlighted this information in the revised manuscript (page 3, paragraph 1 of Introduction part).

7. Line 67. Delete "of"

Reply: Thank you for your kind suggestion. “of” was deleted in the revised manuscript.

Changes in the text: We highlighted this information in the revised manuscript (page 3, paragraph 1 of Introduction part).

8. Line 100. applied -> conducted

Reply: Thank you for your kind suggestion. “conducted” was used in the revised manuscript.

Changes in the text: We highlighted this information in the revised manuscript (page 3, paragraph 1 of Methods part).

9. Line 116. Delete "Elaborate"

Reply: Thank you for your kind suggestion. “Elaborate” was deleted in the revised manuscript.

Changes in the text: We highlighted this information in the revised manuscript (page 4, paragraph 2 of Methods part).

10. Line 141. body -> patient

Reply: Thank you for your kind suggestion. We used “patient” instead of “body” in the revised manuscript.

Changes in the text: We highlighted this information in the revised manuscript (page 4, paragraph 4 of Methods part).

11. Line 141. subjects -> patients

Reply: Thank you for your kind suggestion. “subjects” was deleted in the revised manuscript.

Changes in the text: We highlighted this information in the revised manuscript (page 4, paragraph 4 of Methods part).

12. Line 181-182. Need to say when CROP was measured

Reply: Thank you for your kind suggestion. We added the time when the postoperative blood was collected in the revised manuscript.

Changes in the text: We highlighted this information in the revised manuscript (page 5, paragraph 2 of Results part).

13. Line 249. reduced -> reduce

Reply: Thank you for your kind suggestion. We used “reduce” instead of “reduced” in the revised manuscript.

Changes in the text: We highlighted this information in the revised manuscript (page 7, paragraph 3 of Discussion part).

14. Line 286. incidences -> incidence

Reply: Thank you for your kind suggestion. We used “incidence” instead of “incidences” in the revised manuscript.

Changes in the text: We highlighted this information in the revised manuscript (page 8, paragraph 1 of Conclusions part).

15. Line 295-296. Not necessary, please delete

Reply: Thank you for your kind suggestion. “Line 2950296” was deleted in the revised manuscript.

Changes in the text: We highlighted this information in the revised manuscript (page 8, Acknowledgements part).

16. Please check all references are complete

Reply: Thank you for your kind suggestion. All references are complete.

17. Table 1. Please add units for each variable listed

Reply: Thank you for your kind suggestion. We added units for each variable listed in the revised Table1.

18. Table 1. Please indicate when the post-op measurements were made

Reply: Thank you for your kind suggestion. We added the postoperative measurements time in Table 1.

19. Table 2. Please provide units for post-op stay

Reply: Thank you for your kind suggestion. We added the units of postoperative stay in Table 2.

20. Table 3. Please provide units where necessary

Reply: Thank you for your kind suggestion. We added units for each variable listed in the revised Table3.

## Second round of peer review

This is the revised version of this manuscript. The authors have taken the comments seriously and the revisions greatly improve the manuscript.

**Comment 1:** However, lines 168 to 174 contain insufficiently precise information to a) interpret and b) repeat this research. Currently these lines read:

"The nonprotein energy was 20-25 kcal/kg/day, and the protein energy was 169 1.2-1.5 g/kg/day. The same standardized PN protocol was used in each group, except with or without  $\omega$ -3 PUFAs. The medium- and long-chain fat emulsion injection (C6-24, Fresenius Kabi, Bad Homburg, Germany) was supplemented at a dose of 1.0 and 1.2 g/kg/day in groups with and without  $\omega$ -3 PUFAs. For homeostasis maintenance, the ratio of heat to nitrogen was 100-120 kcal:1 g. The dosage of  $\omega$ -3 PUFAs (Omegaven, Fresenius Kabi, Bad Homburg, Germany) was 0.1-0.2 g/kg/d."

A: Thank you for your suggestions. After discussion, lines 168-174 were corrected in the revised manuscript.

The following points need attention:

**Comment 2:** "protein energy" is described in "g/kg/day" but those units do not refer to energy. I recommend that you state the carbohydrate, fat and protein content of the infusions as g/kg/day.

A: Thank you for your kind advice. We used "the protein content of infusions" instead of "protein energy" in the revised manuscript.

**Comment 3:** The sentences "The same standardized PN protocol was used in each group, except with or without  $\omega$ -3 PUFAs. The medium- and long-chain fat emulsion injection (C6-24, Fresenius Kabi, Bad Homburg, Germany) was supplemented at a dose of 1.0 and 1.2 g/kg/day in groups with and without  $\omega$ -3 PUFAs." are unclear. Please state the lipid emulsion used in the control group both as oil blend (e.g., soybean oil or 50:50 MCT: LCT or suchlike) and as trade name. Also delete the word "injection".

A: In order to make it more clearly, we corrected this sentence in the revised manuscript. The "injection" was deleted.

**Comment 4:** Regarding comment #2 I take this to mean that Omegaven was simply added on top of the existing emulsion so that patients in the Omegaven group received more lipid than in the control group. If that is the case, please say this.

A: Thank you for your kind advice. Actually, the dosage of  $\omega$ -3 PUFAs (Omegaven, Fresenius Kabi, Bad Homburg, Germany) was 0.2 g/kg/d. The medium- and long-chain fat emulsion (Structolipid, Fresenius Kabi, Bad Homburg, Germany) was supplemented at a dose of 1.0 g/kg/day in the group with  $\omega$ -3 PUFAs supplementation and 1.2 g/kg/day in the group without  $\omega$ -3 PUFAs supplementation, respectively. In other words, Omegaven was not simply added on top of the existing emulsion. In order to make it more clearly, we corrected this sentence in the

revised manuscript.

**Comment 5:** I query the statement "the dosage of  $\omega$ -3 PUFAs (Omegaven, Fresenius Kabi, Bad Homburg, Germany) was 0.1-0.2 g/kg/d", but this might be clarified by the response to comment #3.

A: Thank you for your kind advise. The dosage of  $\omega$ -3 PUFAs was 0.2 g/kg/d, and it was clarified by the response to comment #3.

**Comment 6:** Does the figure of 0.1 to 0.2 g/kg/day refer to how much Omegaven was used? If so, this is the dose of Omegaven not the dose of omega-3 fatty acids, because Omegaven is only 30% omega-3. These are all important points to clarify because errors get perpetuated in systematic reviews and meta-analyses.

A: Thank you for your kind advise. The figure of 0.2 g/kg/day refer to how much Omegaven was used, and it was not the dose of omega-3 fatty acids. So, we used fish oil in the revised manuscript.

**Comment 7:** I do not understand what you mean by "heat" when you say "the ratio of heat to nitrogen"

A: Thank you for your suggestion. "The ratio of heat to nitrogen" was deleted in the revised manuscript, and "the glucose to lipid ratio" was used instead of "the ratio of heat to nitrogen".