Author's response to reviews

Title: A prospective, randomized, controlled study of omega-3 fish oil fat emulsion-based parenteral nutrition for patients following surgical resection of gastric tumors

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Author's response to reviews:

Replies to Reviewers’ Comments

Reviewer 1

Title: Effect of omega-3 fish oil fat emulsion contained parenteral nutrition on patients after surgical operation of gastrointestinal tumors

Version: 1 Date: 3 November 2013

Reviewer: Philip Calder

Reviewer's report:

This manuscript describes a study investigating intravenous fish oil in post surgical patients. This is an area of current interest. Compared with soybean oil, use of fish oil offered advantages with reduced inflammation and fewer complications.

Major compulsory revisions

1. The Introduction is inadequate. It does not provide sufficient background not provide a good rationale for doing the study. With the favourable meta-analyses of Chen and of Wei (both 2010) why are more studies necessary?

Answer: Thank you for reviewing our manuscript and for the critical and helpful comments. We have revised the introduction by providing rationales for carrying out the current study.

2. No data on fatty acid status are presented.

Answer: Information on fatty acid status has been added in the revised manuscript.

3. The Discussion is poor and does not put these findings in the context of the existing literature. What is new and what is confirmatory?

Answer: We have revised Discussion by focusing on the major findings of the
current study and their implications and comparing these findings with those reported by other investigators. We further discussed how the current study contributed to improved understanding of the effect of #-3 fish oil fat emulsion-based parenteral nutrition on nutritional status and postoperative recovery.

4. Abstract, lines 3 and 5. Need to link EPA and DHa to fish oil.
Answer: The 1st sentence has been revised to “Immune nutrients such as #-3 fatty acids including fish oil components EPA and DHA suppress the growth and promote apoptosis of tumor cells, improve immune function and reduce the effects of systemic inflammatory response syndrome” according your suggestion.

5. Abstract, lines 8 and 9. Are these tumours "gastrointestinal" or "gastric".
Please clarify and be consistent.
Answer: We have changed it to “gastric”.

6. Abstract - needs to state that control group received soybean oil.
Answer: We have changed it to “In addition, the intervention group received #-3 fish oil fat emulsion and the control group received soybean oil.”

7. Page 4, Patient selection, lines 5-6. What is meant by "Baseline studies ... at the time of hospital discharge after surgery"? Surely baseline data was collected before surgery?
Answer: We have revised the sentence to “Complete history was taken and physical examinations were carried out. General assessment of nutritional status included measurements of height, body weight and body mass index (BMI) (kg/m2).”

8. If the study was randomised why are there different numbers of patients in each group?
Answer: The initial control group had 26 patients and six patients were excluded because of incomplete data. We have revised it to “Fifty-two patients with gastric tumor were enrolled including 26 males and 26 females aged between 29 and 75 years (median, 53.5 years). These patients were randomly divided into the intervention (26 patients) and control (26 patients) group. Six patients were excluded from the control group because of incomplete data and as a result there were 20 patients in the control group.”

9. Page 5, Nutrition, line 1-2. Delete "as shown in Table 2".
Answer: “as shown in table 2” has been removed.

10. Page 5, Nutrition, line 7. What is meant by "sugar"?
Answer: This place should be glucose, not sugar. The mistake has been corrected.

11. Page 5, Nutrition, line 10. "any intake per oral" should read "any oral intake".
Answer: It has been corrected as suggested.

Answer: The kits of cytokine assays come from USA, BD bioscience.
13. Page 7, General, line 1. Should read "no patients showed any severe complication or death".
Answer: It has been revised as suggested.
14. Page 7, General, line 3. Delete "Baseline .... Table 1".
Answer: “Baseline… Table 1” has been deleted.
15. Page 8, line 5. Table 4 should read Table 2.
Answer: The error has been corrected.
16. Page 8, section heading. Strictly speaking, authors did not assess "immunologic function". Rather percentage of some immune cell subsets was measured. No functions are reported.
Answer: We have changed heading to “immunologic parameters”.
17. The language requires significant attention. There are numerous examples. Here are some of them but there are more:
a) in the title of the paper "contained" should read "containing" and "operation" should read "removal".
b) Abstract, line 1. has should read have.
c) Abstract, line 8. "of gi tumors" should read "for removal of gi tumors".
d) Abstract, line 9-10. Delete "in hospital".
e) Abstract, line 14. "the post-operative days" should read "postoperative day".
f) Abstract, line 18. Delete "incidence".
g) Abstract, 4 lines from bottom. Delete "takings".
h) Page 10 (twice). "eicosane" should read "eicosanoid".
Answer: We have asked Dr. Cui at Department of Surgery of Duke University Medical Center to polish the final version of this manuscript.
Statistical review: No, the manuscript does not need to be seen by a statistician.
Declaration of competing interests:
I receive speaking fees from Fresenius-Kabi the producer of Omegaven, used in this study.

Reviewer 2
Title:Effect of omega-3 fish oil fat emulsion contained parenteral nutrition on patients after surgical operation of gastrointestinal tumors Version:1 Date:12 November 2013
Reviewer:Sigrun Friesecke
Reviewer's report:
The authors examined the effect of parenteral fish oil after abdominal cancer
surgery. Their results are in line with other studies. The authors don’t explain, what their results add to the current knowledge.

Answer: Thank you for reviewing our manuscript and for your constructive comments. The new finding of this study is that #3 fish oil fat emulsion-based parenteral nutrition can alleviate the inflammatory reaction and reduce the rate of inflammatory complications. Compared to other nutrition, #3 fish oil fat emulsion–based parenteral nutrition is conducive to postoperative recovery after gastric cancer surgery.

Only very few references are considered at all. I miss a comparison of their own results to those of other groups.

Answer: We have added additional references in the revised manuscript and also revised the discussion by comparing our findings with those reported by other investigators.

The description of the physiologic effects of omega-3-fatty acids is very short and should be revised fundamentally.

Answer: The description of the physiologic effects of omega-3-fatty acids has been provided in greater detail as suggested.

Details:
1. Title: Fish oil instead of fish oil fat; containing instead of contained
2. Abstract: first sentence: at least two sentences necessary. I’m not sure, what is meant by “numers of immune nutrition” in this context.
   please explain the abbreviations here.
   this is numbers in here, not numers.
   the postoperative days 6: do you mean days 1-6 or day 6?
   Answer: We further proofread the manuscript and have also asked Dr. Cui at Department of Surgery of Duke University Medical Center to help revise the manuscript to eliminate any further errors. “
   The 1st sentence is revised to “Nutrients such as #3 fatty acids including fish oil components eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) suppress the growth and promote apoptosis of tumor cells, improve immune function and reduce the effects of systemic inflammatory response syndrome.”
   Abbreviations are defined and in addition, “the postoperative days 6” is revised to “postoperative day 6”.
2. Introduction:
   first sentence: see Abstract.
   please explain abbreviations EPA and DHA.
   Answer: eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA)
   please explain some physiology to the reader already here.
   Answer: Omega-3 fish oil has mutliple physiologic functions and some of them have been described in the introduction in the submitted manuscript. We have
provided additional functions in the revised manuscript. In addition, the following information has been added: “A recent survey revealed that the content of polyunsaturated fatty acids is likely inadequate in the regular diet of Chinese. A randomized controlled study evaluated the effect of omega-3 fatty acid-supplemented total parenteral nutrition on the clinical outcomes of patients with hepatitis B virus (HBV)-associated hepatocellular carcinoma (HCC) showed that postoperative administration of omega-3 fatty acid reduced infection and improved postoperative hepatic function recovery.”

Please explain a bit more detailed (not only "therefore") why you undertook this study.

Answer: The following has been added in the revised manuscript: “A recent survey revealed that the content of polyunsaturated fatty acids is likely inadequate in the regular diet of Chinese[1]. A randomized controlled study evaluated the effect of omega-3 fatty acid-supplemented total parenteral nutrition on the clinical outcomes of patients with hepatitis B virus (HBV)-associated hepatocellular carcinoma (HCC) showed that postoperative administration of omega-3 fatty acid reduced infection and improved postoperative hepatic function recovery[2]. These findings prompted us to speculate that fatty #3 fish oil fat emulsion-supplemented parenteral nutrition (PN) could be beneficial to the overall functional recovery of gastric tumor patients. Here, we designed a prospective, randomized, single-blinded control clinical trial to investigate the effect of fatty #3 fish oil fat emulsion-supplemented PN on nutritional state, immune function, inflammatory reaction, expression of tumor factors and complication incidence in patients after surgery of gastric tumors.”

3. Material and Methods

- How was the randomisation performed, please explain.

Answer: The patients were randomized using alternative numbers. The following has been revised as follows: “Fifty-two patients with gastric tumor were enrolled including 26 males and 26 females aged between 29 and 75 years (median, 53.5 years). These patients were randomly divided into the intervention (26 patients) and control (26 patients) group. Six patients were excluded from the control group because of incomplete data and as a result there were 20 patients in the control group.”

- What are major gastrointestinal diseases (as exclusion criterion)?

Answer: The exclusion criteria has been revised in the revised manuscript: “Exclusion criteria for the selection of patients included: (1) age < 18 or > 75 years; (2) body mass index (BMI) < 16 or > 30; (3) hepatic insufficiency (Child–Pugh grade B or above); (4) abnormal renal function (serum creatinine > 3mg/dL); (5) ongoing infections, fever in the preceding month; (6) major gastrointestinal disease; (7) autoimmune disorders, steroid treatment, and medication which could modulate metabolism or weight; (8) pregnancy or breast-feeding; (9) received total parenteral support 2 months before operation; (10) severely malnourished (weight loss 10% of body weight during the previous 6 months).”
- "the clinical characteristics...." belongs the the section results.
Answer: The clinical characteristics have been put in Results as recommended.

Nutrition:
- why do you say "sugar", which sugar did you applicate?
Answer: It has been corrected to “glucose”.
- why did the patients not receive enteral nutrition earlier?
Answer: Enteral nutrition was not given as the current study was designed to see if postoperative supplementation could improve the function of gastric tumor patients in the parameters examined.
- why was postoperative antibiotic prophylaxis given for 7 days. I would have expected a shorter period in prophylactic indication.
Answer: The antibiotics were in fact given for 3 to 4 days. The error has been corrected: “prophylactic antibiotic treatment was given for 3 to 4 days postoperatively”.

Immunologic function
- the topic “immune indicator” for lymphocytic subpopulations is unusual at least.
Answer: The immunologic function includes many indicators, for example adhesion molecules, differentiation antigen receptor expression, free radicals, peroxides, antibody production, lymphocyte proliferation, antigen-presenting cell function and natural killer cell cytotoxicity. Among them, lymphocyte proliferation and subsets are often used as a general indicator of immunologic function.

3. Results
- i´m not sure, what you mean with "adverse effects to parenteral nutritional support"
Answer: Parenteral nutritional support has many adverse effects. For example, parenteral nutrition-associated liver disease (PNALD) is the most severe complication of long-term parenteral nutrition.

4. Discussion
- 25-30 Kcal/kg is not "low-calorie" in the first postop. days.
Answer: We agree with the reviewer, and have changed it to “standard calorie.”
- i´m not sure, what you mean with "however, it is clear that nutr. support throughout surgery, chemotherapy... to support the body’s immunity."
Answer: It has been corrected to “However, it is clear that nutritional support is important for patients undergoing surgery or recieving chemotherapy, radiation therapy and other cancer treatments, which also helps maintain the body’s immunity.”
- there are many statements without any citation (phagocytic activity enhanced...release of pro-inflamm cytokines inhibited... antiinflamm cytokines enhanced ...reduced incidence of MODS...).
Answer: We have provided citations for statements that are not from our own work or that are not common knowledge.

5. Tables
please explain the abbreviations used in the context of the table for easier understanding.
Answer: We have explained abbreviations as you suggested.
TLC total T lymphocyte cells
CD3+ CD3+ T lymphocyte cells
CD4+ CD4+ T lymphocyte cells
CD8+ CD8+ T lymphocyte cells
Statistical review: No, the manuscript does not need to be seen by a statistician.
Declaration of competing interests:
I have no competing interests.