Author's response to reviews

Title: Prospective Double-Blind Randomized Study on the Efficacy and Safety of an n-3 Fatty Acid enriched intravenous fat emulsion in Postsurgical Gastric and Colorectal Cancer Patients

Authors:

Cheng-Jen Ma (aisa.hsieh@msa.hinet.net)
Jin-Ming Wu (kptkptkpt@yahoo.com.tw)
Hsiang-Lin Tsai (chunpin870132@yahoo.com.tw)
Ching-Wen Huang (baseball5824@yahoo.com.tw)
Chien-Yu Lu (dr820188@pchome.com.tw)
Li-Chu Sun (lichsu@cc.kmu.edu.tw)
Ying-Ling Shih (ylshih@cc.kmu.edu.tw)
Chao-Wen Chen (ytljwc@yahoo.com.tw)
Jui-Fen Chuang (d790256@gmail.com)
Ming-Hsun Wu (m8101027@hotmail.com)
Ming-Yang Wang (suryang1971@hotmail.com)
Ming-Tsan Lin (linmt@ntu.edu.tw)
Jaw-Yuan Wang (cy614112@ms14.hinet.net)

Version: 2
Date: 8 November 2014

Author's response to reviews: see over
Response to referees

Much appreciated again for your kind efforts and assistance in our manuscript. Response to referee’s comments is as following:

Reviewer: Jay Whelan

1. The authors need to clearly articulate how much n-3 PUFAs were provided, ie., mg/d or g/d. It is difficult to calculate these numbers from the tables. Also, the body weights pre and post 7 day should be provided, not just BMI.

A: The amount of n-3 PUFAs provided is 70-130 mg/kg BW/day (Line 175). The body weights are added on Table 3. We are really sorry for that the body weights and BMI were not completed post 7 days.

2. Lines 175-180: The authors collected data on day -1, before and after surgery, and post op days: day 1, day 3, day 7, yet only presents data on day-1 and day 7. The rest of this data should be presented and analyzed.

A: Data on each day are presented and analyzed (Line 183-184, Line 266-275, Line 326-328, Line 341-344, Figure 2 and Table 5)

3. A concern involves the proinflammatory biomarkers IL-6 and CRP. The CRP data is puzzling in that n-3 PUFAs are known to reduce CRP, if any effect is observed. In this study the CRP levels increased 3 fold in the n-3 group, as compared to an increase of 25% in the control treated group. The IL-6 data is also puzzling in that it is consistent with the CRP data. n-3 PUFAs are known to reduce IL-6. In this study the IL-6 levels were increased almost 5 fold in the n-3 group, but only by 50% in the control treated group. While it is recognized that differences between the groups at pre and post sampling was not statistically different, these trends are nevertheless of concern. Having the ability to review all of the data (day -1, before and after surgery, and post op days: day 1, day 3, day 7) might be helpful.

A: There is a trend that lower values of all IL-6, CRP, TNF-α and PCT in study group on day -1, before and after surgery, day 1, day 3, day 7 and follow up
(figure 2). N-3 PUFAs should reduce proinflammatory biomarkers we selected. However, slight elevation of these biomarkers in both groups indicates mild inflammation in patients undergoing elective surgery with non-infectious diseases may mask such immunomodulatory effects.

4. Regarding the changes in lipid profiles, the authors emphasize the fact that while n-3 PUFAs reduced HDL-C levels, these reductions were not as great as observed in the placebo control group. They should guard against putting too much weight on these kinds of results. As the study was very short (only 8 days: Day-1 to Day 7) and the fractional catabolic turnover rates of LDL and HDL are in the neighborhood of days to weeks. Lipoprotein metabolism is very complex and many factors influence their residence time. As such, their comments should be tempered give the design of the study. Data from the other study days would be.

A: Indeed, we overemphasize the observation that n-3 PUFAs reduced less HDL-C levels. Thanks for your comments. We tempered the comments for n-3 PUFAs and HDL-C (Line 355-359)

5. What follow up has been done with these patients; meaning, what is the real advantage to these patients treated with the n-3 emulsion other than relative modifications to a couple biomarkers within a 7 day window?

A: We expect there will be immunomodulation in patients with gastric or colorectal cancer undergoing curative surgery as other studies conducted in surgical patients shows. However, it fails to reproduce such effects. Our study does reveal comparative safety and tolerance and better lipid elimination. (Line 390-394)

Reviewer: Jairam Vanamala

1. Line 95: Helps to define the forms of malnutrition.

A: The forms of malnutrition are defined, as mentioned in the previous paragraph, one form is preoperative poor gastrointestinal function the other is postoperative stress metabolism. (Line 96)
2. Line 208-219: The section needs to be written in present and not in past tense. Authors should check for these type of mistakes all through the manuscript.

A: The tense mistakes are corrected.

3. Line 231-235: The selection of subjects in the results section is not clear. The authors need to rewrite this section for clarity.

A: The selection of subjects is rewritten (Line 231-238).

4. Line 368: The limitations of the study are presented clearly. The authors should include a separate paragraph on the limitations of the study.

A: The limitations of the study is included in a separate paragraph per your suggestions (Line 376-384)

5. Table 1: Essential fatty acids (LA, n-6). Both groups have values ranging 48-58 g/l although the n-3 group had lower levels of soybean oil supplementation. Check the values and/or provide justification.

A: The value of n-6 in Lipoplus is corrected (Table 1)

6. Table 4: Gamma-GT values – there is a trend observed in increased values of gamma-GT between the study group and the control group – this may be linked to differences in the lipid parameters observed. Was there any correlation between gamma-GT and the lipid parameters?

A: The correlation between gamma-GT and lipid parameters is discussed. Elevation of FFA and TG may lead to increase of fat storage that may cause inflammation of hepatocytes. Consequently, liver enzymes may therefore elevate (Line 362-367).

We sincerely appreciate your effort in reviewing our manuscript again and kind assistance for the improvement of the manuscript quality. They are very helpful in presenting our study in a form suitable to be published in Nutrition Journal.

Professor