Parenteral fish oil as a pharmacological agent to modulate post-operative immune response: A randomized, double-blind, and controlled clinical trial in patients with gastrointestinal cancer

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Introduction

- **Parenteral Nutrition (PN)**
  - An intravenous mixture containing multiple nutrients: fluids, proteins, carbohydrates, fats, vitamins, and minerals. It may be used to provide full or partial nutrition to people who are not able to sustain their nutrition via the gastrointestinal tract.

- **Fish Oil Lipid Emulsion (FOLE)**
  - Long-chain omega-3 polyunsaturated fatty acids (n-3 PUFA) consisting primarily of eicosapentanoic (EPA) and docosahehexanoic (DHA) acids.
Introduction

Benefits of PN-FOLE

- Avoids digestive and absorptive losses of n-3 PUFA’s
- Incorporates into plasma and blood cells at a faster rate than enteral nutrition (EN)
- Induces an improved post-operative balance of inflammatory mediators with a decrease in post-operative infection rates
Rationale

- **Aim/Hypothesis**
  - To assess post-operative immune response after short-term pre-operative parenteral infusion of isolated FOLE in gastrointestinal cancer patients

- **Additional goals**
  - To assess post-operative duration of stay in ICU after short-term pre-operative parenteral infusion of isolated FOLE in gastrointestinal cancer patients
  - To assess patients with an additional risk of having complications
    - Elderly age 60+ and/or malnourished patients
Methods

Patients

- Adults ages 18-75 admitted for elective resection of gastric or colon cancer
- 2 blocks of patients, 50 in each block
- Exclusions include
  - Allergy to any ingredient of FOLE, infection (i.e. AIDS), inflammatory disease (i.e. arthritis), immunologic disease (i.e. lupus), metabolic disease (i.e. diabetes mellitus), dementia, and implanted electromagnetic instruments
Methods

- **Lipid Treatment**
  - FOLE – Omegaven 10%
  - Control Group – MCT/LCT – Lipovenos MCT 10%
  - 3 days before surgery, 0.2g fat/kg of total body weight of lipid emulsions (LEs) was continuously infused for 6h per day. Location of the exclusive peripheral venous access was changed daily.
**Methods**

- **Inflammatory mediators**
  - IL-6 and IL-10 by ELISA
  - CRP by immunoturbidimetric method
  - Prostaglandin E$_2$ (PGE$_2$) by Biotrack enzyme immune assay system via spectrophotometer reader
Results

- **84 patients underwent randomization**
  - 40 were assigned to FO infusion
    - 9 were lost to follow-up
    - Random analysis of Immunological markers
      - Interleukin-6 (n = 24)
      - Interleukin 10 (n = 20)
      - C Reactive Protein (n = 8)
      - Prostaglandin E₂ (n = 7)
      - Chemotaxis (n = 13)
      - Phagocytosis (n = 20)
      - Oxidative Burst (n = 20)
      - HLA-DR Expression (n = 20)
      - CD32 Expression (n = 20)
  - 44 were assigned to MCT/LCT Infusion
    - 12 were lost to follow-up
    - Random analysis of Immunological markers
      - Interleukin-6 (n = 26)
      - Interleukin 10 (n = 26)
      - C Reactive Protein (n = 8)
      - Prostaglandin E₂ (n = 7)
      - Chemotaxis (n = 9)
      - Phagocytosis (n = 11)
      - Oxidative Burst (n = 12)
      - HLA-DR Expression (n = 12)
      - CD32 Expression (n = 12)
Results

TO = START OF INFUSION, T1 = PRE-OPERATIVE POST-INFUSION, T2 = POST-OPERATIVE DAY 3, T3 = POST-OPERATIVE DAY 6
**Results**

TO = START OF INFUSION, T1 = PRE-OPERATIVE POST-INFUSION, T2 = POST-OPERATIVE DAY 3, T3 = POST-OPERATIVE DAY 6
RESULTS

E) Leukocyte Oxidative Burst

F) HLA-DR Molecules Expression

TO = START OF INFUSION, T1 = PRE-OPERATIVE POST-INFUSION, T2 = POST-OPERATIVE DAY 3, T3 = POST-OPERATIVE DAY 6
RESULTS

G) CD32 Molecules Expression

H) CD32 Molecules Expression

TO = START OF INFUSION, T1 = PRE-OPERATIVE POST-INFUSION, T2 = POST-OPERATIVE DAY 3, T3 = POST-OPERATIVE DAY 6
Results

Table 3
Inter-group changes in the mean of the difference in variation of immunological markers from patients with gastrointestinal cancer who were pre-operatively treated for 3 days with a peripheral infusion of a fish oil parenteral lipid emulsion (FO) that was rich in omega-3 fatty acids, or a control parenteral lipid emulsion (MCT/LCT) that was rich in medium-chain triglycerides. Data are expressed as mean ± standard deviation and analyzed by the Wilcoxon test.

<table>
<thead>
<tr>
<th>Immunological marker</th>
<th>Group</th>
<th>T1–T0</th>
<th>P value</th>
<th>T2–T0</th>
<th>P value</th>
<th>T3–T0</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Interleukin-6</td>
<td>FO</td>
<td>−0.05 ± 0.30</td>
<td>&lt;0.0001*</td>
<td>0.09 ± 0.52</td>
<td>0.029*</td>
<td>0.22 ± 0.60</td>
<td>0.202</td>
</tr>
<tr>
<td></td>
<td>MCT/LCT</td>
<td>0.15 ± 0.26</td>
<td>1.29 ± 1.18</td>
<td></td>
<td></td>
<td>0.60 ± 0.99</td>
<td></td>
</tr>
<tr>
<td>Interleukin-10</td>
<td>FO</td>
<td>−0.005 ± 0.05</td>
<td>0.019*</td>
<td>0.76 ± 0.32</td>
<td>&lt;0.0001*</td>
<td>−0.07 ± 0.13</td>
<td>&lt;0.0001*</td>
</tr>
<tr>
<td></td>
<td>MCT/LCT</td>
<td>0.01 ± 0.03</td>
<td>−0.10 ± 0.03</td>
<td></td>
<td></td>
<td>0.20 ± 0.04</td>
<td></td>
</tr>
<tr>
<td>Oxidative burst</td>
<td>FO</td>
<td>−0.08 ± 0.65</td>
<td>0.632</td>
<td>−0.96 ± 0.70</td>
<td>0.028*</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td></td>
<td>MCT/LCT</td>
<td>0.11 ± 0.78</td>
<td>−1.16 ± 0.73</td>
<td></td>
<td></td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Percentage HLA-DR (Mφ)</td>
<td>FO</td>
<td>2.67 ± 15.94</td>
<td>0.464</td>
<td>−2.31 ± 7.83</td>
<td>0.046*</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td></td>
<td>MCT/LCT</td>
<td>−8.11 ± 31.20</td>
<td></td>
<td>−15.86 ± 18.92</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Percentage CD32 (Mφ)</td>
<td>FO</td>
<td>1.17 ± 12.98</td>
<td>0.253</td>
<td>0.19 ± 12.48</td>
<td>0.025*</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td></td>
<td>MCT/LCT</td>
<td>−4.96 ± 7.84</td>
<td>−15.11 ± 16.72</td>
<td></td>
<td></td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Intensity CD32 (Nφ)</td>
<td>FO</td>
<td>−0.14 ± 99.87</td>
<td>0.200</td>
<td>65.00 ± 138.84</td>
<td>0.010*</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td></td>
<td>MCT/LCT</td>
<td>−1.23 ± 35.68</td>
<td>20.26 ± 91.61</td>
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<td>–</td>
<td>–</td>
</tr>
</tbody>
</table>

Mφ = Monocytes; Nφ = Neutrophils.
Results

Table 4
Immediate post-operative clinical outcomes of patients with gastrointestinal cancer who were pre-operatively treated for 3 days with a peripheral infusion of a fish oil parenteral lipid emulsion (FO) that was rich in omega-3 fatty acids, or a control parenteral lipid emulsion (MCT/LCT) that was rich in medium-chain triglycerides.

<table>
<thead>
<tr>
<th>Lipid emulsion</th>
<th>Complications (%)</th>
<th>Length of stay (mean of days ± standard deviation)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Infectious</td>
<td>Intensive care unity</td>
</tr>
<tr>
<td></td>
<td>T</td>
<td>R</td>
</tr>
<tr>
<td>FO</td>
<td>6.5&lt;sup&gt;a&lt;/sup&gt;</td>
<td>10&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>MCT/LCT</td>
<td>15.6&lt;sup&gt;b&lt;/sup&gt;</td>
<td>27.8&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>p value</td>
<td>0.426</td>
<td>0.222</td>
</tr>
</tbody>
</table>

T: total patient; R: patient with additional risk (elderly and/or malnourished).  
<sup>a</sup> Local surgical wound (n = 1) and pneumonia (n = 1).  
<sup>b</sup> Local surgical wound (n = 3) and sepsis (n = 2).
Discussion/Conclusions

- Favorable modulation of post-operative immune mediators
  - Preserved or improved leukocyte phenotype
- Rapid immune function modulation with improved clinical outcomes
- Low adverse effects of infusion
  - Nausea, vomiting, local phlebitis n = 3 for FOLE, n = 2 for control
  - All adverse effects disappeared without interruption of LE treatment
- MCT/LCT emulsion contains 50% less n-6 than similar studies utilizing soybean oil
Discussion/Conclusions

- Post-operative CRP significantly increased in patients only treated with control LE
- Favorable IL-10 modulation day 3 post-operation followed by a decrease by day 6
- Decreased HLA-DR positive monocytes, Decreased CD32 expressing monocytes, decreased oxidative burst in control group versus FOLE group preserving leukocyte phenotype
- No significant difference between control group and FOLE group for frequency of post-surgical infection or length of ICU or hospital stay
- Pre-operative infusion of FOLE may attenuate immune dysfunction after surgical trauma
Discussion/Conclusions

- Future research focusing on the elderly and malnourished groups are needed due to smaller variation of length of ICU stay.
- Future research on patients not requiring PN could verify the post-surgical benefits found aiding in avoiding post-operative immune paralysis and multiple organ failure.