The Effect of Omega-3 Enriched Parenteral Lipid Emulsion on Leukotriens B5 in Cancer Patients Undergoing GIT Surgery; A Comparative Study between SMOFlipid and Intralipid

MOHAMMED A. ABDEL WADOD, M.Sc.; MOHAMMED M. HASSAN, M.D.; SAMAH A. LOUTFY, M.D.; WAFA T. SALEM, M.D. and WAEL A. IBRAHIM, M.D.
The Departments of Anesthesiology & Pain Relief and Virology & Immunology*, National Cancer Institute, Cairo University

Abstract

Background: Malnutrition in cancer patients who are candidates for major surgery is considered a problem because it represents a risk factor for postoperative morbidity and mortality. Administration of standard parenteral diets supplemented with omega-3(ω-3) fatty acids (immunonutrition) modulates immune and inflammatory responses and gut function in elective surgical patients, immunonutrition is associated with a reduction in infectious complication rates and a shorter length of hospital stay.

Patients and Methods: The present study included 40 patients divided to two groups, group A: Including 20 patients receiving the traditional intralipid emulsion, and group B: Including 20 patients receiving the new omega-3 SMOFlipid 20% lipid emulsion. The Subjective Global Assessment method of nutrition (class B and C) is used as screening test to select patients in the study which takes into consideration body weight, dietary intake, GIT symptoms. In all patients parenteral nutrition support was started at day 1 to provide 25-30 kcal/kg/d and 1-1.5g protein/kg/d, at least for 7 days post operative. 30-40% of non protein caloric intake was provided from lipid emulsions. All patients received perioperative fluids, electrolytes, trace elements, micronutrients, prophylactic antibiotics, and deep venous thrombosis and stress ulcer prophylaxis as clinically prescribed.

Parameters measured in the study were leukotriens B5 (LTB5) as anti-inflammatory mediator which were quantified using ELISA technique. Other parameter measured were weights, serum Na, K, Ca, Mg and kidney functions (urea & creatinine).

Results: Leukotriens B5 were non significant between the two groups in the first day postoperatively (p=0.22), but are statistically significant at day 7 postoperatively (p=0.001) in group B supplemented by SMOFlipid.

Conclusion: This study demonstrates the beneficial immunomodulation effect of Omega 3 enriched parenteral nutrition represented by elevation of LTB5 after 7 days of nutrition with SMOFlipid compared with intralipid.

Key Words: Omega3 – Lipid emulsion – Leukotriens B5 – Cancer patients – GIT – SMOFlipid – Intralipid.

Introduction

LIPID emulsion in its ideal form should be accessible for metabolic breakdown, but should not raise any inflammatory or oxidative stress or impair the immune system. Novel lipids have recently been introduced in the clinical practice which can modulate inflammatory responses in a favorable manner to improve the outcomes of patients with immune-mediated conditions.

The 3 principal families of unsaturated FAs are the ω-9, ω-6, and ω-3 families. This means of classification indicates the carbon on which the first double bond occurs when counting from the methyl carbon of the hydrocarbon chain. The simplest ω-6 and ω-3 PUFAs are linoleic acid (18:2n-6) and alpha-linolenic acid (18:3n-3), respectively [1].

Linoleic and alpha-linolenic acids are termed essential FAs because their de novo synthesis is not possible and availability, so, completely depends on the diet. Metabolism of linoleic acid yields arachidonic acid (AA, 20:4n-6) as the major end product, while eicosapentaenoic (EPA, 20:5n-3) and docosahexaenoic acid (DHA, 22:6n-3) are end products of the metabolism of alpha-linolenic acid. The metabolism of linoleic acid is quantitatively more important because the diet contains 5 to 20 times more linoleic than alpha-linolenic acid. Therefore, blood and cell lipids contain much more AA than do very-long-chain ω-3 PUFAs. The only rich dietary source of very-long-chain ω-3 PUFAs is seafood, especially fatty fish such as salmon and mackerel [2].
There is competition for metabolism between linoleic and alpha-linolenic acids, and also competition between AA and EPA for incorporation into cell membranes and for metabolism to bioactive eicosanoid mediators [3].

EPA is metabolized by the enzyme cyclooxygenase into 3 series prostaglandins and thromboxanes (such as PGE3, PG13, TXA3) and by the enzyme 5-lipoxygenase to form the 5 series leukotrienes (LTB5, C5, D5, E5). AA is converted by the same enzymes into the 2 series prostaglandins and thromboxanes (such as PGE2, PG12, TXA2) and the 4 series leukotrienes (LTB4, C4, D4, E4). The EPA-derived lipid mediators are markedly different compared to the analogous AA derivatives with regard to their structure and biological activity [4].

The functional significance is that the products formed from EPA are typically less potent than are those formed from AA. Increased provision of EPA results in partial replacement of AA in cell membrane phospholipids, with a resulting decrease in capacity to produce the AA-derived eicosanoids and an increased capacity to produce those from EPA [3].

LTB5 possesses a considerably reduced vasoconstrictive and chemotactic potency in comparison to LTB4. Moreover, EPA and DHA could directly act as LTB4 receptor antagonists. Consequently, the formation of platelet activating factor (PAF), which has a strong pro-inflammatory and platelet aggregating effect, is also reduced by EPA. Also, a reduced formation of the pro-inflammatory cytokines interleukin (IL)-1, IL-6 and TNF-B has been demonstrated [5].

Omega-3 PUFA affects biophysical characteristics of cellular membranes by alteration of the membrane phospholipid composition and the content of cholesterol, which improves membrane fluidity. Furthermore, ω-3 PUFA modify the function of membrane linked enzyme systems, signal transduction and receptor functions [6].

The proportion of ω-6 and ω-3 fatty acids in the precursor pool appears to be important for the pharmacological effects of the resulting eicosanoid profile. Based on multiple data, a ω-6/ ω-3 ratio of 4:1 to 2:1 in lipid emulsions is recommended [7].

Patients and Methods

The study extended over 6 months from May 2014 to end of November 2014 and designed as Prospective randomized controlled trial. The study started by examining all the patients preoperatively at the National Cancer Institute (NCI), Cairo University. Ethical approval was obtained from Research Ethical Committee of National Cancer Institute and informed consent was obtained from participants in the study.

Patients selected to fulfill the inclusion criteria out of the 65 patients examined only 40 patients fulfilled the following inclusion criteria:

**Inclusion criteria:**

- Subjective global assessment class B and C.
- Patient between 18-70 years undergoing elective surgery for GIT cancer.

**Exclusion criteria:**

- Patient less than eighteen years, Denied written consent, History of multiple drug allergies, ASA (American Society of Anesthesiologists) physical status score more than 3, Renal insufficiency (patient on haemodialysis or serum creatine level >3mg/dl or both), Hepatic insufficiency (Child classification C), Ongoing infection and Immunosuppressive diseases (including steroid therapy).

**Duration of the study:**

The study extended over 6 months from May 2014 to end of November 2014.

**Study procedure:**

Forty Patients were randomized using permuted block randomization method into two groups (20 each):

**Group A:** Including 20 patients receiving the traditional intralipid emulsion.

**Group B:** Including 20 patients receiving the new omega 3 SMOflipid 20% lipid emulsion.

In all patients parenteral nutrition support was started at day 1 to provide 25-30 kcal/kg/d and 1-1.5g protein/kg/d, at least for 7 days post operative. 30-40% of non protein caloric intake was provided from lipid emulsions.

All patients received perioperative fluids, electrolytes, trace elements, micronutrients, prophylactic antibiotics, and deep venous thrombosis and stress ulcer prophylaxis as clinically prescribed.

The Subjective Global Assessment method of nutrition (class B and C) is used as screening test to select patients in the study which takes into consideration body weight, dietary intake, GIT symptoms.
All patients will be subjected to full medical history including age, renal diseases, and hepatic diseases, intake of corticosteroids immunosuppressive therapy and known hypersensitivity reaction. Complete medical examination is done including weight, height, blood pressure, pulse, temperature, respiratory rate, urine output, chest and abdominal examination.

Measured parameters:
1. Laboratory investigation for immunological studies:
   Collection of blood and specimens storage: 5ml of venous blood was collected from each patient, part on blood was collected on EDTA and the other part was collected in gel tubes for separation of serum. Patient’s sera were aliquoted and stored at −40ºC for later analysis. On 1st day of regimen and postoperative day 7, the inflammatory related Cytokines leukotriens B5 were measured as anti-inflammatory mediator which was quantified using ELISA technique.

2- Monitor routine labs especially electrolytes closely: Serum Na, K daily. Serum Ca, Mg twice weekly then every week.
3- Serum creatinine & urea.
4- Re-assess caloric needs as clinical situation dictates.
5- Weights every other day.

Statistical analysis:
Sample size estimation:
Minimum sample of 20 patients in each group were enough to detect this change at an alpha level of 0.05, and power of study of 80%.

Statistical methods:
Data management and analysis were performed using Statistical Package for Social Sciences (SPSS) vs. 17.

Data were summarized and analyzed; and the results were reported as mean ± SD. Comparisons between groups with respect to normally distributed numeric variables were done using the t-tests. None normally distributed numeric variables were compared by Mann-Whitney test, a nonparametric test equivalent to the Student’s t-test. The chi-square test or the Fisher’s exact test for small sample size was used to compare between the groups with respect to categorical data.

Results

There is no statistical difference between the 2 groups; p-value is 0.59 and 0.45 regarding age and height respectively. Table (1).

Regarding weight, there is no statistical difference between the 2 groups at day 1, 3, and 7 postoperatively; p-value is 0.75, 0.77 and 0.83 respectively. Table (2).

Regarding LTB5 (leukotriene B5), there is no statistical difference between the 2 groups at day 1; p-value is 0.22 but showing statistical difference between both groups at day 7 postoperatively where the level of LTB5 in SMOFl lipid group increases more than in intralipid group; p-value is 0.001. Table (3), Fig. (1).

Table (1): Demographic data (age and height) in both lipid groups [Mean ± (SD)].

<table>
<thead>
<tr>
<th>Item</th>
<th>Lipid Group</th>
<th>Mean ± (SD)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>Intra</td>
<td>51.00 ± (12.64)</td>
<td>0.59</td>
</tr>
<tr>
<td></td>
<td>SMOF</td>
<td>53.00 ± (10.198)</td>
<td></td>
</tr>
<tr>
<td>Height</td>
<td>Intra</td>
<td>171.33 ± (7.738)</td>
<td>0.45</td>
</tr>
<tr>
<td></td>
<td>SMOF</td>
<td>173.20 ± (7.466)</td>
<td></td>
</tr>
</tbody>
</table>

SD = Standard Deviation. p<0.05 is significant.

Table (2): Demographic data (weight) in both lipid groups [Mean ± (SD)].

<table>
<thead>
<tr>
<th>Item</th>
<th>Lipid Group</th>
<th>Day 1</th>
<th>Day 3</th>
<th>Day 7</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight</td>
<td>Intra</td>
<td>76.667 ± (10.4149)</td>
<td>76.306 ± (10.6165)</td>
<td>75.944 ± (10.914)</td>
<td>0.75</td>
</tr>
<tr>
<td></td>
<td>SMOF</td>
<td>77.700 ± (8.986)</td>
<td>77.175 ± (8.9872)</td>
<td>76.650 ± (9.022)</td>
<td>0.83</td>
</tr>
</tbody>
</table>

p<0.05 is significant.

Table (3): LTB5 in both groups [Mean ± (SD)].

<table>
<thead>
<tr>
<th>Item</th>
<th>Lipid Group</th>
<th>Day 1</th>
<th>Day 7</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>LTB5</td>
<td>Intra</td>
<td>0.21306 ± (0.145536)</td>
<td>0.22</td>
<td>0.001 *</td>
</tr>
<tr>
<td></td>
<td>SMOF</td>
<td>0.28845 ± (0.217699)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*p<0.05 is significant.
Intra
SMOF
0.45
0.4
0.35
0.3
0.25
0.2
0.15
0.1
0.05
0
0
LTB5
LTB5 in both groups.

Fig. (1): LTB5 in both groups.

Discussion

Postoperative care of cancer patients underwent major surgeries necessitates infusion of total parenteral nutrition in which lipid infusion is one of its constituents. Intravenous lipid emulsion is not only supplying energy through the essential fatty acids contained but also these essential fatty acids affect the immune system and may lead to immunosuppression and excessive inflammation. This effect is important in critically ill patients and it may lead to organ failure which is the main cause of death among ICU patients [3].

It has been found that the ratio of \( \text{C16:6} \) to \( \text{C18:3} \) PUFAs in parenteral lipids, to support the immune system, should mirror the nutritional environment in which human evolution occurred. A novel emulsion has been developed which is so-called SMOFlipid (Fresenius-Kabi) is a 20% lipid emulsion with the lipid being a mix of 30% MCT, 30% SO, 25% OO, and 15% FO, resulting in a ratio of \( \text{C16:6} \) to \( \text{C18:3} \) PUFAs of 2.5:1 [8].

Intravenous infusion of fish oil rapidly leads to an incorporation of \( \text{C18:3} \) fatty acids in leukocyte cell membrane phospholipids, leading to a reduced production of proinflammatory cytokines because of a higher ratio of \( \text{C16:6} \) to \( \text{C18:3} \) fatty acids [9].

SMOFlipid has beneficial advantage over Intralipid that it contains 30g fish oil/1000ml (15% of the mixture). It is valuable source of very long-chain \( \text{C18:3} \) fatty acids (eicosapentaenoic acid, EPA and docosahexaenoic acid, DHA), which improve standard clinical therapy especially in hyperinflammatory conditions and as an adjunct therapeutic measure after trauma, injury, and during episodes of early sepsis.

Demographic data including age, height and weight showed statistically non significant results between the two groups.

We got laboratory investigations for immunological studies including measuring of leukotriens B5 (LTB5) as anti-inflammatory mediator related cytokines that would be quantified using ELISA technique at day 1 and 7 postoperatively.

In our study, results regarding LTB5 were non significant between the two groups in the first day postoperatively (\( p=0.22 \)), but are statistically significant at day 7 postoperatively (\( p=0.001 \)) showing the beneficial immunomodulation effect of Omega 3 enriched parenteral nutrition represented by elevation of LTB5 after 7 days of nutrition with SMOFlipid compared with Intralipid.

In agreement with our results, Grimm et al., 2006 [10], study conducted to assess the effects of SMOFlipid emulsion with reduced content of \( \text{C16:6} \) fatty acids (FA), increased share of \( \text{C18:3} \) FA on leukotriens pattern in surgical patients. They study 33 patients received isonitrogenous, isocaloric TPN over 5 postoperative days following major abdominal surgery. 19 patients received SMOFlipid 20% and 14 patients a standard soybean oil emulsion (intralipid 20%). Leukotriens B5 (LTB5) release in leukocytes was assessed. They found that LTB5 release was enhanced on day 6 significantly with SMOFlipid. The study conclude that treatment with SMOFlipid is well tolerated and modulates FA and leukotriens pattern suggesting favorable anti-inflammatory effects and further clinical benefits.

Another study conducted by Wichmann et al., in 2007 [11], to prove safety and effectiveness of a lipid emulsion enriched with \( \text{C18:3} \) fatty acids from fish oil within the setting of parenteral nutrition of patients after major abdominal surgery. Patients were randomized to receive either SMOF (group I; \( n = 127 \) patients) or Intralipid (group II; \( n = 129 \) patients). Parenteral nutrition was initiated immediately after surgery and ended on day 5 after surgery. Results show that plasma levels of LTB5 were significantly increased in group I.

Also study conducted by Koeller et al., 2003 [9], comparing between two groups; Group 1 (n=14) received an omega-3 fatty acid enriched 20% lipid emulsion SMOF for 5 days postoperatively. Group 2 (n=16) received a standard 20% fat emulsion Intralipid. There was a significant increase in the generation of LTB5 (\( p=0.0035 \)), but not in the reference group after 5 days infusion of the lipid emulsions. The study conclude that nutritive enrichment with omega-3 fatty acids in a balanced ratio with omega-6 fatty acids is an important step to avoid hyperinflammatory situations in patients after major surgery.
Conclusion:
Data obtained in this study showed that SMOF-lipid is better than Intralipid regarding immunomodulation of the inflammatory response to surgery and better function of the immune system with improved outcomes regarding morbidity and mortality.

References