Investigation for the Effects of Omega 3 Fatty Acid and Glutamine-L-Alanine on Morbidity and Mortality in the Critically ILL Patients after Major Abdominal Surgery

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Abstract: *Background & Objectives*: This study investigated the effects for the addition of omega 3 fatty acids and glutamine-L-alanine to the standard enteral and/or parenteral nutrition regimen on infection and mortality in the critically ill patients after major abdominal surgery.

Methods: This is a prospective, randomized, single center study. A total of 43 patients (age range: 18-85 years), who were in the critical care unit after major abdominal surgery, were included. Patients were divided into two groups according to simple randomized selection [Control group, n=20; Study Group, n=23 (omega3 fatty acids and glutamine-L-alanine)] and were monitored for 21 days. Patients were examined for the assessment of APACHE II Score and existence of ALI (acute lung injury)/ARDS (acute respiratory distress syndrome) requiring mechanical ventilation. In addition to standard enteral or parenteral nutrition, patients in the study group were given parenteral pharmaconutrition products for 10 days postoperatively. Groups were compared for the duration of mechanical ventilation, duration of stay in the intensive care unit and hospitalization, and mortality. Laboratory parameters including CRP, TNFα, IL6, IL8, nitrogen balance, albumin, and total lymphocyte count were recorded.

Results: Although the mean APACHE score was higher in study group in which patients received omega-3 fatty acids and glutamine-L-alanine support, the clinical infection rate seemed to decrease insignificantly.

Conclusions: A clinically decreased rate of infection was observed in patients with a high APACHE II score, or who received omega-3 fatty acids, glutamine-L-alanine, are required to be administered more selectively and in larger patient groups in different doses and in combination protocols in accordance with the current pharmaconutritional support and in different timing combinations, including preoperative period.

Keywords: Omega-3, glutamine- L-alanine, enteral nutrition, parenteral nutrition, ICU.

INTRODUCTION

Nutritional support has been a major component of the treatment for the critically ill patients. While it is only a supportive treatment in some elective patients, it may even increase chance of life when administered appropriately in the critically ill patients. Although the etiology of the ICU admission is based on a large spectrum of diseases, the process of developing systemic inflammatory response syndrome (SIRS) is similar in all patients. In addition to the efforts the treatment of primary cause in those patients, nutritional support has gained an absolute place among the methods that prevent SIRS or modulate its progression and even treat it after it develops [1, 2].

In light of this knowledge, in the critically ill patient group that underwent major abdominal surgery, the addition of pharmaconutrition agents (omega-3 fatty acid and glutamine-L-alanine) which help regulate the body's response to illness and increase infections ratio was planned to investigate the effects of these agents on the duration of hospitalization in the intensive care unit, biochemical parameters (CRP, TNFα, IL6, IL8), and mortality.

MATERIALS AND METHODS

Approval was obtained from Haydarpasa Numune Teaching and Research Hospital's Ethics Committee for the study. Forty-three patients (19 females, 24 males), who required intensive care after major abdominal surgery, were monitored for 21 days. Patients were randomised into two groups according to the closed envelope method; the control group had standardized enteral and/or parenteral nutrition and the study group of patients were administered omega-3 fatty acid and glutamine-L-alanine, in addition to the standart nutrition protocol.

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Patients with APACHE II > 25, lipid metabolism disorders (serum triglyceride level > 400 mg/dl), renal failure (serum creatinine > 3 mg/dl), liver failure, requirement in high dose of vasoconstrictors, and allergic reactions to fish and egg proteins were excluded from the study.

Daily energy requirements (25-30 kcal/kg/day) were calculated in each patient in both groups. Patients with enteral intolerance or who had a contraindication for enteral nutrition were started on parenteral nutrition. The patients were frequently reassessed for enteral nutrition and were started on enteral nutrition as soon as possible. Full dose parenteral nutrition was continued in patients who had inadequate enteral tolerance or both enteral and parenteral nutrition were administered simultaneously.

Enteral nutrition was administered as per routine protocol *via* a nasogastric or orogastric catheter continuously for 24 hours. A central parenteral nutrition solution containing 1400 kcal, 51 g amino acids, 150 g glucose, 60 g lipid in 1540 ml (Kabiven, Fresenius Kabi, Sweden) and a standard enteral nutrition solution containing 1000 kcal (1 kcal/ml), 40 g of amino acids, 33.6 g of fat, and 135.6 g glucose (Ensure, Abbott Laboratories, Zwolle, Holland) was used. Omega-3 fatty acids (fish oil) (Omegaven, Fresenius Kabi, Bad Homburg, Germany) (112 kcal/10 g) in a dose of 0.1-0.2 g/kg/day and glutamine-L-alanine amino acids (Dipeptiven Fresenius Kabi) (20 gr / 100 ml) in a dose of 0.3-0.4 g/kg/day were administered additionally to the patients in the study group starting from the first day of admittance to the intensive care unit and continued for 10 days parenterally as 24-hour infusions. For the calculations, omega-3 fatty acids were added to calorie requirements and glutamine-L-alanine dose was added to the nitrogen intake.

Lipid requirements were titrated according to the serum lipid levels which were assessed at routine intervals. Omega-3 fatty acid infusion was lowered to 0.1g / kg/day when the serum triglyceride level was > 400 mg/dl during the follow-up. If the serum triglyceride level was still > 400 mg/dl after 2 days, first omega-3 fatty acid supplements were terminated and then lipids in the TPN were titrated. An attempt was made to maintain blood glucose levels under 150 mg/dl and by administrating short acting insulin infusion was administered intravenously as required.

The nutrition level of the patients was monitored by assessing daily total lymphocyte count, plasma albumin levels, and the daily nitrogen balance. The nitrogen balance was calculated according to the 24-hour urinary nitrogen levels. Plasma TNFα, IL6 and IL8 levels were assessed on the 1st, 6th, and 12th days.

All patients were recorded for infection rates, requirement of ventilation, duration of stay in the ICU, and in the hospital, and mortality. Blood, urine, and tracheal cultures were obtained twice weekly. Infection surveillance was performed according to the '*Centers for Disease Control (CDC)*' criteria [1]. The presence or development of respiratory failure, acute lung injury and acute respiratory distress syndrome, sepsis, septic shock, and multiple organ dysfunction syndrome (MODS) were also assessed and recorded .

Statistical Analysis

SPSS 17.0 package program was used in the analysis of the data. For comparisons between the

Table 1: Demographic Comparison of the Groups

	Control (n = 20)	Study (n = 23)	P
	Mean ± SD	Mean ± SD	
Weight (kg)	68.50±12.05	71.17±14.17	0.512
Height (cm)	162.60±8.17	165.52±7.56	0.230
BMI	25.73±3.32	25.68±3.79	0.968
Age(year)	66.10±13.18	58.78±19.02	0.156
APACHE II	12.05±3.41	14.04±4.10	**0.094**
Diagnosis Intraabdominal abscess	4 patients	7 patients	
Gastrointestinal Tract Cancer	16 patients	14 patients	
Mesenteric ischemia	0	2 patients	

groups, the t-test for independent groups was used for normally distributed numerical data, and the Mann-Whitney U-test was used for numerical data not distributed normally. The chi-square test and Fisher's exact test were used compare categorical values between the groups.

RESULTS

Demographic data (weight, height, body mass index, age APACHE II score and diagnose) are presented in Table **1**. No statistically significant difference was observed in the duration of mechanical ventilation, lenght of stay in the ICU, and duration of hospitalization between groups. Similarly, no statistically significant difference was found in the distribution of enteral nutrition administration among the groups.

The nutrition level of the patients was monitored through the daily total lymphocyte count and albumin levels, in addition to the daily nitrogen balance (Table **2**).

Significant differences were found only at the first day in CRP levels, the CRP level in the study group was significantly higher than the CRP level in the control group (p = 0.045). No significant differences

Table 2: Nutritional Follow-Up Parameters

		1st day	6th day	12th day	
Albumin (g/dl)	Control	2.12±0.37	2.43±0.51	2.54±0.42	2.35±0.54
	Study	2.51±0.36	2.27±0.50	2.21±0.67	2.49±0.86
	p	0.001	0.306	0.089	0.685
Nitrogen balance	Control	-3.73±5.45	-1.60±4.50	-0.84±4.87	-1.32±2.44
	Study	-2.41±7.66	-3.01±7.15	-2.90±7.74	-3.10±10.36
	p	0.528	0.463	0.407	0.75
Total Lymphocyte Count (µL)	Control	923.11±623.90	1499.50±939.54	1085.83±653.61	-
	Study	1130.45±788.99	1140.48±613.72	1328.33±839.20	-
	p	0.362	0.153	0.438	-

Table 3: Comparison of CRP Levels between the Groups

	Control			Study			P
	Mean		SD	Mean		SD	
1st day	11.54	±	9.85	18.78	±	12.72	0.045*
6th day	23.64	±	42.45	15.32	±	9.73	0.884
12th day	13.48	±	13.02	14.22	±	12.28	0.870
21st day	14.12	±	9.66	9.71	±	5.94	0.226

Table 4: Comparison of TNFα, IL-6, IL-8 Levels

Cytokines	Study Group (n=23)	P	Control Group (n=20)	P
TNFα (1st day)	0.148±0.046	0.416	0.122±0.027	0.236
TNFα (6th day)	0.200±0.207		0.223±0.240	
TNFα (12th day)	0.143±0.045		0.152±0.042	
IL-6 (1st day)	0.741±0.754	0.256	0.618±0.422	0.049*
IL-6 (6th day)	0.285±0.314		0.161±0.164	
IL-6 (12th day)	0.667±1.124		0.447±0.817	
IL-8 (1st day)	0.895±0.458	0.387	1.077±0.659	0.479
IL-8 (6th day)	0.657±0.404		0.727±0.613	
IL-8 (12th day)	0.766±0.794		0.923±0.922	

(*) One-way repeated measurements variance analysis.

Table 5: Presence of Sepsis, Septic Shock, and MODS in the Groups (At the 10th Day)

		Positive		Negative		p
		n	(%)	n	(%)	
Sepsis	Control	11	-55%	9	-45%	0.697
	Study	14	-61%	9	-39%	
Septic Shock	Control	5	-25%	15	-75%	0.801
	Study	5	-22%	18	-78%	
MODS	Control	5	-25%	15	-75%	0.711
	Study	4	-17%	19	-83%	

Fisher's exact test.

were found between the groups for the CRP levels on the other days (Table **3**).

Cytokine is an important mediator of the immune reaction in the innate immune system response.Mean IL-6 (pro-inflammatory cytokine) levels on admission were significantly higher in the control group compared to the mean 6th day level ($p<0.05$) (Table **4**).

The number of patients with ALI/ARDS in the study group (10 patients, 45 %) was significantly higher when compared to the control group (3 patients, 15%) on the 6th day. There were no significant differences in the rates of ALI/ARDS on the other analyzed days. Groups were similar in the rates of presence of sepsis, septic shock, and MODS (Table **5**).

Survival analysis of the patients was assessed using the Kaplan-Meier method taking into account the dates the patients were in the hospital or in the intensive care unit. Mortality rate was no statistically differences between two groups.

DISCUSSION

Recently, immunonutritional support, including agents such as omega-3 fatty acids, arginine, glutamine-L-alanine, and nucleotides, has been gaining interest [1, 2]. While the benefits of immunonutrition were demonstrated in some studies [3-5], others report increased mortality rates with the use of those agents [6-8]. Separate uses of glutamine-L-alanine and omega-3 fatty acids can be seen in the reports in the literature [9, 10].

In a study consisting of 661 intensive care patients, omega-3 fatty acids were administered in different doses in addition to the standard clinical nutrition and the effects of different doses on diagnosis and organ failure were assessed. In that study, 225 patients underwent major abdominal surgery, 27 patients had abdominal sepsis, 16 patients had non-abdominal sepsis, 59 patients had multiple trauma, 18 patients had severe head injury, and 37 patients had other

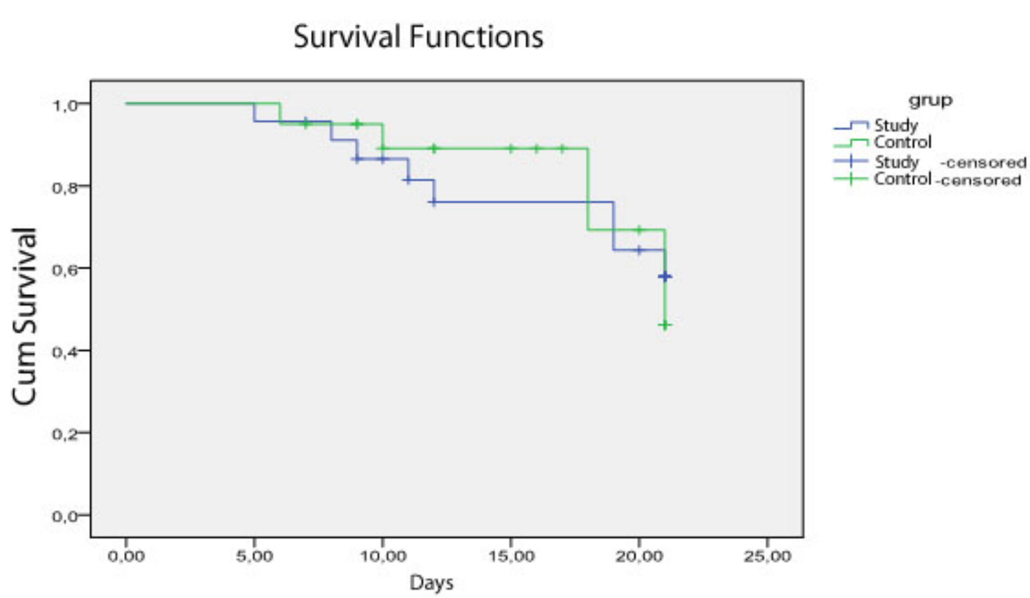

Figure 1: Survival analysis of the patients.

diagnoses. Patients were administered omega-3 fatty acids in three different doses (0,05, 0,15 and 0,2 g/kg/day). When administered in a dose of 0.1-0.2 g/kg/day in addition to the total calorie requirements, omega-3 fatty acids were found to be associated with decreases in mortality rate, duration of mechanical ventilation, and duration of hospitalization. Researchers reported that the significance was even higher in cases with major abdominal surgery [9]. The effects of glutamine addition in the enteral nutrition in 72 patients with trauma were evaluated in another study. Bacteremia, pneumonia, and sepsis were seen in markedly lower rates in the treatment group [10]. No differences were found in the infection, duration of hospitalization, or mortality in some four other studies, including complex critical intensive care patients [11-13].

When administered in the highest possible dose and longest possible duration, omega-3 fatty acids and glutamine-L-alanine were reported to have more beneficial effects [14-18]. The effects of this type of nutrition were monitored in the patients using laboratory values and nutrition criteria. In general, it is reported that the administration of these two agents together in high doses is well tolerated by patients with no metabolic complications [19-21].

The APACHE II score was found to be high in this study group, though not significant (study group: 14.03, control group: 12.05: p=0.094). However, the mortality rate is expected to be 18% with an APACHE II score of 11-15, and increases to 62% when the score is 16-20 [22]. Taking this into account, although the numerical differences between the two groups are not prominent, considering that the parameters increasing the score in the study group are derived from infection and hemodynamic responses, it can be concluded that the infection rate is higher in the study group compared to the control group and thus the study group is a higher risk patient group.

First day CRP levels were significantly higher in the study group compared to the control group. CRP levels were markedly decreased in the following days in the study group and the difference disappeared during follow-up. The disappearance of the differences in the laboratory parameters suggests that the pharmaconutrition that was used was effective. There have been studies reporting significantly decreased CRP levels in patients with abdominal sepsis who were administered omega-3 and parenteral nutritional support [23].

There were no statistical significances between the groups in the rates of ALI/ARDS, sepsis, severe sepsis, septic shock, and MODS development. However, the ALI/ARDS rate was significantly increased in the control group. While there was no significant increase in the study group in infection rates during the 10-day treatment period, infection rates were found to be increased in the control group. It is believed that the pharmaconutrition applied may have had clinical significance on this parameter.

There were no significant differences between the groups in the hospital stay, stay in the intensive care unit, duration of mechanical ventilation, and mortality. When reviewing other studies with glutamine-L-alanine or omega-3 fatty acids, ICU stay and mortality rates were decreased in some studies, though not statistically significant [24-26], or unchanged or increased mortality were reported in others [27-29].

The authors of the performed studies concluded that decreased infection rates were more significant. Heys *et al*. analyzed 1009 patients in medical and surgical intensive unit cares. The rate of septic complications such as wound infection, intraabdominal abscesses, and pneumonia had an insignificant tendency to decrease in the study in which glutamine, arginine, and other pharmaconutrients were administered. That study concluded with a decreased rate of infectious complications in critical patients and patients with past gastrointestinal tumor surgery; however, mortality was not affected [30].

In another study, 54 patients with abdominal sepsis were administered parenteral products containing a mixture of soy oil/fish-oil or soy oil only. Mortality was similar in the two groups, while reoperation (7 % / 31 %), ICU stay (3 days /9 days), and hospital stay (12 days/20 days) were found to decrease in the group who received fish oil compared to the control group, respectively [23]. No differences were found in the survival rates between the groups.

In conclusion, a clinically decreased rate of infection was observed in patients with a high APACHE II score, or who received pharmaconutritional support; omega-3 fatty acids, glutamine-L-alanine, and other pharmaconutrients are required to be administered more selectively and in larger patient groups in different doses and in combination protocols in accordance with the current pharmaconutritional support and in different timing combinations, including preoperative period.

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