A Pilot Study of Preoperative Immunonutrition with Antioxidants in Living Donor Liver Transplantation Donors

Nagata, Shigeyuki
Department of Surgery and Science, Graduate School of Medical Sciences, Kyushu University | Department of Surgery, Nakabaru Hospital

Shirabe, Ken
Department of Surgery and Science, Graduate School of Medical Sciences, Kyushu University

Sugimachi, Keishi
Department of Surgery and Science, Graduate School of Medical Sciences, Kyushu University

Ikegami, Toru
Department of Surgery and Science, Graduate School of Medical Sciences, Kyushu University

他

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A Pilot Study of Preoperative Immunonutrition with Antioxidants in Living Donor Liver Transplantation Donors

Shigeyuki NAGATA[1)2)*], Ken SHIRABE[1)], Keishi SUGIMACHI[1)], Toru IKEGAMI[1)], Tomoharu YOSHIZUMI[1)], Hideaki UCHIYAMA[1)], Yo-ichi YAMASHITA[1)], Hiroshi SAEKI[1)], Hirofumi KAWANAKA[1)], Koshi MIMORI[3)], Masayuki WATANABE[4)], Tomonobu GION[1)], Yuji SOEJIMA[1)], Tetsuo IKEDA[1)], Shunichi TSUJITANI[1)] and Yoshihiko MAEHARA[1)]

[1)] *Department of Surgery and Science, Graduate School of Medical Sciences, Kyushu University, Fukuoka, Japan*
[2)] *Department of Surgery, Nakabaru Hospital, Fukuoka, Japan*
[3)] *Department of Surgery, Kyushu University Hospital, Beppu Japan*
[4)] *Department of Gastroenterological Surgery, Kumamoto University, Japan.*

Abstract

Introduction : Previous studies have demonstrated that oxidative stress by mediating the excessive production of reactive oxygen species is involved in tissue damage and organ failure during and after surgery. The impact of the preoperative immunonutrition including antioxidants on the postoperative course of patients undergoing hepatic surgery was investigated in this pilot study.

Patients and Methods : Twenty-three living donor liver transplantation (LDLT) donors were randomly assigned to either an experimental (AO) group, received a commercial supplement enriched with antioxidant nutrients for each of the 5 days immediately prior to surgery while maintaining normal food intake, or a control (CT) group, administered no supplement. Antioxidative capacity was measured by spectrophotometry of patient serum using a free-radical analytical system.

Results : The antioxidative capacity of 90.9% patients in the AO group increased after immunonutrition. Compared to the CT group, the AO group was found to have higher antioxidant capacity and transferrin levels ; lower WBC, lymphocyte, and neutrophil counts ; and briefer duration of postoperative fever during the postsurgical period. No significant differences were found between the 2 groups regarding the nutritional parameters ; liver functioning parameters ; immunological parameters ; intraoperative factors ; postoperative outcomes.

Conclusion : Preoperative immunonutrition including antioxidants might play a beneficial role in improving postsurgical immunological response but the modest biological advantage was not associated with any significant clinical outcome.

Key words : Reactive oxygen species・Antioxidant・Preoperative immunonutrition ; Immune response・Living donor liver transplantation

Introduction

One of the various strategies currently used to reduce the morbidity of patients undergoing major abdominal surgery is the preoperative provision of specific nutrients, called immunonutrition. Immunonutrition has been hypothesized to alter cytokine production and immune functioning in a manner that inhibits excessive postoperative immune and inflammatory responses and improves intestinal barrier function[1)~5)]. Previous clinical studies have suggested that preoperative immunonutrition significantly decreases the incidence of infectious complications and the length of hospital stay after surgery[6)~12)]. The current recommendation regarding the preoperative

*Corresponding author : Shigeyuki NAGATA, MD
Department of Surgery, Nakabaru Hospital, 2-12-1 Befukita, Shimemachi, Kasuyagun, Fukuoka 811-2233, Japan
Tel : +81-92-621-2802 Fax : +81-92-623-2247
E-mail : punchnagata@live. jp

immunonutrition of surgical patients is the administration of preoperative oral supplementation for 5–7 days as part of an immunomodulating diet[13]. Up to the present date, the preoperative administration of no commercial product except for that of IMPACT (Novartis, Bern, Switzerland) has been clearly demonstrated to have an optimal benefit on clinical outcome.

Reactive oxygen species (ROS) have been implicated in the etiology of multiorgan dysfunction syndrome and the development of infectious complications among critically ill patients[14]. Several recent studies have cited the effectiveness of antioxidant supplementation in improving the outcome of critically ill patients[15)~17]. Although the precise mechanism by which antioxidant supplementation benefits these patients is unclear, it is hypothesized that it replenishes endogenous antioxidants that have been prematurely depleted by the profound oxidative stress that occurs during critical illness. Without supplementation, the premature depletion of endogenous antioxidants may lead to impairment of antioxidant capacity and, ultimately, organ dysfunction and tissue injury. Such dysfunction and injury is mediated at least in part, by ROS or oxidative metabolites derived from inflammatory cells or injured tissue.

The central hypothesis of this study was that antioxidant supplementation might play an important role in the preoperative immunonutrition like IMPACT, and patients undergoing surgery would benefit from prophylactic antioxidant supplementation prior to the development of postoperative organ damage. To test this hypothesis, various parameters reflecting the clinical outcome of hepatectomy patients serving as living donor liver transplantation (LDLT) donors who had been administered preoperative immune-enhancing diet enriched antioxidants as an adjunct to their standard oral food were compared to those of patients with similar baseline characteristics and preoperative laboratory findings, also serving as LDLT donors, but who had not been administered preoperative immunonutrition enriched antioxidants.

Patients and Methods

Twenty-three LDLT donors who had undergone right or left hepatectomy between August 2008 and March 2009 at the Department of Surgery and Science, Kyushu University, Japan were the subjects of this investigation. All donors had been assessed to be biochemically and immunologically healthy with no malignant disease prior to surgery. Using a procedure described in previous studies[18,19], LDLT was performed by hepatectomy of the left or right hepatic lobe with the caudate lobe. Fully informed consent was obtained from all donors and recipients. Randomization was performed using sealed envelopes after a decision had been made regarding transplantation at the outpatient department. Donors were randomly allocated into 2 groups. One group (n = 11) drank 400ml (included polyfenol : 220mg) of liquid diet (ANOM ; Otsuka Pharmaceutical Factory, Tokushima, Japan) per day for 5 consecutive days prior to surgery supplemented with a standard food intake (AO group). Another group (n = 12) was given a standard diet without ANOM (CT group). The dietary composition of ANOM is summarized in Table 1. After surgery, both groups were given a standard oral food intake. Body temperature was measured at a set time in early morning everyday

Table 1 Dietary contents of ANOM

Total calories (kcal/mL)	1
Protein (g/L)	50
Arginine (g/L)	4.6
Glutamine (g/L)	7.5
Fat (g/L)	28
Omega-3 fatty acids (g/L)	1.5
Fiber (g/L)	5.3
Vitamin C (mg/L)	1000
Vitamin E (ug/L)	50
Zn (mg/L)	15
Sel (ug/L)	46
Nucleic acid (DNA) (g/L)	0.13
Polyfenol (mg/L)	550

during the hospital stay. Our study was approved by the institutional Ethics Committees of the hospital involved and conducted in accordance with the ethical guidelines of the declaration of Helsinki.

To measure antioxidative capacity, nutritional and immunological parameters, and liver function parameters, preoperative baseline levels of key factors, as determined by blood drawn at the outpatient department prior to admission, were compared to postimmunonutritional levels, as determined by blood drawn immediately prior to surgery (Day 0) and postoperative levels, as determined by blood drawn on the first, third, and seventh day (Days 1, 3, and 7) after the surgery. The nutritional parameters included serum total protein, albumin, prealbumin, transferrine, retinol binding protein (RBP) levels. The immunological parameters included white blood cell (WBC), lymphocyte, neutrophil, and T-cell (CD4/CD8) subpopulation counts. Liver functioning was determined by assessing total bilirbin, asparate amino transaminase (AST), alanine amino transaminase, gamma-GTP, and lactate dehydrogenase (LDH) levels. The antioxidative capacity of patient serum was measured by spectrophotometry using the BAP commercial test kit (Diacron, Grosseto, Italy) on a free-radical analytical system (FRAS) 4 (Diacron). Briefly, the BAP measures serum ROS levels, which reflect the ability of ROS molecules to reduce free radicals in the presence of transition metals (Fe, Cu, etc.) that are acting as catalyzers. When free radicals react with a correctly buffered chromogenic substance, they develop a colored complex proportional to the ROS concentration-this process can be measured photometrically.

Statistical Analysis

All data are expressed as mean ± standard error of the mean (SEM). Continuous variables were compared by performing two-tailed unpaired t-testing for independent samples. Categorical data were compared by performing chi-square testing. All statistical analyses were performed at a $p < 0.05$ level of significance using the Prism Version 4.0 software (GraphPad Software Inc., San Diego, CA).

Results

All of the members of the AO group were able to comply with the protocol throughout the duration of the study. As shown in Table 2, no significant differences were found between the

Table 2 Preoperative clinical characteristics of the 2 groups

Characteristic	CT group (n=12)	AO group (n=11)	*P* value
Age (yr)	31.4 ± 7.9	38.5 ± 11.9	0.1051
Sex (Male/female)	9/3	7/4	0.6668
Body weight (kg)	61.9 ± 8.1	60.5 ± 7.7	0.3464
Body mass index (m^2)	20.9 ± 1.8	22.0 ± 2.4	0.1286
Albumin (g/dL)	4.47 ± 0.33	4.25 ± 0.30	0.0709
Hemoglobin (g/dL)	13.7 ± 1.3	12.7 ± 1.6	0.0772
Total cholesterol (mg/dL)	177.8 ± 8.8	154.6 ± 7.8	0.0639

Table 3 Surgical characteristics of the 2 groups

Characteristic	CT group (n=12)	AO group (n=11)	*P* value
Duration of surgery (min)	445.5 ± 108.2	454.4 ± 63.1	0.4066
Operative blood loss (mL)	429.7 ± 182.4	432.7 ± 199.4	0.4853
Surgical procedures (Rt/Lt)	4/8	7/4	0.2203
Resected liver volume (g)	453.7 ± 114.2	506.9 ± 90.7	0.1160
Residual liver volume (%)	55.9 ± 15.6	48.1 ± 13.2	0.1035

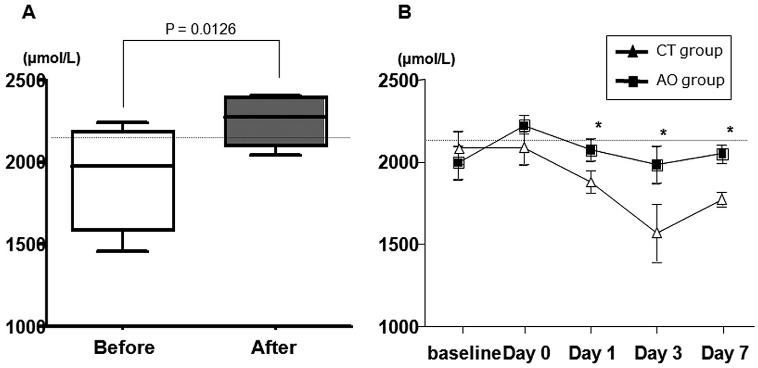

Fig. 1 Comparison of antioxidative capacity.

A. The AO group received antioxidant supplementation in the form of 400 kcal/day of AO on each of the 5 days immediately prior to surgery. The white bar represents the value of antioxidative capacity before supplementation and the grey bar represents the value after supplementation. The dotted line shows the borderline of standard value.

B. Mean values of antioxidative capacity in the CT (triangle) and AO (square) groups. The error bars represent the standard error of the mean ; $^{*}p < 0.05$.

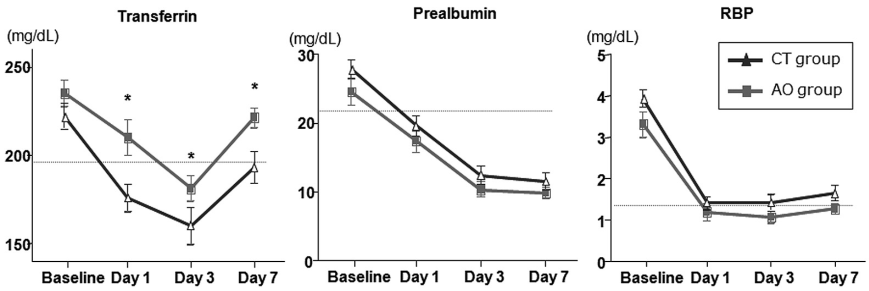

Fig. 2 Comparison of nutritional parameters.

Mean values of transferrin, preAlb, and RBP levels in the CT (triangle) and AO (square) groups. The error bars represent the standard error of the mean ; $^{*}p < 0.05$.

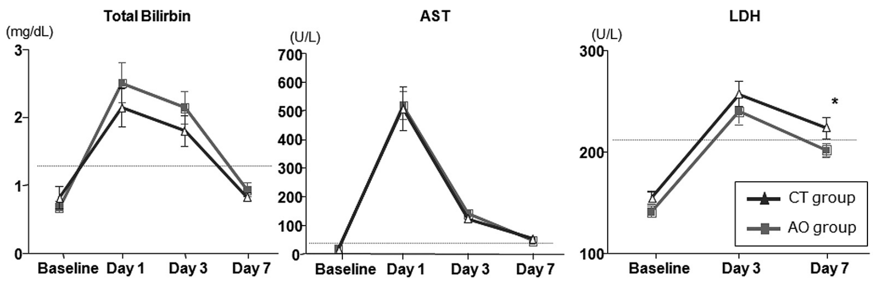

Fig. 3 Comparison of liver function parameters.

Mean values of total bilirbin, AST, and LDH levels in the CT (triangle) and AO (square) groups. The error bars represent the standard error of the mean ; $^{*}p < 0.05$.

Table 4 Postoperative characteristics of the 2 groups

	CT group (n=12)	AO group (n=11)	*P* value
Duration of abdominal drainage (days)	2.9 ± 1.3	3.1 ± 1.4	0.3734
Duration of fever (days)	7.4 ± 2.8	4.4 ± 3.7	0.0437
Hospital stay (days)	12.4 ± 4.0	12.9 ± 3.5	0.7587

AO group and the CT group regarding baseline characteristics or preoperative laboratory findings. As shown in Table 3, no significant differences were found between the 2 groups regarding intraoperative factors, including operation time, blood loss, surgical procedure, hepatic graft volume, or estimated residual liver volume.

Regarding factors related to antioxidative capacity, no significant differences were found between the 2 groups at baseline. However, as shown in Figure 1A, the antioxidative capacity of 10 (90.9%) patients in the AO group increased after ingesting designated volume of ANOM. As can be observed in Figure 1B, which shows the postoperative profile of antioxidative capacity of both groups, the AO group was found to maintain a higher level of antioxidative capacity than did the CT group at each postoperative day of testing.

Concerning the nutritional parameters, the level of transferrin was found to be significantly higher in the AO group during the 7 days after surgery (Fig. 2). However, no significant difference was found between the 2 groups regarding other nutritional parameters. Regarding parameters of liver functioning, a significant decrease in the LDH level of the AO group was observed on Day 7 (Fig. 3). However, no significant difference was found between the 2 groups regarding any other parameters (Fig. 3). Regarding immunological parameters, the WBC, lymphocyte, and neutrophil counts of the AO group at Days 3 and 7 were found to be lower than those of the CT group (Fig. 4), but no difference was found in the T-cell (CD4/CD8) subpopulation count between the 2 groups (data not shown). Although the immunoglobulin level of the AO group displayed a tendency to increase more rapidly, no significant differences were found in the overall immunoglobulin level between the 2 groups (Fig. 4).

Both groups experienced no postoperative complications, including surgical-site infection (SSI), general infectious disease, postoperative fever, biliary complications, and morbidity. However, the duration of postoperative fever

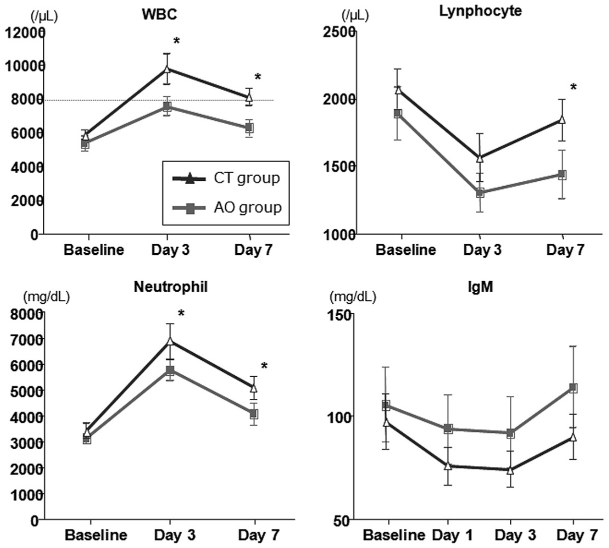

Fig. 4 Comparison of immunological parameters.
Mean values of WBC, lymphocyte, and neutrophil count and IgM level in the CT (triangle) and AO (square) groups. The error bars represent the standard error of the mean ; *$p < 0.05$.

(over 37.5C) was found to be briefer for the AO group than the CT group. Timing of removal of abdominal drainage tube and length of postoperative stay was found not to significantly differ between the 2 groups (Table 4).

Discussion

Liver transplantation has become an accepted therapy for end-stage of liver disease and hepatic neoplasm. LDLT has become an established alternative to cadaveric donor liver transplantation in Japan, which has about 500 cases performed in Japan each year[20]. A primary goal of LDLT is ensuring the safety of the donor in the perioperative period, which usually results in impairment of immune defense mechanisms and altered inflammatory response after surgery.

Over the past decade, several clinical and experimental studies have reported on the beneficial effects of administering immunomodulating diets to patients who have undergone major abdominal surgery as a means of counteracting these responses[5)~12)]. Though a variety of mechanisms, immunonutrients attenuate the negative effects of surgery on the architecture and functioning of the gastrointestinal tract, and thus may help prevent multiple organ dysfunction syndrome. Although the functioning of these mechanisms has not been precisely identified, there is strong evidence that they preserve the integrity of gut structure and functioning, balance intestinal microflora, and maintain effective local and systemic immunocompetence[1)~3)]. Based on this evidence, provision of enteral nutritional support initially became popular in the treatment of patients undergoing major abdominal surgery[21)]. Many studies have demonstrated that preoperative administration of arginine-dominant nutrition is useful for immunonutrition in surgical patients.

Invasive damage resulting from surgery increases the inflammatory reaction by prompting the production of inflammatory cytokines which in turn stimulate immune and vessel endothelial cells to upregulate the production of ROS. These molecules typically assume an important role in providing biochemical protection against foreign substances and processing necrotized tissue or unnecessary proteins. However, continuous inflammation may lead to excessive production of inflammatory cytokine, which in turn leads to excessive production of ROS, which injures cellular and mitochondorial membranes and may lead to cell death[14)]. The imbalance between ROS and the body's defense system results in a state of oxidative stress, which may lead to a form of free-radical-mediated damage that gradually worsens the clinical condition and ultimately leads to patient death. Antioxidant substances, including vitamins, trace elements, CoQ_{10}, and polyphenols, can help prevent the damage from oxidative stress by neutralizing ROS. Therefore, preoperative supplementation of antioxidative nutrients appears to offer the possibility of great benefits for patients undergoing surgery. One means of providing antioxidative supplementation is the administration of ANOM, a relatively novel supplement that contains an abundance of antioxidants. Additionaly, any amount of glutamine, arginine, and fish oil are included in ANOM other than the antioxidants (Table 1). In contrast to almost all previous immunonutritional studies, which replaced a subjects' normal diet with an immune-enhanced diet, in this study, the standard diet was not replaced or changed in any manner but merely supplemented by the addition of an immune-enhancing supplement. The reason for this less drastic approach to dietary manipulation was that restricting the oral intake of living donors who did not suffer from any disease could create unnecessary stress for them, as well as lead them to view LDLT in a more negative light. As a result, the volume of antioxidative nutrients setting in this study were enough to maintain the minimally antioxidative capacity in the perioperative period.

As previously described, the antioxidative capacity of 10 of the11 subjects in the AO group increased after ANOM administration (Fig 1A), and maintained a higher level of antioxidative potency until postoperative Day 7, compared with the CT group (Fig 1B). In terms of nutritional parameters, the AO group maintained a higher transferrin level (Fig 2) and in terms of biochemistry, the AO group experienced a more rapid decrease in LDH level rapidly after surgery (Fig 3). Despite these differences, no significant differences in terms of clinical outcome, postoperative complications, or length of hospital stay was observed between the 2 groups (Table 4). Specifically, none of the donors experienced any complications, including SSI, and almost all experienced a hospital stay of under 2 weeks. While most hepatectomy patients usually experience fever for a brief period after surgery, a greater number of the CT group experienced fever-up over 37. 5C for an extended period compared to the AO group. In the analysis of immunological parameters, a significant difference was found in cellular immunity, but not in humoral immunity, with the AO group found to experience a more rapid decrease in leukocyte, neutrophil, and lymphocyte count.

Previous research has indicated that antioxidant supplementation may reduce inflammatory response[15)~17)], which has been found to be related to excessive ROS production and implicated in the development of many diseases[22)~26)]. Although the impact of preoperative antioxidant supplementation on liver functioning cannot be directly observed, the beneficial outcomes identified in this study suggest that antioxidant supplementation may play an important role in improving immunological response after surgery. Recently some reports have shown that preoperative immunonutrition don't improve clinical outcome in well-nourished patients undergoing abdominal surgery[27)28)]. As this pilot study examined a small number of patients, who were healthy donors of LDLT, administered a small volume of an immune-enhancing supplement over a relatively brief period, future studies should endeavor to examine a larger number of mal nourished patients administered a greater volume of supplement over an extended period.

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Competing interests

The authors declare that they have no competing interests.

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（和文抄録）

生体肝移植ドナーに対する抗酸化物質を用いた術前免疫栄養に関する予備試験

[1]九州大学　消化器・総合外科
[2]社会保険　仲原病院　外科
[3]九州大学病院　別府病院
[4]熊本大学　消化器外科

永田茂行[1,2]，調　　憲[1]，杉町圭史[1]，池上　徹[1]，吉住朋晴[1]，内山秀昭[1]，山下洋市[1]，佐伯浩司[1]，川中博文[1]，三森功士[3]，渡邊雅之[4]，祇園智信[1]，副島雄二[1]，池田哲夫[1]，辻谷俊一[1]，前原喜彦[1]

【目的】活性酸素が過剰に産生されることで外科手術後に組織破壊や臓器機能不全を招来することがこれまで報告されている．本研究では肝切除を受ける患者に抗酸化物質を含む術前免疫栄養を行い，術後経過に与える効果を検討した．
【対象と方法】23 名の生体肝移植ドナーを対象とした．通常の食事に加え，術前 5 日間抗酸化物質を豊富に含む栄養剤を摂取した実験群（AO 群）と通常の食事のみのコントロール群（CT 群）に無作為に分けた．フリーラジカル自動分析装置を用いて患者血清を吸光光度分析法にて抗酸化力を測定した．
【結果】AO 群の 90.9% において免疫栄養後に抗酸化力が増加した．CT 群に比較して AO 群は術後により高い抗酸化力とトランスフェリン値を示した．また AO 群は術後の白血球数，好中球数が低く，術後発熱期間が短かった．それ以外の栄養学的指標，肝機能，免疫学的指標，手術因子や術後経過に 2 群間に差を認めなかった．
【結論】抗酸化物質を含む術前免疫栄養による明らかな臨床的アウトカムを示せなかったが，術後免疫応答を改善するのに有用である可能性が示唆された．