Perioperative immunonutrition ameliorates the postoperative immune depression in patients with gastrointestinal system cancer (prospective clinical study in 42 patients)

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Abstract

Cancer surgery is a major challenge for patients to develop immune depression in postoperative period. Several cytokines can depress immune cell subpopulations. Increased cytokine response after surgery is assumed to arise mainly from lipooxygenase pathway acting on membrane arachidonic acid. Therefore ; investigators focused their efforts to alter the membrane fatty acid profile by changing the nutritional regimen with ε-3 fatty acid supplementation and encouraging results were obtained after surgery. Despite the theoretical and clinical advantage of enteral nutrition many surgeons remain committed to parenteral nutrition for feeding of patients due to maintain bowel rest and fear of anastomosis leakage at the postoperative period. Several studies investigating role of the postoperative immunonutrition reported that beneficial immunological changes were associated with reduction of infectious complications. Interestingly ; these findings were observed at least five days after the surgery in which the highest incidence of complications was seen. In this prospective study including 42 patients eligible for curative gastric or colon cancer surgery ; we investigated the beneficial effect of enteral immunonutrition (EEN) compared to total parenteral hyperalimentation (TPN) beginning from the preoperative period. Cortisol and CRP levels as stress parameters significantly increased one day after surgery in both groups but they rapidly returned to (on POD1) preoperative baseline level in EEN group whereas these values remained high in the TPN group. Additionally a significant decrease in natural killer (NK) cells and CD8+ levels were observed in both groups. However they recovered on POD3 in EEN group and on POD6 in TPN group. CD4+ subset remained almost same as preoperative value in the TPN group whereas it increased from (%) 40.14 to 46.40, 51.29 and 54.7 on PO 6th hr, POD3 and POD6 in the EEN group. Our findings suggest that preoperative nutrition via the enteral route provided better regulation of postoperative immune system restoration than parenteral nutrition. On the basis of our findings we recommend enteral immunonutrition to be started at the preoperative period rather than postoperatively before a major operation whenever the enteral route is feasible. (Acta gastroenterol. belg., **2004**, 67, **250-254**).

Key words : immunonutrition, enteral nutrition, parenteral nutrition.

Introduction

It is obviously known that severe depression in immunological responses of both cellular and humoral functions can be seen following major surgery as well as malnutrition (1). Host immunological responses in particular severe T cell depression and natural killer (NK) cell dysfunction can be mediated by IL-6 and IL-8 following surgery (2).

It has been established that improved nutritional status in malnourished cancer patients is associated with less infection and hospital stay, less treatment cost and increased survey after surgery. Thus, the provision of protein and calories in any way has been shown to improve host immune function in malnourished cancer patients (3). Moreover, adequate nutrition is crucial for these patients to shorten the recovery period from catabolic state and to ameliorate the immune depression seen during the postoperative period.

Increased cytokine response after surgery was assumed to arise mainly from lipooxygenase pathway acting on membrane arachidonic acid, which led to generation of encouraging efforts that would alter the membrane fatty acid profile by changing the nutritional regimen with omega-3 fatty acid (ε-3 FA) supplementation (4). Furthermore ; the operative treatment performed for the tumor per se can also result in depression of the response of T cells to mitogens. Arginine, which becomes an essential amino acid in catabolic states, was observed to promote the T cells after stimulation. Glutamine was also shown to provide local nutrition to enterocytes and to play a role on provision of alanine for liver in catabolic states (5). Accumulating data on special immune-enhancing substances have led to the concept of enteral immunonutrition, which is based on supplementation of standard enteral nutrition with the so called 'immune-stimulatory' dietary factors.

Despite the theoretical and clinical advantage of enteral nutrition, many surgeons remain committed to TPN for feeding of patients in order to maintain bowel rest and prevent anastomosis leakage at the postoperative period. Several studies about the postoperative immunonutrition reported that beneficial immunological changes associated with reduction of infectious complication were seen at least five days after the surgery (6). However, the most feared infectious complications are observed in this vulnerable period. Therefore, new approaches should be developed to shorten the period needed for immune effective action of these nutrients to appear. Giving the enteral nutrition at the preoperative period may give enough time for these substrates to reach the adequate plasma levels for their beneficial

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Table I. — **Patient characteristics and clinical backgrounds of the groups**

	EEN	TPN
Male/females	18/4	16/4
Mean age (years)	58.3 ± 6.2	60.1 ± 4.2
Tumor site (Stage II / III)		
Stomach	6 (2 / 4)	5 (2 / 3)
Colorectal	16 (4/12)	15 (3 / 12)
Mean operation time (min)	168 ± 32	184 ± 35
Estimated mean blood loss (cc)	380 ± 135	330 ± 155

effect. There is not enough study dedicating the efforts to shorten the recovery period via specific kinds of nutrients for the cancer-bearing patients in the literature, so this prospective study was conducted to assess the beneficial effect of EEN in terms of immune and stress parameters of gastric and colorectal cancer patients compared to TPN initiated five days before surgery and extending to 7 days postoperatively.

Material and Methods

This study was designed as a prospective, randomised clinical trial. Forty-two patients between 38-80 years of age who were eligible for curative surgery for gastric and colorectal cancer and had a weight loss of more than 10% in 6 months were included in the study between June 1998 and December 2001 (Table I). All patients had stage II or III disease. Written informed consent was obtained from each patient following giving information about the study and the study was approved by Local Ethical Committee of University.

Subjects and nutritional regimens

Forty-two patients who underwent curative surgery received one of the nutritional regimens written below. Patients were divided into two groups including 20 and 22 patients in each treatment group as follows : a) TPN group received standard total parenteral nutrition containing glucose (% dextrose as needed, Eczacibasi, Turkey), amino acid (Freeamine III*, 8.5%, Eczacibasi, Turkey), lipids (20% lipid*, Fresenius-Kabi, Deutschland), vitamins (Bemix-C*, Roche, Switzerland) and trace elements (Tracutil*, Braun, Deutschland). b) EEN group received an enteral diet supplemented with immune-enhancing substrates containing arginine (1.25 g/100 ml), ε-3 FA (n-3/n-6 ratio $^1/_4$), RNA (0.12 g/100 ml) (Impact* Sandoz Nutrition Berne, Switzerland), trace elements and vitamins. Both regimens were isonitrogenous and isocaloric in amount. Forty-two patients were enrolled into the study out of one-hundered-twenty patients operated between the study period. Any patient with laboratory and clinical signs of hepatic (total serum bilirubin concentration > 3 mg/dl), pulmonary (abnormal chest X-ray), cardiac (New York Heart Association functional class > III, stroke history), renal dysfunction (serum creatinine concentration > 2.5 mg/dl) demonstrated by specialized clinician and seeking medical therapy for that insufficiency was excluded. Any patient with proven infectious disease with leukocytosis/leukopenia, tachicardia, tachipnea, and fever above 38˚C was also excluded from the study. These nutritional regimens were started 5 days before the surgery and were continued to deliver during the postoperative 7 (POD7) days. At the preoperative phase the patients assigned to receive enteral nutrition were fed with per oral route and for the remaining patients, a subclavian catheter was placed percutaneusly and TPN regimen was given through this way. After the completion of curative surgery the patients in EEN group were fed through a nasoduodenal catheter (or a nasojejunal catheter for patients with gastric resection) for 7 days. Remaining patients in the TPN group received the nutritional regimen for 7 days at the postoperative period through the subclavian catheter that was placed previously. The patients in TPN group received 35 kcal/kg/day non-protein calorie, 0.25 g nitrogen/kg/day and 1 g/kg/day lipid solutions. Carbohydrate/lipid ratio was approximately 5. The patients in EEN group received same amount of non-protein calorie, 0.26 g nitrogen/kg/day. Carbohydrate/ lipid ratio in EEN group was also approximately 5.

In EEN group infusion was started as a rate of 0.2ml/kg/hr at postoperative period and increased progressively until the nutritional goal (2ml/kg/hr) was reached at POD4. Enteral nutrition was integrated with parenteral nutrition to reach the nutritional energy goal until POD4 in all patients of EEN group. All patients were given single dose antibiotic prophylaxis with a second generation cephalosporin (cefuroxime axetyl, 250 mg, Zinnat*, Glaxo-Wellcome). Patients who experienced a longer operative procedure received an additional antibiotic dose. Prophylactic low molecular weight heparin (Heparin sodium, 5000 IU/0.4 ml, Fragmin*, Pharmacia & Upjohn) was used for all patients to prevent deep venous thrombosis. Total cost of the regimen was also calculated by the sum of the price of nutritional solutions plus the price of silicon subclavian catheters for TPN and the price of feeding tubes (nasogastric or nasojejunal) for EEN groups.

Blood samples and periods

Baseline blood samples were taken preoperatively for all parameters evaluated. In addition, stress factor parameters (CRP and cortisol levels), hematological parameters (blood counts) and nutritional parameters (total protein and albumin levels) were measured at the POD1, POD3 and POD7. Blood samples were also taken at the postoperative 6th hour, POD3 and POD6 for measurement of lymphocyte, CD4+, CD8+ and NK levels and at POD7 and POD14 for IgG, IgA, and IgM levels in order to analyze the patient's immune function. CRP values were evaluated with Beckman Image immunochemistry

Table II. — **Infectious postoperative complications of the groups**

	EEN	TPN
Abscess formation	–	–
Peritonitis	–	–
Surgical wound infection	1	2
Pulmonary infiltration	2	4
Urinary tract infection	2	1
Undiagnosed fever above 38°C	2	4

system. Lymphocyte subgroups were determined by using conjugated monoclonal antibody system with Becton Dickonson double colour analyzes method.

Detection of the postoperative infection

Postoperative infection was accepted as any of abscess formation comfirmed by USG, the detection of microorganism in drain, catheter and urine at microscopic evaluation, infiltration on chest X-ray and undiagnosed fever above 38˚C for at least three days.

Statistical analysis

Data are expressed as means ± SEM. Mann-Whitney U test and Student's t test were used to compare the groups and p value of less than 0.05 was accepted as significant.

Results

Eleven patients with gastric cancer underwent total or subtotal gastrectomy ; while 31 patients with colorectal cancer had colon or rectum resections. There were no statistical differences about the demographic features of the patients. The clinical features of both groups were also comparable. Duration of the operation and mean operative blood loss were also similar in two groups (Table I). Catheter dislocation or obstruction was not observed in any patient in the EEN group. There were no catheter related infectious complications or thoracic organ injury in the TPN group. Excluding a temporary interruption in the EEN group at early postoperative period all patients in both groups reached their nutritional goal. Six patients were needed the temporarily cessation of the enteral nutrition for abdominal distention and gastric residues (n = 4), vomiting (n = 1), and abdominal cramps and diarrhoea (n = 1), but they tolerated enteral nutrition well thereafter by gradual increase and no patient was excluded from this group due to intolerance. Overall enteral nutrition was well tolerated and no patient was excluded from this group due to intolerance. Total cost of feeding for 12 days was 591.30 USD for the EEN group and 551.50 USD for the TPN group.

The preoperative albumin levels were 3.2 ± 0.25 g/dl and 3.1 ± 0.31 g/dl for TPN and EEN groups respectively ($p > 0.05$). The infectious complications are shown in table II. It was 55% and 32% for the TPN and the EEN group respectively ($p < 0.05$). Total length of hospital stay was also shorter in the EEN group than in the TPN group (12.8 ± 4.2 days versus 15.2 ± 5.1 days, $p < 0.05$). All nutritional and immunological indices and stress factors were similar at the preoperative period between the groups. The protein, albumin, Ig G, IgA and Ig M levels did not change throughout the study period.

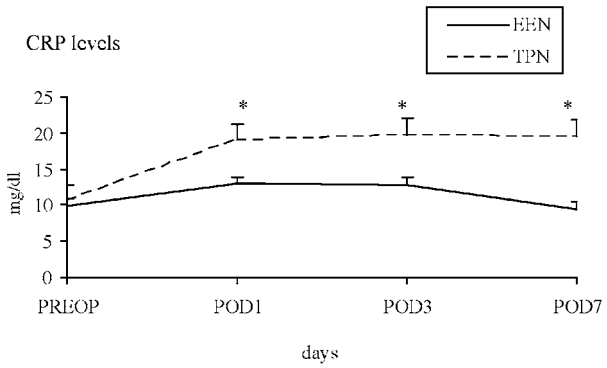

Fig. 1. — CRP levels significantly increased one day after operation in both groups. But this was lower in group receiving EEN ($p < 0.05$). It returned to baseline level on POD7 in EEN group but TPN group showed a stable trend on its maximum level (*$p < 0.05$ for corresponding levels for each group).

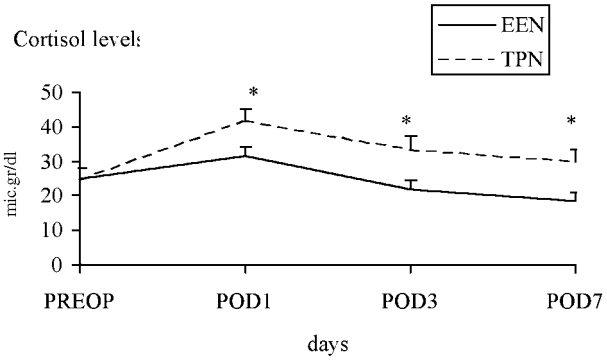

Fig. 2. — Plasma cortisol levels increased in EEN and TPN group ($p < 0.05$ for POD1), but remained almost same with preoperative level following a peak on POD1 in EEN group ($p > 0.05$ for POD3 and POD 7 vs preop). But it never returned to baseline level in TPN group and remained higher throughout the study period.

CRP levels significantly increased one day after the operation in both groups but in patients receiving EEN this increase was significantly lower compared to the TPN group. CRP values reached the highest level on POD1, started to decline and eventually returned to preoperative levels on POD7 in EEN group. The results were quite different for TPN group. CRP values started to increase and reached the maximum level on POD1. It remained here until the POD7 (Fig. 1, $p < 0.05$ between the groups and $p < 0.05$ for intra-group variations except for TPN group on POD3 vs POD7). The plasma cortisol levels are shown in figure 2. It increased to 31.0 mg/dl

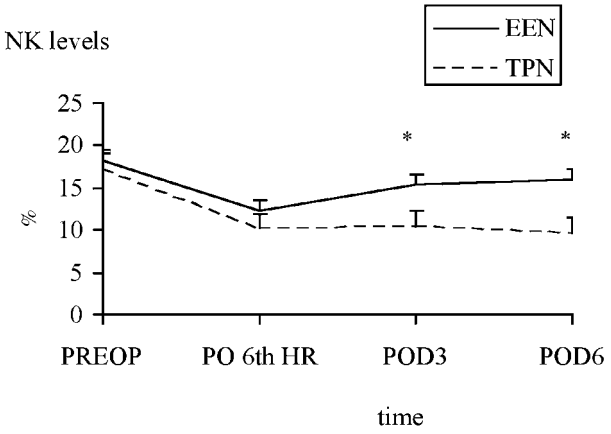

Fig. 3. — There was a significant decrease in NK levels in both groups on POD1. But it remained depressed until POD6 in TPN group (*p < 0.05 between both groups).

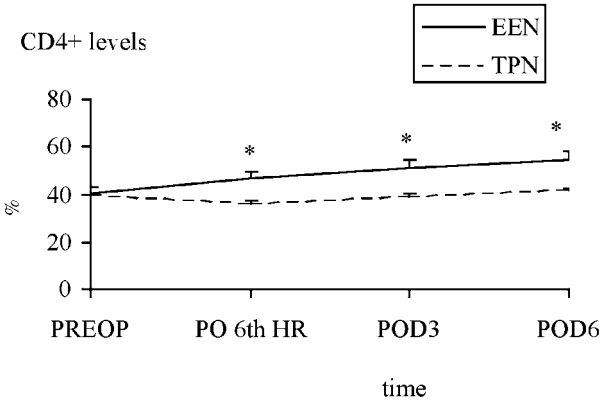

Fig. 4. — CD4+ subsets remained almost same with preoperative value in TPN group, whereas it increased in EEN group on PO 6th hr, POD3 and POD6 (* p < 0.05 between both groups).

from 25.1 mg/dl and to 41.6 mg/dl from 24.4 mg/dl in EEN and TPN group respectively ($p < 0.05$ between the groups for POD1). In the EEN group plasma cortisol levels remained almost same during the preoperative period ; followed by a peak on POD1 ($p > 0.05$ for POD3 and POD 7 versus preoperative in EEN group), but it never returned to baseline values in the TPN group and remained higher throughout the study period.

A significant postoperative decrease in NK cells was observed in both groups. However it started to recover on POD3 and POD6 in EEN group, but did not reach the preoperative value (Fig. 3). Additionally, a significant decrease in NK level was observed in TPN group on POD1 and it remained depressed until POD6. Preoperative level of CD4+ and CD8+ levels were similar to each other in both groups. So one week of nutrition with TPN or EEN did not affect the T cell subpopulation lines. CD8+ levels decreased from preoperative value of (%) 23.89 ± 6.34 to 21.46 ± 6.34 ($p < 0.05$), 19.32 ± 5.63 and 18.33 ± 4.22 ($p > 0.05$), on PO 6th hr, POD3 and POD6 respectively in TPN group. However these values were (%) 21.8 ± 7.32 at preoperative period, 16.9 ± 6.43, 16.2 ± 9.57 and 17.5 ± 5.0 on postoperative periods in EEN group. CD4+ subset remained almost same with preoperative value in TPN group whereas it increased from (%) 40.14 ± 8.32 to 46.40 ± 7.91, 51.29 ± 9.89 and 54.7 ± 10.0 on PO 6th hr, POD3 and POD6 in the EEN group (Fig. 4).

Discussion

Specific defects in lymphocyte subpopulation and reduction in both the helper and suppressor T lymphocyte population and natural killer cell were observed after major surgery (7). Endogenous release of corticosteroids following surgery is a reliable explanation for postoperative lymphocytopenia because a reciprocal relationship between lymphocyte count and serum cortisol level was observed at the postoperative period (8). Our present study demonstrated that postoperative cortisol increase was coincided with a decrease in lymphocyte subpopulations in the TPN group, but not in the EEN group as shown in fig. 3 and 4. The current data also showed that postoperative systemic CRP response was greater in patients who received TPN than in patients who received EEN (Fig. 1). In this study TPN solution lacked glutamine, ω-3 FA and nucleotide which were present in the enteral diet given to EEN group. TPN itself may prime the reticuloendothelial cell and this may lead to enhanced production of cytokine production. Therefore, the route itself may be the important cause of different systemic cytokine response following surgery (9). The administration of EEN starting 5 days preoperatively improved the host defense mechanism by preventing the lymphocyte drop on PO 6th hour and ameliorating the CRP and cortisol increase on POD1. These findings suggest that EEN leads to restoration of immune state earlier than in TPN at postoperative period.

The patients given enteral nutrition starting at the postoperative period gain their immunological competence at least 4-5 days later ; however the reduction of immunoglobulin levels and the reduction in number of activated T and B cells can be restored at early postoperative period in this group if enteral nutrition is started at preoperative period (6).

A sharp increase in CRP levels as acute phase protein was found after surgery in both groups as clearly demonstrated in figure 1, but this level increased progressively until POD7 in the TPN group whereas it started to drop on POD1 and POD3 and returned to baseline levels on POD7 in the EEN group. This finding suggests that EEN may decrease the acute phase protein. This effect may be attributed to arginine supplementation, which is shown to maintain the postoperative nitrogen balance. Arginine also acts as a promoter for T cell proliferation and stimulation, which is in concordance with our data showing that EEN may have a role in restoring

the T lymphocyte subpopulation as early as PO 6th hour when started at the preoperative period. Specific defects in lymphocyte subpopulation can be observed after surgery as demonstrated by Lennard *et al.* (1). Our present data showed that EEN reverted the postoperative decrease in the CD4+ subpopulation. CD8+ levels also decreased at postoperative period in both groups, but the depression in EEN group was more pronounced. The precise mechanism of the negative effect of EEN on CD8+ levels remains to be clarified. Riso *et al.* also showed that the group fed with enteral diet supplemented with arginine demonstrated a significant increase of total lymphocyte count, CD4+ level and CD4+/CD8+ ratio on POD4 and POD8 in patients with head and neck cancer (10). NK levels improved on POD3 in EEN group, but it was more deeply attenuated in TPN group and did not return to preoperative values. Furthermore ; Braga *et al.* reported that early postoperative enteral nutrition improved gut oxygenation in patients with gastric cancer (11). Since enteral nutrition protects the bowel mucosal integrity, bacterial translocation is seen more often following TPN. Therefore NK activity is assumed to decrease due to inefficient bowel stimulation following TPN administration (12). The lower rate of infection in EEN group seems to be related not only to route but also to the composition of the nutritional regimens.

Total cost of nutrition was surprisingly higher in EEN group since the immune enhanced enteral solutions are imported products. But the TPN solutions are produced in Turkey under licence so the prices of latter are much lower than of former.

Enteral nutrition with supplemented immune-enhancing substances was associated with lower rate of infection and shorter hospital stay in the present study. These results were similar to other studies reported in literature (13).

Conclusion

Preoperative nutrition via the enteral route may provide better regulation of postoperative cytokine response and immune system restoration than parenteral nutrition. Based on our findings, we recommend immune-enhanced enteral nutrition to be started at the preoperative period rather than postoperatively before a major in patients with accessible enteral route.

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