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ORIGINAL ARTICLE

Can the Interleukin-1 Receptor Antagonist (IL-1ra) Be a Marker of Anti-Inflammatory Response to Enteral Immunonutrition in Malnourished Patients after Pancreaticoduodenectomy?

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ABSTRACT

Objective To investigate whether early enteral immunonutrition in comparison with standard enteral feeding affects the systemic production of pro- and anti-inflammatory cytokines in malnourished patients after pancreaticoduodenectomy with an uneventful postoperative course.

Design Prospective, randomized study.

Participants Forty-one patients who had undergone pancreaticoduodenectomy.

Interventions Patients received early enteral standard nutrition (No. 22) or enteral immunonutrition (No. 19).

Main outcome measures Cytokines and cytokine inhibitors (IL-1beta, TNF-alpha, IL-6, IL-8, IL-10, IL-1ra, and sTNFRI) were determined before and on days 1, 3, 7, 10 and 14 after surgery using the ELISA test.

Results Serum concentrations of IL-1ra in the early post-operative period were significantly higher in patients treated with enteral immunonutrition than in those treated with the standard diet (day 7: P<0.001; day 10: P=0.002; day 14: P=0.005). Similar results were observed for IL-6 (day 10: P=0.017; day 14: P=0.001), IL-8 (day 1: P=0.011; days 3, 7, 10, and 14: P<0.001) and IL-10 (days 3 and 10: P<0.001) whereas the post-operative levels of IL-1beta (day 7: P<0.001; day 14: P=0.022) and TNF-alpha (day 3: P=0.006; day 7: P<0.001) were significantly higher in patients with standard enteral nutrition.

Conclusion Early enteral immunonutrition as compared to standard nutrition has an immunomodulative effect on the changes in the immune response after extensive surgical trauma resulting in the selective stimulation of cytokines and cytokine inhibitors. The interleukin-1 receptor antagonist is the earliest sensitive marker of anti-inflammatory response to enteral immunonutrition in malnourished patients after pancreatico-duodenectomy.

INTRODUCTION

Surgical trauma increases immune system suppression and deepens malnutrition occurring in approximately 50% of patients with digestive system cancers [1, 2]. The immune disorders and malnutrition are worse in the early postoperative period which considerably affects the process of wound healing, intestinal barrier function and the number of post-operative complications [3, 4, 5, 6]. This period can feature an enhanced pro-inflammatory response (SIRS: systemic inflammatory response syndrome) and an anti-inflammatory response (CARS: compensatory anti-inflammatory response syndrome) to extensive surgical trauma which leads to immune function breakdown [7, 8]. While pro-inflammatory cytokine production (IL-1, TNF, IL-6) is an essential part of the response to surgical injury, the excessive production of these molecules may result in increased morbidity and mortality [9].

One way to improve immunity and to lower the number of post-operative complications in oncological patients after extensive surgical trauma was the introduction of enteral immunonutrition. In patients suffering from neoplasms of the colorectum, stomach or pancreas, the perioperative administration of a supplemented enteral formula (enriched with arginine, RNA, and omega-3 fatty acids) reduced the number of postoperative infections and the length of the hospital stay [10].

Despite the advantage of the positive effects of immunonutrition on the treatment of surgical patients, the impact of this nutrition on the immune system still remains unclear. Of the patients who underwent curative operations for gastric or pancreatic cancer with delayed hypersensitivity responses, phagocytic ability of monocytes and the concentration of IL-2 receptors more recovered in the group receiving the enriched solution (with arginine, RNA and omega-3 fatty acids) on postoperative days 4 and 8, but there was no difference in the post-operative infection rates as compared to the standard enteral diet or the group receiving parenteral nutrition only in the post-operative period [11]. A study performed by other authors [12] showed that, in patients who have undergone major operations for gastrointestinal cancer, the supplementation of postoperative early enteral nutrition with glutamine, arginine, and omega-3-fatty acids positively modulated post-surgical immunosuppressive and inflammatory responses. In this study, the feedings started within 48 hours after surgery and immune responses were determined by phagocytosis ability, the respiratory burst of polymorphonuclear cells, total lymphocytes, lymphocyte subsets, nitric oxide, cytokine concentration, and inflammatory responses as seen by plasma levels of C-reactive protein and the level of prostaglandin E2. The post-operative levels of IL-6 and TNF-alpha were lower in the supplemented group. Another study showed that, in patients with gastric carcinoma, after 7 days of postoperative enteral nutritional support, the immuno-nutrition-treated group (enteral formula enriched with glutamine, arginine and omega-3 fatty acids) had higher levels of IL-2 than those in the control group who received standard nutrition whereas IL-6 and TNF-alpha levels were significantly lower in the immunonutrition-treated group [13]. In patients after pancreaticoduodenectomy, immunonutrition enhances the immuno-metabolic response (phagocytosis ability of polymorphonuclear cells and plasma interleukin-2 receptors on day 8) and improves outcome as compared to parenteral feeding [14]. Immunonutrition enhances the host response and induces a switch from the acute-phase to constitutive proteins. An inverse correlation between IL-6 and pre-albumin levels was noted only in the immunonutrition group [15].

Any further insight into the possibility of using immunonutrition to regulate immune disorders after an extensive operative injury requires further investigation of the changes in pro- and anti-inflammatory cytokine concentrations during immunonutrition. The aim of our study was to compare the effect of early post-operative enteral immunonutrition and standard enteral nutrition on the concentration of cytokines and cytokine inhibitors (IL-1beta, TNF-alpha, IL-6, IL-8, IL-10, IL-1ra, and sTNFRI) in malnourished patients after pancreaticoduodenectomy.

MATERIALS AND METHODS

Treatments

Two enteral diets were evaluated: an early standard diet (Nutrison®, Nutricia Export BV, Zoetermeer, Holland) and an immune-enhancing diet (Stresson®, Nutricia Export BV, Zoetermeer, Holland).

Patients

Sixty patients operated on for pancreatic cancer were randomized (by using numbered sealed envelopes stratified by the surgeon) to receive either the early standard diet (30 patients) or the immune-enhancing enteral diet (30 patients). After full clinical diagnostic procedures (image and laboratory tests), all patients were operated on for resection of the head of the pancreas (Whipple's pancreatico-duodenectomy). Histopathological examination confirmed the diagnosis.

The indication for early post-operative enteral nutrition treatment was the pre-operative loss of body mass (greater than 6% within 2 months) and the extent of surgery (including the advancement of the tumor) questioning the possibility of receiving an oral diet covering the calorific and protein demand within 7 days after the procedure [16]. Nutritional status (loss in body mass, body mass index (BMI), albumin concentration and total lymphocyte count) was assessed before surgery and on day 7 after surgery. In order to evaluate the loss in the body mass, the body weight assessed before surgery was compared to that of the previous two months, while the body weight assessed after surgery was compared to that evaluated before surgery**.**

The present investigation did not include patients with post-operative infectious complications, with unrespectable pancreatic cancer, those who had had transplantation of organs, patients treated with chemo- or radiotherapy or immunosuppressors, patients with autoimmune diseases, with diabetes type 1 (insulin-dependant), chronic respiratory insufficiency (chronic obstructive pulmonary disease), cardiovascular insufficiency, and kidney and liver diseases (biopsy-proven cirrhosis or a serum total bilirubin greater

Table 1. Patient characteristics and surgical parameters of the two groups of patients.

Characteristics	**Standard diet (No. 22)**	**Supplemented diet (No. 19)**	**P value**
Age (years)	54.2±4.1	59.8±6.0	0.001 [a]
Gender:			0.744 [b]
- Males	15 (68.2%)	14 (73.7%)	
- Females	7 (31.8%)	5 (26.3%)	
Tumor staging (TNM classification):			0.507 [c]
- I	8 (36.4%)	9 (47.4%)	
- II	11 (50.0%)	8 (42.1%)	
- III	3 (13.6%)	2 (10.5%)	
Duration of surgery (min)	343±45	330±60	0.434 [a]
Operative blood loss (mL)	600±350	550±300	0.629 [a]
Transfused patients	7 (31.8%)	6 (31.6%)	1.000 [b]
Nutritional status before surgery			
Weight loss (%)	6.3±3.4	6.5±2.1	0.825 [a]
BMI (kg/m^2)	22.2±3.2	23.4±4.5	0.326 [a]
Albumin (g/L)	28.5±3.1	29.8±0.8	0.076 [a]
Total lymphocyte count (cells/mm^3)	1,900±624	2,151±253	0.109 [a]
Nutritional status after surgery			
Weight loss (%)	9.2±3.2	9.1±2.8	P=0.916 [a]
BMI (kg/m^2)	21.8±3.0	22.4±6.3	P=0.693 [a]
Albumin (g/L)	20.3±6.8	24.1±5.4	P=0.057 [a]
Total lymphocyte count (cells/mm^3)	930±145	1,140±262	P=0.003 [a]

Data are reported as mean±SD or frequencies.

[a] One-way ANOVA

[b] Fisher's exact test

[c] Chi-squared: linear by linear association

Table 2. Composition of diets in patients with standard and supplemented diets (data refer to 100 mL).

Variables	Standard diet	Supplemented diet
Calories (kcal)	100	125
Protein (g)	4.00	7.50
Glutamine (g)	-	1.34
Arginine (g)	-	0.89
Fat (g)	3.9	4.2
LCT (g)	0.4	2.0
MCT (g)	1.2	1.5
EPA (g)	-	0.079
DHA (g)	-	0.028
n6:n3	5:1	3.5:1
L-carnitine (mg)	-	7.5
Inositol (mg)	-	63
Taurine (mg)	-	13
Choline (mg)	37	46
Vitamin A (µg RE)	82	91
Vitamin E (mg alpha-TE)	1.3	13.0
Vitamin C (mg)	10.0	25.0
Osmolarity (mOsm/L)	260	410

DHA: docosahexaenoic acid
EPA: eicosapentanoic acid
LCT: long chain triglyceride
MCT: medium chain triglyceride
RE: retinyl equivalents
TE: tocopherol equivalents

than 3.0 mg/dL). According to these criteria, 19 out of the 60 patients were excluded: 8 patients in the standard nutrition and 11 patients in the supplemented group. Therefore, this prospective and randomized study included 41 patients (29 males, 12 females; mean age: 56.8±10.2 years): 22 patients received the standard diet and 19 patients received the supplemented diet. The characteristics of the two groups of patients are shown in Table 1.

Enteral Nutrition

In both groups the post-operative nutrition was carried out by using a pump and a tube installed in the distal small bowel loop during surgery. The rate of increase in the diet was gradually increased from 30 mL/h for the first 24 to 48 hours and then increased to full feeding depending on the passage of flatus and bowel action. All patients reached their nutritional goal within 72 h. The mean total feeding time for the entire group of patients was 12.3±2.0 days. The extension of enteral immunonutrition time in several patients resulted from delayed gastric emptying frequency which made it impossible to earlier introduce oral feeding, and occurred with similar frequency in both groups. The daily supply of the main nutritional substances in standard enteral nutrition was, on the average: 10.8±1.3 g nitrogen, 208±24 g glucose, 66.0±7.7 g fat (including 102±12 g of protein and 1,693±198 kcal) whereas, in enteral immunonutrition, it was: 14.7±2.2 g nitrogen, 177±26 g glucose, 51.4±7.5 g fat, 16.4±2.4 g glutamine, 10.9±1.6 g arginine (including 91.8±13.5 g protein and 1,529±224 kcal). The supply of calories was significantly greater ($P=0.017$) in the standard diet (glucose: $P<0.001$; fat: $P<0.001$; protein: $P=0.014$) while the nitrogen content was significantly higher in the supplemented group ($P<0.001$). Table 2 shows the composition of the diets. Tolerance for both formula diets was excellent.

Therapy

All patients received antibiotics for prophylaxis (1.2 g amoxicillin-potassium clavulanate combination and 2.0 g of cefoperazone) and low-particle heparin; they were given crystalline fluids intravenously as well as electrolytes, depending on actual demand.

Cytokine and Cytokine Antagonists Measurement

In all patients, blood samples were collected from the peripheral vein on the day preceding surgery and on post-operative days 1, 3, 7, 10 and 14. Serum samples were prepared and stored at -80°C for further use. The serum concentrations of IL-1beta, TNF-alpha, IL-6, IL-8, IL-10, IL-1ra and sTNFRI (p55) were determined using commercially available enzyme immunoassay kits (Quantikine R&D Systems Europe Ltd, Barton Lane Abingdon, Oxon, United Kingdom). Samples were prepared and tested in duplicate according to the manufacturers' instructions. The lower limit of sensitivity of the assay for serum samples was 1 pg/mL for IL-1beta, 4.4 pg/mL for TNF-alpha, 0.7 pg/mL for IL-6, 10 pg/mL for IL-8, 3.9 pg/mL for IL-10, 22 pg/mL for IL-1ra and 3.0 pg/mL for sTNFRI.

ETHICS

The patients gave a written consent after the details of the protocol were fully explained. The protocol of the study was approved by the Medical University Ethics Committee and conforms to the ethical guidelines of the World Medical Association Declaration of Helsinki.

STATISTICS

The data are presented as frequencies, means and standard deviations. Patient characteristics and surgical parameters of the two groups (standard *vs*. supplemented) were compared by using one-way ANOVA, chi-squared (linear by linear association) and Fisher's exact tests according to the type of variable (continuous, ordinal, and dichotomous). A two-tailed P value less than 0.05 was selected to indicate significance. All computations were performed using the SPSS 12.0 statistical package.

RESULTS

The pre-operative concentrations of IL-1beta, IL-8, IL-10 and IL-1ra were significantly higher in the supplemented than in the standard group while TNF-alpha and IL-6 were significantly higher in the standard diet group (Table 3, Figure 1). When comparing the two groups during the post-operative period, significantly higher concentrations of IL-6 (days 10 and 14), IL-8 (from 1 to 14 days), IL-10 (days 3 and 10) and IL-1ra (from day 7 to 14) were found in patients receiving early enteral immunonutrition (Table 3, Figure 1) whereas post-operative levels of IL-1beta (days 7 and 14) and TNF-alpha (days 3 and 7) were significantly higher in patients with standard enteral nutrition (Table 3).

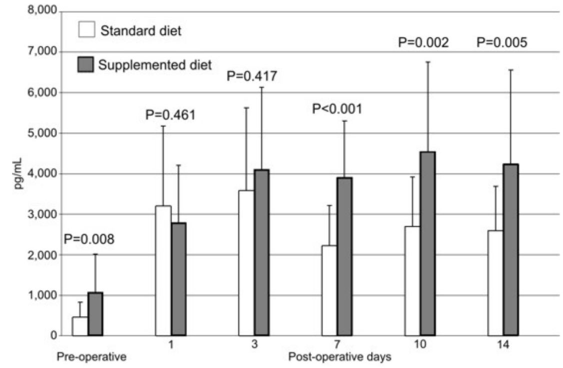

Figure 1. Serum interleukin-1 receptor antagonist concentrations before and after surgery in patients with standard and supplemented diet.

Table 3. Serum cytokine and cytokine antagonist levels (pg/mL) in patients with standard and supplemented diets.

Variables	Diet	Pre-operative	Post-operative days 1	3	7	10	14
IL-1beta	Standard	3.6±1.8	3.0±2.1	3.8±2.6	2.9±0.8	4.9±3.5	4.8±1.6
	Supplemented	5.8±2.3	3.6±1.7	2.8±1.5	1.4±0.9	4.6±2.6	3.5±1.9
		P=0.001	P=0.326	P=0.148	P<0.001	P=0.760	P=0.022
IL-6	Standard	55±45	355±143	189±154	100±43	96±45	74±43
	Supplemented	13±9	281±65	234±160	81±41	151±86	142±78
		P<0.001	P=0.045	P=0.365	P=0.158	P=0.017	P=0.001
IL-8	Standard	20.0±19.1	66.0±38.7	39.0±29.7	26.5±18.8	47.0±36.1	35.5±19.2
	Supplemented	85.0±40.1	105.0±53.8	140.0±58.1	85.0±34.6	110.0±63.9	105.0±44.7
		P<0.001	P=0.011	P<0.001	P<0.001	P<0.001	P<0.001
IL-10	Standard	7.5±6.5	17.7±10.9	8.3±7.7	20.2±14.7	7.0±6.0	18.0±9.3
	Supplemented	14.3±5.3	17.5±11.5	18.1±6.4	24.3±15.4	45.0±31.7	24.0±13.3
		P<0.001	P=0.955	P<0.001	P=0.389	P<0.001	P=0.099
TNF-alpha	Standard	5.6±2.5	5.9±3.0	4.6±3.7	9.7±8.4	7.4±5.4	6.4±4.7
	Supplemented	3.1±2.1	4.1±3.8	2.0±1.2	2.5±1.1	8.0±5.3	7.5±4.2
		P=0.001	P=0.098	P=0.006	P<0.001	P=0.722	P=0.437
sTNFRI	Standard	1,888±818	3,479±1,178	3,821±2,140	3,036±1,224	3,561±2,024	3,481±2,220
	Supplemented	1,531±717	3,256±1,144	3,491±1,386	3,298±1,053	3,179±929	3,286±1,695
		P=0.147	P=0.544	P=0.166	P=0.314	P=0.905	P=0.757

P values: standard *vs*. supplemented diet (one-way ANOVA)

Nutritional status assessment after surgery also revealed significantly increased total lymphocyte count (P=0.003) in patients receiving the supplemented diet (Table 1).

DISCUSSION

Pancreaticoduodenectomy is one of the most invasive operations in upper abdominal surgery with a high incidence of postoperative complications [17, 18, 19]. The immune disorders occurring together with the surgical injury as well as the malnutrition which worsens after surgery usually worsens outcome. The attempt to correct the post-operative nutritional disorders by introducing immunonutrition is a promising way of improving outcome, but as yet little is known about the mechanisms of correcting post-operative immune disorders by using this type of nutrition. The most controversial is the effect of immunonutrition on the post-operative cytokine level which is very important for the immune response to surgical trauma, infection and malnutrition.

The current study investigated whether early enteral immunonutrition as compared to standard enteral feeding affected the systemic production of pro- and anti-inflammatory cytokines in patients after pancreatico-duodenectomy with an uneventful post-operative course.

The results of our investigations confirm the modulative effect of immunonutrition on changes in immune response to surgical trauma in the post-operative periods which have been emphasized by other authors. Unlike previous investigations which did not cover the wide range of pro- and anti-inflammatory cytokines in malnourished patients after pancreatic cancer surgery, in the current study, early enteral immunonutrition had asignificant effect on the post-operative concentration of majority of assessed cytokines and their inhibitors (IL-6, IL-8, IL-10 and IL-1ra, especially on day 7-14 after surgery) as compared to standard nutrition whereas the post-operative levels of IL-1beta and TNF-alpha were elevated in patients with standard enteral nutrition. The post-operative changes in the concentration of cytokines on subsequent post-operative days can be associated with the effect of enteral immunonutrition. Prolonged and excessive elevations of circulating cytokines in patients after major surgery have also been associated with complications but, in our study, patients with postoperative infection complications were excluded. Other studies revealed that, in patients who underwent major thoracic and abdominal surgery (which included only 3 patients after pancreaticoduodenectomy) and treated with an enteral diet containing arginine, omega-3 fatty acids and RNA (IMPACT), the elevated concentrations of IL-1beta and IL-2 were found as late as day 16 whereas the decreased concentration of IL-6 depending on the sample collection time was noted on day 8 or between days 3 to 7 [20]. In the latest study, the interleukin concentrations were measured either without stimulation of a mitogen or after phytohemagglutinin (PHA) stimulation, and glutamine was not used in the immunonutrition. In patients after a gastrectomy for cancer, the perioperative versus post-operative administration of an enteral immune-enhancing diet (without glutamine) ameliorated the host defense mechanisms and controlled the inflammatory response (lower levels of IL-6 on postoperative days 1, 4, and 8 were detected) [21]. The postoperative systemic IL-6 and IL-8 responses in small groups of patients with colorectal cancer who received standard TPN preoperatively were greater than in patients who received an enteral diet. Preoperative nutrition via the enteral route may provide better regulation of the cytokine responses after surgery than parenteral nutrition [22]. In patients with cancer of the stomach or colo-rectum, perioperative nutrition with a supplemented enteral diet (arginine, omega-3 fatty acid and RNA) without glutamine modulates cytokine production (higher interleukin-2 receptors alpha and lower IL-6, and IL-1 soluble receptors II were noted) [23]. Studies of other authors [24] showed that early enteral immunonutrition (IMPACT) without glutamine after colorectal cancer surgery was not associated with increased post-operative complications nor was it related to any change in cytokine profiles, but only IL-6 and TNF-alpha plasma levels were measured. The differences in the results of the above-mentioned studies can be caused by many factors including, among others, differences in the number of patients and in the level of surgical trauma, time and method of diet administration, nutritional mixture composition, nutritional status and differences in the selection of immune parameters or in the selection of test methods for immune changes. The short “diagnostic windows”, especially in the case of assessing the dynamics of change in the level of pro-inflammatory cytokines (IL-1beta and TNF-alpha), are another problem, making it difficult for immunonutrition to have an impact on the immune system. In our studies, the effect of preoperative nutritional status, the extension of surgery and the advancement of cancer were almost the same whereas the supply of calories was significantly greater in the standard group and the nitrogen level was greater in the supplemented group which may significantly influence the higher cytokine levels and increased total lymphocyte count after surgery.

Unlike the investigation results of other researchers, where immunonutrition was mainly enriched with arginine and non-saturated fatty acids, in our study, the nutritional mixture also included glutamine. In an experimental study, the addition of glutamine to cultured rat macrophages stimulated with lipopolysaccharides increased IL-6 mRNA [25], but the production of TNF-alpha,IL-1beta and IL-6 by human blood monocytes appears to be only slightly affected by glutamine availability [26]. Parenteral administration of glutamine after colorectal surgery increased the mitogen-stimulated proliferation of blood lymphocytes, but did not affect *ex vivo* TNF-alpha or IL-6 production [27]. There were also no effects of the glutamine dipeptide on the production of TNF-alpha or IL-6 by LPS-stimulated whole blood after major abdominal surgery [28]. In the group of patients examined, the stimulation of IL-6 production, which is produced mainly by monocytes and macrophages, by enteral immunonutrition could increase the immunosuppressive response to surgical trauma. Interleukin 6 is a multifunctional cytokine whose functions also include the modulation of the anti-inflammatory response after surgical trauma. For example, IL-6 enhances the synthesis of glucocorticoids which possess immuno-suppressive properties and also directly inhibits the expression of TNF-alpha and IL-1. Our study showed that serum TNF-alpha and IL-1 beta levels were significantly decreased in the supplemented (immuno-nutrition) group of patients after surgery. In addition, IL-6 stimulates the macrophage expression of the IL-1 receptor antagonist and soluble TNF receptor [29] which bind to the proinflammatory cytokine (IL-1, TNF). The administration of recombined human interleukin-1 antagonist receptor (rhIL-1ra) extended the survival time of mice having experimentally-induced septic shock [30].

In comparison to standard nutrition, the significantly higher concentrations of IL-1ra (between day 7 and 14) were found only in patients receiving enteral immunonutrition. The results obtained can be explained by the stimulating effect of immunonutrition (mainly glutamine) on the immune system of the bowel (GALT). First of all, glutamine as a nitrogen donor for the synthesis of purines and pyrimidines is the major energy source for the immune system and cells of the small intestine, such as enterocytes. Glutamine maintains the integrity of the gut mucosa. After the enteral administration of glutamine, the number of T-lymphocytes increases in Peyer’s glands [31] whereas, after parenteral administration, the concentration of serum IgA, IL-4 and IL-10 decrease in the intestinal mucous membrane [32]. In our study, the IL-6, IL-8 and IL-10 serum concentrations were also elevated after enteral nutrition in the supplemented group. Some previous studies have shown that glutamine depletion increases spontaneous apoptosis and oxidant-induced cell death in intestinal epithelial cell lines [33] and glutamine prevents cytokine-induced apoptosis in human colonic epithelial cells [34]. Intestinal requirements for glutamine appear to increase during catabolic conditions associated with decreased plasma glutamine concentrations and increased cytokine generation by gut mucosal cells [35]. These changes can worsen in malnourished patients after extensive surgical trauma.

The most prominent effect of supplemental arginine is in abrogating trauma-induced immunosuppresion and improving wound healing. In the mechanism of arginine administration, we should especially remember the key role of nitric oxide and the increased activity of T-lymphocytes (increased production of IL-2 and expression of the receptor for IL-2 on lymphocytes) whereas in the studies of innate immunity, the activity of NK cells and macrophages were also increased [36, 37]. The excessive administration of arginine may lead to an uncontrolled increase in nitric oxide concentration. The elevated concentration of nitric oxide was also observed in various inflammatory states and in septic shock which implies that great care be taken in the administration of arginine, especially in patients suffering from serious infections. The intravenous administration of arginine in septic patients may decrease blood pressure and vascular resistance whereas the excess of nitric oxide can damage the gut barrier and promote bacterial translocation. Therefore, giving high doses of arginine may worsen the outcome in septic patients. During our investigations, the Nutricia Export BV (Zoetermeer, Holland) company stopped the production of Stresson® and we had to end itsthe administration after surgery which had been programmed in our patients with pancreatic cancer.

In our opinion, the stimulation of intestinal immune system cells by applying immunonutrition to especially increase the production of IL-1ra in an early period after extensive surgical trauma can have a positive effect on the regulation (decrease) of the post-operative inflammatory response. At the same time, we have to ask the following question. How long should we maintain the effect (stimulation of IL-1ra production) and to what extent can it be increased by immunonutrition, for example, either by raising the dose of glutamine or arginine, or by introducing immunonutrition as early as possible in the pre-operative period. Our previous studies of malnourished patients operated on for esophageal cancer showed that the application of standard parenteral and enteral pre-operative nutrition for a period of 10 days resulted in a significant increase of IL-6 and IL-1ra concentration in the peripheral blood even before surgery, but it did not affect the concentration of sTNFRI and pre-operative improvement of the nutrition status [38]. Recent results of studies performed on patients operated on for colonic cancer suggest that both pre- and post-operative immune disorders (Th1/Th2 imbalance) can be corrected by applying short-term (five days) pre-operative immunonutrition [39]. It is known that, in the group of patients suffering from colonic cancer, malnutrition occurs less frequently than in patients with pancreatic or esophageal cancer.

In conclusion, our study has clearly indicated that the anti-inflammatory mechanisms are activated early in malnourished patients after pancreaticoduodenectomy receiving enteral immunonutrition.

Early enteral immunonutrition in comparison to standard nutrition has an immuno-modulative effect on the changes in the immune response after extensive surgical trauma. These consist in selective stimulation of IL-6, IL-8, IL-10 and IL-1ra production and down-regulation of IL-1 beta and TNF-alpha production. Among all the cytokines investigated and their inhibitors, IL-1ra is the most sensitive marker of post-operative anti-inflammatory response to enteral immuno-nutrition in malnourished patients with pancreatic cancer. The temporary increase in IL-1ra concentration between post-operative days 7-14 obtained as a result of enteral immunonutrition decreases the inflammatory response to extensive surgical trauma and shortens its duration; this accelerates the wound healing process/tissue regeneration and may help avoid late complications (fistulas, abscesses). It can be presumed that the lack of physiological immune response (unelevated IL-1ra concentration) after enteral immunonutrition may indicate that the intestinal immune system is impaired which may lead to bacterial translocation. Further research needs to be undertaken to examine the interaction between nutrients and to establish the levels and time of intake required to optimize immune responsiveness in malnourished patients after pancreatic cancer surgery.

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Keywords Cytokines; Immunologic Factors; Pancreatic Neoplasms; Surgery

Abbreviations CARS: compensatory anti-inflammatory response syndrome; SIRS: systemic inflammatory response syndrome

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References

1. Edington J, Boorman J, Durrant ER, Perkins A, Giffin CV, James R, et al. Prevalence of malnutrition on admission to four hospitals in England. The Malnutrition Prevalence Group. Clin Nutr 2000; 19:191-5. [PMID 10895110]

2. Bruun LI, Bosaeus I, Bergstad I, Nygaard K. Prevalence of malnutrition in surgical patients: evaluation of nutritional support and documentation. Clin Nutr 1999; 18:141-7. [PMID 10451474]

3. Haydock DA, Hill GL. Impaired wound healing in surgical patients with varying degrees of malnutrition. JPEN J Parenter Enteral Nutr 1986; 10:550-4. [PMID 3098996]

4. Detsky AS, Baker JP, O'Rourke K, Johnston N, Whitwell J, Mendelson RA, Jeejeebhoy KN. Predicting nutrition-associated complications for patients undergoing gastrointestinal surgery. JPEN J Parenter Enteral Nutr 1987; 11:440-6. [PMID 3656631]

5. Reynolds JV, O'Farrelly C, Feighery C, Murchan P, Leonard N, Fulton G, et al. Impaired gut barrier function in malnourished patients. Br J Surg 1996; 83:1288-91. [PMID 8983631]

6. Farreras N, Artigas V, Cardona D, Rius X, Trias M, Gonzalez JA. Effect of early postoperative enteral immunonutrition on wound healing in patients undergoing surgery for gastric cancer. Clin Nutr 2005; 24:55-65. [PMID 15681102]

7. Bone RC. Immunologic dissonance: a continuing evolution in our understanding of the systemic inflammatory response syndrome (SIRS) and the multiple organ dysfunction syndrome (MODS). Ann Intern Med 1996; 125:680-7. [PMID 8849154]

8. Partrick DA, Moore EE, Moore FA, Biffl WL, Barnett CC Jr. Release of anti-inflammatory mediators after major torso trauma correlates with the development of postinjury multiple organ failure. Am J Surg 1999; 178:564-9. [PMID 10670873]

9. Mokart D, Capo C, Blache JL, Delpero JR, Houvenaeghel G, Martin C, Mege JL. Early postoperative compensatory anti-inflammatory response syndrome is associated with septic complications after major surgical trauma in patients with cancer. Br J Surg 2002; 89:1450-6. [PMID 12390391]

10. Braga M, Gianotti L, Radaelli G, Vignali A, Mari G, Gentilini O, et al. Perioperative immunonutrition in patients undergoing cancer surgery: results of a randomized double-blind phase 3 trial. Arch Surg 1999; 134:428-33. [PMID 10199318]

11. Braga M, Vignali A, Gianotti L, Cestari A, Profili M, Carlo VD. Immune and nutritional effects of early enteral nutrition after major abdominal operations. Eur J Surg 1996; 162:105-12. [PMID 8639722]

12. Wu GH, Zhang YW, Wu ZH. Modulation of postoperative immune and inflammatory response by immune-enhancing enteral diet in gastrointestinal cancer patients. World J Gastroenterol 2001; 7:357-62. [PMID 11819790]

13. Chen DW, Wei Fei Z, Zhang YC, Ou JM, Xu J. Role of enteral immunonutrition in patients with gastric

carcinoma undergoing major surgery. Asian J Surg 2005; 28:121-4. [PMID 15851366]

14. Gianotti L, Braga M, Gentilini O, Balzano G, Zerbi A, Di Carlo V. Artificial nutrition after pancreaticoduodenectomy. Pancreas 2000; 21:344-51. [PMID 11075988]

15. Gianotti L, Braga M, Vignali A, Balzano G, Zerbi A, Bisagni P, Di Carlo V. Effect of route of delivery and formulation of postoperative nutritional support in patients undergoing major operations for malignant neoplasms. Arch Surg 1997; 132:1222-9. [PMID 9366716]

16. Weimann A, Braga M, Harsanyi L, Laviano A, Ljungqvist O, Soeters P, et al. ESPEN Guidelines on Enteral Nutrition: Surgery including organ transplantation. Clin Nutr 2006; 25:224-44. [PMID 16698152]

17. Yeo CJ, Cameron JL, Sohn TA, Lillemoe KD, Pitt HA, Talamini MA, et al. Six hundred fifty consecutive pancreaticoduodenectomies in the 1990s: pathology, complications, and outcomes. Ann Surg 1997; 226:248-57. [PMID 9339931]

18. Halloran CM, Ghaneh P, Bosonnet L, Hartley MN, Sutton R, Neoptolemos JP. Complications of pancreatic cancer resection. Dig Surg 2002; 19:138-46. [PMID 11979003]

19. Alexakis N, Halloran C, Raraty M, Ghaneh P, Sutton R, Neoptolemos JP. Current standards of surgery for pancreatic cancer. Br J Surg 2004; 91:1410-27. [PMID 15499648]

20. Senkal M, Kemen M, Homann HH, Eickhoff U, Baier J, Zumtobel V. Modulation of postoperative immune response by enteral nutrition with a diet enriched with arginine, RNA, and omega-3 fatty acids in patients with upper gastrointestinal cancer. Eur J Surg 1995; 161:115-22. [PMID 7539633]

21. Braga M, Gianotti L, Vignali A, Cestari A, Bisagni P, Di Carlo V. Artificial nutrition after major abdominal surgery: impact of route of administration and composition of the diet. Crit Care Med 1998; 26:24-30. [PMID 9428539]

22. Lin MT, Saito H, Fukushima R, Inaba T, Fukatsu K, Inoue T, et al. Preoperative total parenteral nutrition influences postoperative systemic cytokine responses after colorectal surgery. Nutrition 1997; 13:8-12. [PMID 9058440]

23. Gianotti L, Braga M, Fortis C, Soldini L, Vignali A, Colombo S, et al. A prospective, randomized clinical trial on perioperative feeding with an arginine-, omega-3 fatty acid-, and RNA-enriched enteral diet: effect on host response and nutritional status. JPEN J Parenter Enteral Nutr 1999; 23:314-20. [PMID 10574478]

24. Baker EA, Williams L, El-Gaddal Sanaa, Bergin F, Leaper DJ. Does early enteral feeding affect clinical outcome or cytokine profiles after elective surgery for colocectal cancer? Turk J Med Sci 2005; 35:229-34.

25. Yassad A, Husson A, Bion A, Lavoinne A. Synthesis of interleukin 1beta and interleukin 6 by stimulated rat peritoneal macrophages: modulation by glutamine. Cytokine 2000; 12:1288-91. [PMID 10930315]

26. Yaqoob P, Calder PC. Cytokine production by human peripheral blood mononuclear cells: differential senstivity to glutamine availability. Cytokine 1998; 10:790-4. [PMID 9811533]

27. O'Riordain M, Fearon KC, Ross JA, Rogers P, Falconer JS, Bartolo DC, et al. Glutamine-supplemented total parenteral nutrition enhances T-lymphocyte response in surgical patients undergoing colorectal resection. Ann Surg 1994; 220:212-21. [PMID 8053744]

28. Spittler A, Sautner T, Gornikiewicz A, Manhart N, Oehler R, Bergmann M, et al. Postoperative glycyl-glutamine infusion reduces immunosuppression: partial prevention of the surgery induced decrease in HLA-DR expression on monocytes. Clin Nutr 2001; 20:37-42. [PMID 11161542]

29. Tilg H, Trehu E, Atkins MB, Dinarello CA, Mier JW. Interleukin-6 (IL-6) as an anti-inflammatory cytokine: induction of circulating IL-1 receptor antagonist and soluble tumor necrosis factor receptor p55. Blood 1994; 83:113-8. [PMID 8274730]

30. Alexander HR, Doherty GM, Buresh CM. A recombinant human receptor antagonist to interleukin-1 improves survival after lethal endotoxemia in mice. J Exp Med 1991; 173:1029-32. [PMID 1826127]

31. Manhart N, Vierlinger K, Akomeah R, Bergmeister H, Spittler A, Roth E. Influence of enteral diets supplemented with key nutrients on lymphocyte subpopulations in Peyer's patches of endotoxin-boostered mice. Clin Nutr 2000; 19:265-9. [PMID 10952798]

32. Kudsk KA, Wu Y, Fukatsu K, Zarzaur BL, Johnson CD, Wang R, Hanna MK. Glutamine-enriched total parenteral nutrition maintains intestinal interleukin-4 and mucosal immunoglobulin A levels. JPEN J Parenter Enteral Nutr 2000; 24:270-4. [PMID 11011781]

33. Simon A, Plies L, Habermeier A, Martine U, Reining M, Closs EI. Role of neutral amino acid transport and protein breakdown for substrate supply of nitric oxide synthase in human endothelial cells. Circ Res 2003; 93:813-20. [PMID 14512444]

34. Evans ME, Jones DP, Ziegler TR. Glutamine prevents cytokine-induced apoptosis in human colonic epithelial cells. J Nutr 2003; 133:3065-71. [PMID 14519785]

35. Labow BI, Souba WW. Glutamine. World J Surg 2000; 24:1503-13. [PMID 11193715]

36. Reynolds JV, Daly JM, Zhang S, Evantash E, Shou J, Sigal R, Ziegler MM. Immunomodulatory effects of arginine. Surgery 1988; 104:142-51. [PMID 2840748]

37. Bistrian BR. Practical recommendations for immune-enhancing diets. J Nutr 2004; 134:2868S-72S. [PMID 15465803]

38. Slotwinski R, Olszewski WL, Szczygiel B, Szawlowski A, Talarek M, Szczesny T, et al. Changes in Interleukin-6 [IL-6] and cytokine antagonists [IL-1ra and sTNFRI] serum concentration in patients after esophagectomy for esophageal cancer receiving nutritional support both pre- and postoperatively. In: 40th Congress of the European Society for Surgical Research - ESSR. May 25-28, 2005. Konya, Turkey. Bologna, Italy: Medimond S.r.l. - Monduzzi Editore International Proceedings, 2005, 69-76. [ISBN 978-88-7587-151-2]

39. Matsuda A, Furukawa K, Takasaki H, Suzuki H, Kan H, Tsuruta H, et al. Preoperative oral immune-enhancing nutritional supplementation corrects TH1/TH2 imbalance in patients undergoing elective surgery for colorectal cancer. Dis Colon Rectum 2006; 49:507-15. [PMID 16421661]