



Effect of preoperative immunonutrition and other nutrition models on cellular immune parameters

Yusuf Gunerhan, Neset Koksak, Umit Yasar Sahin, Mehmet Ali Uzun, Emel Ekşioğlu-Demiralp

Yusuf Gunerhan, Department of Surgery, Kafkas University Faculty of Medicine, Pasacayiri 36100, Kars, Turkey

Neset Koksak, Mehmet Ali Uzun, 2nd Department of General Surgery, Haydarpaşa Numune Training and Research Hospital, Istanbul 34480, Turkey

Umit Yasar Sahin, Department of Surgery, Esenler Basakşehir State Hospital, Istanbul 34480, Turkey

Emel Ekşioğlu-Demiralp, Department of Hematology-Immunology, Marmara University Faculty of Medicine, Istanbul 34480, Turkey

Author contributions: Gunerhan Y, Koksak N, Sahin UY contributed equally to this work; Gunerhan Y, Koksak N, Sahin UY, Uzun MA designed research; Gunerhan Y, Koksak N, Sahin UY, Uzun MA and Ekşioğlu-Demiralp E performed research; Koksak N, Uzun MA contributed new reagents/analytic tools; Gunerhan Y, Koksak N, Sahin UY analyzed data; Gunerhan Y, Koksak N, Sahin UY wrote the paper.

Correspondence to: Yusuf Gunerhan, Department of Surgery, Kafkas University Faculty of Medicine, Pasacayiri 36100, Kars, Turkey. ygunerhan@gmail.com

Telephone: +90-474-2122566 Fax: +90-474-2120996

Received: October 18, 2008 Revised: December 27, 2008

Accepted: January 3, 2009

Published online: January 28, 2009

Abstract

AIM: To evaluate the effects of preoperative immunonutrition and other nutrition models on the cellular immunity parameters of patients with gastrointestinal tumors before surgical intervention. In addition, effects on postoperative complications were examined.

METHODS: Patients with gastrointestinal tumors were randomized into 3 groups. The immunonutrition group received a combination of arginine, fatty acids and nucleotides. The second and third group received normal nutrition and standard enteral nutrition, respectively. Nutrition protocols were administered for 7 d prior to the operation. Nutritional parameters, in particular prealbumin levels and lymphocyte subpopulations (CD4+, CD8+, CD16+/56+, and CD69 cells) were evaluated before and after the nutrition protocols. Groups were compared in terms of postoperative complications and duration of hospital stay.

RESULTS: Of the 42 patients who completed the

study, 16 received immunonutrition, 13 received normal nutrition and 13 received standard enteral nutrition. prealbumin values were low in every group, but this parameter was improved after the nutritional protocol only in the immunonutrition group (13.64 ± 8.83 vs 15.98 ± 8.66 , $P = 0.037$). Groups were similar in terms of CD4+, CD16+/56, and CD69+ prior to the nutritional protocol; whereas CD8+ was higher in the standard nutrition group compared to the immunonutrition group. After nutritional protocols, none of the groups had an increase in their lymphocyte subpopulations. Also, groups did not differ in terms of postoperative complications and postoperative durations of hospital stay.

CONCLUSION: Preoperative immunonutrition provided a significant increase in prealbumin levels, while it did not significantly alter T lymphocyte subpopulation counts, the rate of postoperative complications and the duration of hospital stay.

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Key words: Malnutrition; Gastrointestinal tumours; Immunonutrition; Prealbumin; Lymphocyte subpopulations

Peer reviewer: Charles M Mansbach, MD, Professor, University of Tennessee Health Science Center, Suite 240, 920 Madison Ave, Memphis, TN, 38163, United States

Gunerhan Y, Koksak N, Sahin UY, Uzun MA, Ekşioğlu-Demiralp E. Effect of preoperative immunonutrition and other nutrition models on cellular immune parameters. *World J Gastroenterol* 2009; 15(4): 467-472 Available from: URL: <http://www.wjgnet.com/1007-9327/15/467.asp> DOI: <http://dx.doi.org/10.3748/wjg.15.467>

INTRODUCTION

Protein-energy malnutrition occurs in 30% to 90% of patients with cancer^[1]. Malnutrition causes adverse effects on immunity through several mechanisms, including atrophy in lymph nodes, decreased lymphocyte count and IgA production and suppression of cellular immunity. Many studies have shown beneficial effects of nutritional support in patients with malnutrition^[2-4].

Immunonutrient compounds with a suggested positive effect on immune parameters such as arginine, glutamine, omega 3 fatty acids, and ribonucleic acid are now being studied with regard to their contribution to immune response when given as supplements to nutritional treatments^[5-8].

Immunonutrition is usually given preoperatively, since it prevents the decrease in cellular immunity and phagocytic capacity of polymorphonuclear neutrophils (PMN's) during the early postoperative period^[9]. There have been several prospective studies examining the effects of immunonutrition support on the rate of postoperative complications, infection rates, length of hospital stay, wound repair, weight gain, cost, and mortality^[10-15]. However, the mechanisms through which beneficial effects occur have not been studied in detail. The basic immune response in the host against the tumor is mediated by cellular immunity. Studies looking at the changes in cellular immunity after immunonutrition-especially those that occur before surgical trauma- are scarce^[9,16,17].

In this prospective randomized study, we examined different nutritional models in preoperative patients with endoscopically and histopathologically documented gastrointestinal tumors. The effects on nutritional parameters, quantitative measures including changes in lymphocyte subpopulations responsible for the cellular immunity [CD4+ (T helper), CD8+ (T cytotoxic, suppressor), CD16+/56+ (natural killer) cells], and qualitative measures such as changes in the expression of CD69+ were explored in immunonutritional and other nutritional models. Our objective was to avoid the possible effects of the inflammatory process due to surgical trauma on the results by evaluating the preoperative effect of immunonutrition on immunological parameters.

MATERIALS AND METHODS

A total of 56 patients with gastrointestinal tumors admitted to the General Surgery Unit of Haydarpasa Numune Hospital were included in this study. Patients with diabetes mellitus, renal and/or hepatic failure, and active infection were excluded, as were the patients with a history of immunosuppressive drug use or clinical signs of vitamin or trace element deficiency.

Informed consent was obtained from all patients. Height, weight, and midarm muscle circumference measurements were made, and weight changes in the previous six months period were evaluated. PPD and cytometric measurements were used to evaluate the cellular response. C-Reactive Protein (CRP), an acute phase reactant, and prealbumin levels were measured to demonstrate and monitor any effect that may be due to the inflammatory process.

Subjective global assessment (SGA) was based on history taking and physical examination, and patients were categorized as follows: normal nutritional status, or mild, moderate, or severe malnutrition.

Body mass index was calculated as follows: BMI =

Table 1 Distribution of patients by nutrition models

	Patients (n)	Nutrition model	Nutritional products ¹
Group 1	n = 16	Immunonutrition	Enteral product with addition of arginine, omega-3 fatty acids and RNA (IMPACT®)
Group 2	n = 13	Normal nutrition	Normal feeding planned by a dietitian
Group 3	n = 13	Standard enteral nutrition	Standard enteral product without RNA or Omega-3 fatty acids (FRESUBIN®)

¹One liter of Impact (Novartis Nutrition, Bern, Switzerland) contains 780 non-protein calories, 43 g of protein, 12.5 g of arginine, 3.3 g of ω -3 fatty acids and 1.2 g of RNA.

kg/m², weight in kilograms and height in meters. The midarm muscle circumference, forearm circumference (C) and triceps skin fold thickness (TST) were measured and calculated according to the modified Heymsfield formula^[18].

Before nutrition, blood samples were obtained for the measurement of hemoglobin, albumin, prealbumin, CRP, and lymphocyte, CD4+, CD8+, CD16+/56+, CD69+ counts.

T-lymphocyte subpopulations were determined with immunofluorescent stained mouse anti-human monoclonal antibodies. At least 5000 cells from each subpopulation were evaluated in the flow cytometry device (Becton Dickinson, Mountainview, Ca, USA) using the Cell Quest program. For this purpose, lymphocytes were initially plotted according to their size and granularity. The accuracy of lymphocyte frames was confirmed by using CD45 FITC and CD14 FE monoclonal antibodies. CD45(+) and CD14(-) cells formed the basis for the assessments. All other cell surface markers were evaluated within this context. In another tube, cells were labeled with CD69 for the qualitative assessment of T lymphocyte responsiveness. Some of these cells were counted in flowcytometry, and others were incubated with phytohemagglutinin for 2.5 h. Then cells were re-counted in flowcytometry and the changes in CD69 expression before and after the stimulation were recorded.

Subsequently, patients were randomized to one of the preoperative nutrition models shown in Table 1 for 7 d. The energy needs were calculated using Harris-Benedict formula. For patients not receiving standard enteral nutrition, an isonitrogenous and isocaloric feeding was provided. The ratio of non-protein energy to nitrogen was 1/142 in the standard enteral product and 1/78 in the immunonutrition group.

The efficacy of nutritional support was evaluated using CRP and prealbumin measurements on days 4 and 7, and nitrogen balance on day 4. On the morning of day 8, blood samples were obtained for the assessment of the changes in nutritional parameters before patients were operated. In patients undergoing radical surgical procedures, duration of the procedure, blood loss, infection rate and duration of hospitalization

Table 2 Patient characteristics and distribution (mean \pm SD)

	IM	NN	SE	P
Number of patients	16	13	13	
F/M ratio	(8/8)	(9/4)	(8/5)	
Age	64.56 \pm 16.16	64.38 \pm 11.67	61.31 \pm 12.13	> 0.05
BMI	24.11 \pm 3.67	23.02 \pm 5.66	22.24 \pm 4.87	> 0.05
Malnutrition index	7.96 \pm 1.36	7.25 \pm 0.79	8.40 \pm 1.68	> 0.05
Muscle circumference	22.34 \pm 3.01	21.11 \pm 4	20.41 \pm 2.31	> 0.05
Strength of hand grasping	0.46 \pm 0.20	0.40 \pm 0.15	0.41 \pm 0.18	> 0.05
Albumin	3.6 \pm 0.59	3.46 \pm 0.57	3.26 \pm 0.51	> 0.05
Prealbumin	13.64 \pm 8.83	15.71 \pm 6.97	17.72 \pm 8.39	> 0.05
Number of lymphocytes	1454 \pm 462	1281 \pm 779.2	1277 \pm 546.4	> 0.05
Subjective global assessment (SGA) ¹				
Moderate malnutrition	9	7	6	
Severe malnutrition	7	6	7	

¹No statistical evaluation was made for subjective global assessment; IM: Immunonutrition; NN: Normal nutrition; SE: Standard enteral nutrition.

Table 3 Changes in prealbumin values with repeated measurements (mean \pm SD)

Prealbumin ¹	IM	NN	SE	P
Baseline	13.64 \pm 8.83	17.72 \pm 8.39	15.71 \pm 6.97	0.414
Day 4	17.12 \pm 9.13	18.34 \pm 6.71	16.24 \pm 7.20	0.792
Day 8	15.98 \pm 8.66	18.13 \pm 6.76	16.41 \pm 7.81	0.750
P	0.037	0.834	0.876	

¹Normal value of prealbumin: 20-40 mg/dL; IM:Immunonutrition; NN: Normal nutrition; SE: Standard enteral nutrition.

Table 4 Percentage of lymphocyte subgroups in the peripheral blood of patients before nutritio

	IM	NN	SE	P
CD4 (<i>n</i> = 32%-54%)	46.13 \pm 10.69	41.46 \pm 9.11	49.92 \pm 7.30	< 0.05
CD8 (<i>n</i> = 34%-37%)	36.81 \pm 7.08	46 \pm 11.34	42.08 \pm 10.4	< 0.05
CD4/8 (<i>n</i> = 0.8-1.8)	1.32 \pm 0.44	1.01 \pm 0.54	1.26 \pm 0.38	< 0.05
CD69	4.25 \pm 5.6	1.40 \pm 1.09	2.02 \pm 2.01	> 0.05
CD69F	12.95 \pm 13.05	2.70 \pm 1.73	17.31 \pm 10.69	< 0.001
CD16/56	4.45 \pm 3.74	7.30 \pm 5.54	5.81 \pm 6.38	> 0.05
(<i>n</i> = 8%-22%)				
CD4+, CD8+	4.26 \pm 2.03	3.61 \pm 1.80	4.08 \pm 2.43	> 0.05
(<i>n</i> = \leq 1%)				

IM: Immunonutrition; NN: Normal nutrition; SE: Standard enteral nutrition.

were recorded.

The Graph Pad Prisma V.3 software package was used for statistical evaluations. For data analysis, in addition to descriptive statistics (mean \pm SD), the Friedman test for repeated multiple measures, the Kruskal-Wallis test for independent multiple group comparisons, Dunn's multiple comparison test for sub-group comparisons, the Wilcoxon test for paired group comparisons, and Fisher and χ^2 tests for repeated measures of qualitative data were used. A *P* value < 0.05 at the 95% confidence interval was considered significant.

RESULTS

A total of 14 patients were excluded from the study due to following reasons: gastrointestinal bleeding

Table 5 Percentage of lymphocyte subgroups in the peripheral blood of patients after nutrition (mean \pm SD)

	IM	NN	SE	P
CD4	44.5 \pm 10.09	41.62 \pm 10.97	48.08 \pm 12.98	> 0.05
CD8	41.5 \pm 10.02	46.08 \pm 12.77	40.23 \pm 14.95	> 0.05
CD4/8	1.33 \pm 0.56	1.04 \pm 0.63	1.54 \pm 1.34	> 0.05
CD69	9.22 \pm 24.36	1.73 \pm 1.06	3.02 \pm 4.41	> 0.05
CD69F	23.11 \pm 27.74	3.23 \pm 1.68	14.3 \pm 13.16	< 0.001
CD16/56	5.63 \pm 5.05	7.52 \pm 3.98	6.15 \pm 8.68	> 0.05
CD4, CD8	4.58 \pm 2.62	4.96 \pm 3.44	3.02 \pm 1.62	> 0.05

IM: Immunonutrition; NN: Normal nutrition; SE: Standard enteral nutrition.

that started after the nutrition programme, emergency surgery to relieve obstruction, and uncontrolled blood sugar levels. A total of 42 of patients completed the study. There were no significant differences between nutrition groups with regard to age, gender, albumin, prealbumin, lymphocyte count, and body mass index (BMI) values (Table 2).

At baseline, prealbumin levels were low in all groups, with no significant between-group differences (Table 3). Repeated measurements showed a significant increase only in the IMN group compared to baseline (15.98 \pm 8.66, *P* = 0.037).

The number of lymphocytes with a CD4+ surface marker was higher in patients receiving SE nutrition before nutritional support (Table 4), but the difference was not significant. Within and between-group comparisons at the end of nutrition showed no significant differences between groups with regard to CD4+ lymphocyte counts (Table 5).

In patients that received normal nutrition (NN) and SE, the number of CD8+ cells was higher compared to normal counts (Table 5). Also, in patients who received NN, the proportion of CD8+ lymphocytes was significantly higher compared to IMN (*P* < 0.05). Following the nutrition, although a slight increase above the normal values was observed in IMN patients, the difference was not significant compared to baseline and other groups (*P* > 0.05).

CD4+/CD8+ ratio was within the normal range

Table 6 Data on the operation and postoperative follow-up (mean \pm SD)

	IM <i>n</i> = 13	NN <i>n</i> = 9	SE <i>n</i> = 11	<i>P</i>
Duration of operation (min)	303.8 \pm 160.1	248.9 \pm 87.67	288.6 \pm 71.28	> 0.05
Blood transfusion (U)	2.84 \pm 2.85	3 \pm 2.20	2.54 \pm 1.80	> 0.05
Wound infection	5	3	2	> 0.05
Pneumonia	2	1	4	> 0.05
Urinary infection	-	-	1	> 0.05
Sepsis	-	-	1	> 0.05
Non-infectious complications	5	3	2	> 0.05
Duration of hospital stay (d)	16.54 \pm 14.83	12 \pm 3.69	14.22 \pm 9.12	> 0.05

IM: Immunonutrition; NN: Normal nutrition; SE: Standard enteral nutrition.

before the nutrition (0.8%-1.8%) in all groups. There was a non-significant increase in that parameter in all groups after nutrition.

CD16+/56+ cell counts were below normal in all groups before and after the nutrition period, with no significant differences compared to baseline in any group. Similarly, there were no significant differences in the proportion of T cells with CD4+, CD8+ (double positive) surface markers before and after the nutrition in any group. Also, groups were similar with regard to these parameters at both time points.

CD69+ counts did not differ between or within the groups before and after the nutrition. In IM group, CD 69 counts after nutrition were obtained higher than the before nutrition group, however it was not statistically significant. Also, when the proportional increase in CD69 surface marker in response to a non-specific immune stimulator such as phytohemagglutinin (PHA) is considered, a significantly higher increase was observed in IM group compared to NN group and SE group ($P < 0.05$).

Of the 42 patients completing the study, 33 underwent radical surgical procedures. Among these patients, there were also no intergroup differences with regard to the duration of operation, incidence of infection, and length of hospital stay ($P > 0.05$) (Table 6).

DISCUSSION

Initially, nutritional support was aimed at meeting the energy needs and providing proteins and other essential micronutrients in order to prevent muscle breakdown and immunosuppression, while now it is more directed at modulation of the immune functions^[5].

Among the nutrients with a suggested positive effect on immune functions, arginine, glutamine, fatty acids, and nucleotides have been studied most extensively. The two products that have been studied most are IMPACT, which contains arginine, fatty acids, and nucleotides, and IMMUNE-AID, which contains glutamine in addition^[5]. In our study IMPACT was used.

Arginine stimulates T lymphocytes, provides a substrate for nitric oxide, and increases the secretion

of insulin and growth hormone. Nitric oxide enhances the splanchnic micro-perfusion *via* vasodilator effects. Ornithine and proline are synthesized from arginine. Polyamine, an important factor for cell division, is synthesized from ornithine. Again, arginine causes volume increase in the thymus, and enhances the functions of macrophages and NK cells. It also accelerates wound healing^[7,8,19-22].

Omega 3 fatty acids are the precursors for eicosanoids which include prostaglandin, prostacyclin, thromboxane and leukotrienes. They have anti-inflammatory properties which act through three different mechanisms^[8,23].

Nucleotides are the precursors for RNA and DNA and are believed to enhance protein synthesis and T-cell functions^[9,24]. Addition of nucleotides in nutrients has led to decreased incidence of fungal infections^[25].

T lymphocyte activation, interferon γ , NK cell, immunoglobulin M, phagocytic capacity of leukocytes and increase in the number of lymphocytes have commonly been used by the investigators for the assessment of immune functions^[5,26-29]. In the present study we examined certain lymphocyte subpopulations such as CD4+ (T helper), CD8+ (T cytotoxic, suppressor), CD16+/56+ (Natural killer), and CD69 cells.

The value of preoperative immunonutrition has now gained widespread acceptance. A shift from the production of acute phase proteins to building-block protein production, effective control of the immune disorder during the early postoperative period, and improved intestinal micro perfusion and oxygen metabolism have been reported in patients receiving immunonutrition^[13,30]. At 2001 Consensus Meeting, a 5 to 10 d period was recommended for preoperative immunonutrition^[31]. Thus, in this study nutrition was given for 7 d.

The suppression of immunity has been proposed to affect the prognosis adversely in cancer patients by increasing the growth and metastatic potential of residual tumor cells^[32]. It can be expected that the preoperative nutrition may attenuate this suppression.

The patient group(s) most likely to benefit from immunonutrition has not been defined yet. Immunonutrition has been proposed to provide benefits in patients undergoing elective surgery for GIS tumors, while no benefit has been reported for intensive care patients, and increased mortality has been reported in patients with sepsis^[12,33,34]. Generally, malnourished patients are accepted as candidates for artificial nutrition. On the other hand, Braga *et al*^[15] recommend the use of perioperative immunonutrition in all patient groups regardless of the nutritional status. Our patient group consisted of subjects with moderate or severe malnutrition compared to SGA.

Despite continuing controversy, many studies have been examining the role of immunonutrition in patients with upper GIS tumors, trauma, or in ICU patients. Usually a lower incidence of infections and shortened length of hospital stay were observed in patients with

upper GIS tumors and in ICU patients^[5].

Braga *et al.* found that in the first postoperative day, standard diet and immunonutrition did not differ significantly in their effects on phagocytic capacity, cytokine profile, immunoglobulin levels, number of active T and B lymphocytes, and lymphocyte mitogenicity. However, from the 4th postoperative day, an improvement in immunodepression was observed. In patients receiving normal nutrition preoperatively for whom a significant level of immunosuppression is expected, preoperative immunonutrition has been shown to decrease the postoperative infection rate^[15]. Matsuda *et al.* observed an improved TH1/TH2 balance with the use of pre- and postoperative immunonutrition^[34].

Most of the patients with cancer suffer from protein-energy malnutrition. The prealbumin levels were low in every 3 patient groups. After nutrition there was a significant increase only in the immunonutrition group. However, Riso *et al.* declared that there was no increase in the prealbumin levels between postoperative immunonutrition and control patients^[35].

The association between major surgery and the decrease in total number of T lymphocytes, suppressor or cytotoxic T lymphocytes and NK cells has been recognized since 1975^[36]. In the present study, in contrast with many other studies, preoperative assessment of immune functions allowed us to examine the effect of immunonutrition on immunosuppression caused exclusively by the tumor and malnutrition. No effect on CD4+ and CD8+ cells was observed, although a partial improvement was observed in the IMN group.

Before nutrition, the number of natural killer cells (CD16+/56+) were below the normal range, and none of the nutritional models caused a significant increase in this parameter. CD69+ counts did not differ significantly between the groups.

In the present study, cellular immune response was assessed only by peripheral blood measurements shortly after the termination of nutrition on day 8. On the other hand, Sakurai *et al.*^[37] (in non-surgical patients) administered enteral immunonutrition to their patients for 12 wk with positive results. In our opinion, such a delay is not acceptable for patients who will undergo cancer surgery.

In conclusion, in the present study preoperative immunonutrition provided a significant increase in prealbumin levels, but did not alter the T lymphocyte subpopulation counts significantly. Further studies are warranted for the assessment of the effect of immunonutrition on antitumor immune response, and we believe that evaluation of tumor infiltrating cells in addition to peripheral blood parameters may provide new insights on this issue.

COMMENTS

Background

Malnutrition is known to have adverse effects on immunity, such as atrophy in lymph nodes, decrease in lymphocyte count and IgA secretion, and suppression in immunity. It is reported in several studies that nutritional

support is useful in patients with malnutrition. With addition of immunonutrient products to nutritional therapies, their beneficial effect on immune response is searched for in many prospective clinical studies. Most of the studies are about postoperative complications, frequency of development of infection, hospital stay, wound healing, weight gain, cost, and mortality. The basic defensive response developed by the host against tumors is directed by cellular immunity. There are few studies detecting the changes in cellular immune response after immunonutrition and before the patient has had the surgical trauma. By evaluating the effect of immunonutrition on immunologic parameters preoperatively, the effects of the inflammatory process produced by surgical stress on the results can be avoided.

Research frontiers

The advantages of the nutritional support can be evaluated by the operative mortality, morbidity, and hospital stay. However, how and with which mechanisms this useful effect develops must be detected separately. For that we must see the nutritional subparameters, albumin, prealbumin, immunoglobulin, and immune parameters such as lymphocyte count, change in T lymphocytes, and NK cells.

Innovations and breakthroughs

The authors emphasized changes in T lymphocytes responsible for cellular immunity with immunonutrition before the operation, and measurement of other parameters responsible for immune response, such as tumor infiltrating lymphocytes.

Application

Immune parameters can also be evaluated when the patients are prepared for operations and patients can be supported with immunonutrition if found deprived.

Peer review

This study is a straightforward analysis of the effects of immunonutrition on immune cellular markers and prealbumin on the postoperative course of patients with tumors. Although this is a negative study, it is helpful in avoiding expensive nutritional supplements in those patients requiring cancer surgery.

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S- Editor Tian L L- Editor Li M E- Editor Zheng XM