Turk J Med Sci
31 (2001) 79-86

Nihal Zekiye ERDEM[1]
İ. Hakan KULAÇOĞLU[1]
Mehtap Akçil TEMEL[2]
Ahmet Çınar YASTI[3]
Nuri Aydın KAMA[3]
Nazan BOZKURT[4]

Perioperative Oral Supplement with Immunonutrients in Gastrointestinal Cancer Patients

Received: February 15, 2000

Departments of [1]Clinical Nutrition Unit, [3]4th Surgical, Ankara Numune Teaching and Research Hospital, [2]Department of Statistics and Computer Science, Başkent University Faculty of Science and Letters, [4]Department of Dietetics and Nutrition, Hacettepe University, Ankara-TURKEY

Abstract: Significant benefits have been gained with pre or peri-operative nutritional support in surgical patients with malnutrition. Recent studies have also shown that some enteral formulas including certain nutrients like glutamine could provide more benefit than the standard formulas. In this prospective-randomized study, the effects of perioperative oral supplement with enteral formulas containing glutamine in comparison with a standard enteral formula in patients who were operated on for GI malignancies were examined. Thirty-two patients were divided into two groups: the study group was given oral supplement with an elemental diet (Alitraq®) for 7 days preoperatively and 10 days postoperatively as 30-35% of total daily requirement (standard hospital diet: 65-70%), while the control group received a polymeric formula (Ensure®) as the same proportion of the daily intake for the same duration. Freidman two-way ANOVA test, Wilcoxon matched pairs signed ranks test and Mann Whitney U test were used for statistical analysis. One patient developed a minor complication (wound infection) and another had a major complication (anastomotic disruption) in the control group, whereas no surgical complications were encountered in the study group. The difference between the two groups did not reach statistical significance (p=0.21). There was no significant difference between the groups with respect to the intolerance of dietary supplements. No nutritional indices showed any difference between preoperative day 0 and preoperative day 8. Obvious declines were observed in all plasma proteins immediately following surgery. Prealbumin values in both groups reached significantly high levels after 10-day postoperative nutritional support, but albumin, prealbumin and transferrin levels increased significantly only in the group on the diet with glutamine during the postoperative period. The results of the study group in lymphocyte percentage and skin tests were significantly better on postoperative day 11. The present study revealed that the patients given enteral nutrition with glutamine had improved immunologic measurements, and developed no postoperative complications. In addition, postoperative nutritional support seemed to be more effective than preoperative feeding.

Key Words: Enteral nutrition, oral supplement, glutamine, gastrointestinal cancer.

Introduction

Malnutrition increases postoperative morbidity, mortality and also hospitalization time in surgical patients (1). This is an especially important problem for patients with malignancies who undergo major operations (2, 3). The mechanism is multifactorial: imparied oral food intake, loss of appetite and tumor-related disorder in the host metabolism. Patients with gastrointestinal (GI) cancer have a particularly higher risk due to local effects of the tumor (4, 5).

Clinically, significant benefits have been gained with pre- or peri operative nutritional support in surgical patients with malnutrition. Early studies on nutritional manipulation usually used the parenteral route. In recent years, the enteral route has gained in popularity. Enteral access is easier than parenteral access, avoids catheter infection and subsequent sepsis, which is one of the serious complications of total parenteral nutrition (TPN), and preserves gut immunity, integrity and motility. It has been demonstrated that cancer patients given enteral formulas have had improved immune function and lowered surgical complication rates when compared with patients who received no nutritional support (6). Some recent studies have also shown that some enteral formulas including certain nutrients like arginine, glutamine and ω-3 fatty acids could provide more benefit than the standard formulas (7-12).

In this clinical study, we evaluated the effect of perioperative oral supplement with enteral formulas containing glutamine in comparison with a standard enteral formula in patients who were operated on for GI malignancies.

Materials and Methods

Thirty-two patients who were operated on for GI (esophagus, stomach, colon, rectum) malignancies with no distant metastasis in Surgical Department 4 of Ankara Numune Teaching and Research Hospital between May 1995 and March 1997 were included in this prospective-randomized study. The patient population was divided into two groups: patients in the study group (SG) were given oral supplement with an elemental diet containing glutamine (Alitraq®-10 g glutamine/178 g, Ross Laboratories, Columbus, Ohio) for 7 days preoperatively and 10 days postoperatively as 30-35% of total daily requirement (standard hospital diet: 65-70%), while patients in the control group (CG) received a polymeric formula (Ensure®, Ross Laboratories, Columbus, Ohio) as the same proportion of the daily intake for the same duration. Table 1 shows the compositions of the two formulas used in the study.

All patients were evaluated according to the following immunological parameters before commencing nutritional support: white blood cell count (WBC: 4100-10900), total lymphocyte percentage (10.0-58.5%) [ABBOTT CD-1700 autoanalyzer], and skin sensitivity

Table 1. Composition of the standard and enriched diets.

		Standard diet (Ensure)	Enriched diet (Alitraq)
Protein			
	% kcal	14.0	21.0
	g / 1000 kcal	42.0	52.5
	sources	sodium and calcium caseinate soy protein isolate	hydrolyzed soy and lactalbumin 11% whey protein 47% free amino acids Glutamine (g/L): 14.2 arginine (g/L): 4.5 % BCAA protein: 18.5
Carbohydrate			
	% kcal	54.5	66.0
	g / 1000 kcal	133.6	165.0
	sources	non-hydrolyzed corn starch sucrose lactose-free gluten-free	85% maltodextrin 5% fructose 10% sucrose lactose-free gluten-free
Fat			
	% kcal	31.5	13.0
	g / 1000 kcal	33.6	15.5
	sources	corn oil linoleic acid (g/L): 20 MCT (g/L): 0.07 ω-fatty acids (g/L): 0.46	safflower oil linoleic acid (g/L): 6.6 MCT (g/L): 6.5 ω-fatty acids (g/L): 1.55
Caloric density	(kcal / mL)	1.0	1.0
NPC : N *		124 : 1	94 : 1
Osmolality	(mOsm / kg H_2O)	470	575
Total nitrogen	(g / L)	6.72	8.40

* NPC : N: Non-protein calorie : Nitrogen (g) ratio

tests [Greer Derma PIK]. These tests were repeated on the day before surgery and before starting oral intake in the postoperative period. Finally all tests were done after ten-day administration of nutritional supplement. Nutritional support-related complications and surgical complications were recorded.

Freidman two-way ANOVA test, Wilcoxon matched pairs signed ranks test and Mann Whitney U test were used for statistical analysis. A p value of less than 0.05 was considered significant.

Results

Thirty-two patients hospitalized for GI cancer without distant metastasis during the study period were evaluated. Each group consisted of 16 patients. The age and sex characteristics of the groups were similar (mean age: 52.94, S.E.: 13.09; 9 women and 7 men in the SG vs mean age: 56.50, S.E.: 11.22; 8 women and 8 men in the CG). Six patients in the CG and one patient in the SG were excluded from the analysis because of an unresectable tumor found in laparotomy. These seven patients were not given enteral nutritional support postoperatively. Of these patients, two patients in the CG developed evisceration. One of them died of subsequent sepsis. The tumor location and resectability rate in each group are shown in Table 2.

One patient developed a minor complication (10%: wound infection) and another had a major complication (10%: anastomotic disruption, biliary peritonitis and sepsis) in the CG, whereas no surgical complications were encountered among the 15 patients in the SG. Overall surgical complication rate was 20% in the CG. However, the difference between two groups did not reach statistical significance (p=0.21). There were no statistically significant differences between the groups with respect to the intolerance of dietary supplements in the pre- and the postoperative periods (Table 3). In no cases was it necessary to discontinue the enteral formula due to side effects. The average postoperative stay in hospital was similar for the two groups (mean: 18.3, S.E.:5 for the CG vs mean: 15, S.E.:3 for the SG, p=0.17).

No nutritional indices showed any difference between preoperative day 0 and preoperative day 8. Obvious declines were observed in all plasma proteins immediately following surgery. Prealbumin values in both groups reached significantly high levels after 10-day postoperative nutritional support. However, albumin and transferrin levels increased significantly only in the enriched diet group during the postoperative period (Table 4).

Immunological parameters of the groups in the pre- (day-0 and day-8) and post operative (day 1 and day 11) periods are shown in Table 5. There were significant differences between the CG and the SG in lymphocyte percentage and skin tests on postoperative day 11.

Table 2. The tumor locations, surgical procedures and resectability rates.

	CG (n=16)	SG (n=16)	Total (n=32)
Tumour site			
Esophagus	-	1	1
Stomach	7	8	15
Colon	2	1	3
Rectum	7	6	13
Surgical procedure			
Total gastrectomy	3	3	6
Subtotal gastrectomy	2	5	7
Colectomy	2	1	3
Anterior resection of the rectum	2	1	3
Non-therapeutic laparotomy due to unresectable tumor	6	1	7
Resectability rate*	62.5%	93.8%	78.1%

*p=0.03

Table 3. Intolerance of dietary supplements.

Preoperative period		CG (n=16)	SG (n=16)
	Nausea-vomiting	1	1
	Total *	1 (6.3%)	1 (6.3%)
Postoperative period		CG (n=10)	SG (n=15)
	Nausea-vomiting	-	2
	Cramping-diarrhea	2	1
	Total †	2 (20.0%)	3 (20.0%)

* p=0.31
† p=1.00

Table 4. Nutritional indices.

	Control Group			Study Group			
	Day	n	Mean (SD)	Day	n	Mean (SD)	
Total protein (g/L)	Preop-0	16	67.67 (4.03)	Preop-0	16	67.73 (4.91)	NS
	Preop-8	16	70.87 (4.31)	Preop-8	16	67.80 (5.41)	NS
	Postop-1	10	57.10 (6.47)	Postop-1	15	55.00 (5.00)	NS
	Postop-11	10	67.80 (7.04)	Postop-11	15	70.47 (3.48)	NS
Albumin (g/L)	Preop-0	16	37.93 (4.77)	Preop-0	16	38.67 (3.92)	NS
	Preop-8	16	42.47 (5.22)	Preop-8	16	38.27 (3.95)	p<0.05
	Postop-1	10	32.40 (4.72)	Postop-1	15	29.07 (9.70)	NS
	Postop-11	10	36.60 (6.69)	Postop-11 *	15	40.00 (3.59)	NS
Prealbumin (mg/dL)	Preop-0	16	18.09 (10.25)	Preop-0	16	18.97 (8.84)	NS
	Preop-8	16	17.50 (9.16)	Preop-8	16	19.67 (4.28)	NS
	Postop-1	10	13.03 (7.87)	Postop-1 †	15	9.78 (2.57)	NS
	Postop-11	10	21.52 (10.12)	Postop-11 ‡	15	25.35 (9.13)	NS
Transferrin (mg/dL)	Preop-0	16	281.01 (66.30)	Preop-0	16	287.29 (43.05)	NS
	Preop-8	16	293.65 (63.11)	Preop-8	16	285.74 (38.35)	NS
	Postop-1	10	218.78 (47.89)	Postop-1	15	187.53 (20.85)	p<0.05
	Postop-11	10	251.68 (79.34)	Postop-11 ∫	15	307.69 (50.39)	NS

NS: Non-significant
* p<0.05 compared with postoperative day 1.
† p<0.05 compared with preoperative day 8.
‡ p<0.01 compared with postoperative day 1.
∫ p<0.05 compared with postoperative day 1.

Discussion

It has been shown that patients with malnutrition in the preoperative period may stay in hospital for a long time after major gastrointestinal surgery (1), and this time can be reduced with nutritional support (7, 8). In patients with an intact gastrointestinal tract, the preferred route for nutritional support is enteral access. Several studies have revealed that enteral nutrition may be a better way to improve nutritional parameters such as prealbumin, retinol-binding protein and transferrin

Table 5. Immunologic measurements.

	Control Group			Study Group			
	Day	n	Mean (SD)	Day	N	Mean (SD)	
WBC (K/μL)	Preop-0	16	8.77 (3.12)	Preop-0	16	8.30 (2.23)	NS
	Preop-8	16	8.29 (3.20)	Preop-8	16	8.36 (1.97)	NS
	Postop-1	10	12.06 (6.90)	Postop-1	15	8.08 (2.90)	NS
	Postop-11	10	10.07 (4.90)	Postop-11	15	9.32 (6.65)	NS
Lymphocyte %	Preop-0	16	27.49 (7.92)	Preop-0	16	29.15 (9.05)	NS
	Preop-8	16	28.46 (7.88)	Preop-8	16	26.64 (7.42)	NS
	Postop-1	10	20.23 (8.38)	Postop-1	15	20.29 (9.70)	NS
	Postop-11	10	21.20 (7.91)	Postop-11	15	30.03 (11.06)	p<0.05
Lymphocyte count (/mm^3)	Preop-0	16	3823 (2854)	Preop-0	16	3471 (2085)	NS
	Preop-8	16	3922 (4671)	Preop-8	16	3577 (1963)	NS
	Postop-1	10	5766 (4223)	Postop-1	15	5286 (3859)	NS
	Postop-11	10	5913 (4701)	Postop-11	15	5032 (1791)	NS
Skin tests (mm)							
Candida albicans	Preop-0	16	5.81 (0.91)	Preop-0	16	4.73 (0.70)	NS
	Preop-8	16	5.56 (1.21)	Preop-8 *	16	6.33 (1.39)	NS
	Postop-1	10	4.40 (0.84)	Postop-1	15	3.73 (0.70)	NS
	Postop-11	10	5.20 (1.39)	Postop-11 †	15	7.80 (2.48)	p<0.05
Trichophyton rubrum	Preop-0	16	5.56 (1.15)	Preop-0	16	4.73 (0.96)	NS
	Preop-8	16	5.69 (1.20)	Preop-8	16	6.53 (1.51)	NS
	Postop-1	10	4.30 (1.25)	Postop-1	15	3.60 (0.82)	NS
	Postop-11	10	5.20 (1.93)	Postop-11 ‡	15	8.00 (2.67)	p<0.01

NS: Non-significant

* p<0.05 compared with preoperative day-0.

† p<0.05 compared with preoperative day-0 and p<0.01 compared with postoperative day-1.

‡ p<0.01 compared with preoperative day-0 and postoperative day-1.

(13), and immunological measurements such as monocyte phagocytosis ability and delayed hypersensitivity test (7).

Oral supplements and tube feeding formulas are usually well tolerated by surgical patients when their concentrations and administration rates are adjusted carefully. Daly (8) reported that postoperative enteral feeding via jejunostomy caused only mild and infrequent gastrointestinal complications. The main side effect of enteral nutrition in that series was long standing diarrhea, while vomiting occurred in only 3 of 30 patients. Kenler and coworkers (12) investigated the results of early enteral feeding in postsurgical cancer patients recorded that 15 of 18 patients given a standard diet via jejunostomy developed gastrointestinal complications. In the same study, the gastrointestinal complication rate among the patients fed a formula enriched with ω-3 fatty acids was significantly lower.

Not surprisingly, it has been observed that intolerance to oral supplemental diet is less frequent than that to total enteral nutrition. First of all, the specific complications of feeding tubes were eliminated in oral supplement studies. Furthermore, the hyperosmolality related problems were diminished because oral food intake was still allowed and the enteral formula was not the sole ingredient in the intestinal lumen. In the present study, intolerance to oral supplement was lower in comparison with the results of the previous studies which investigated the results of the total enteral nutrition. The postoperative intolerance rates were similar in SG and

CG. There were significant differences between pre- and post operative intolerance rates in each group. These differences probably originated from the surgical trauma. However, these results do not mean that postoperative enteral feeding is not well tolerated by the postsurgical patients.

Many studies in the recent literature have shown that some enteral formulas enriched with arginine-ω-3 fatty acids and nucleotides (6-8, 10, 11) and glutamine (14, 15) are superior to standard diets for surgical patients. Daly and coworkers (8) investigated the advantages of enriched enteral formulas in patients with esophageal, gastric or pancreatic cancer. In their enriched diet group, only 10% of the patients developed major postoperative complications. This was significantly lower than the 43% complication rate of the standard diet group. The mean hospital stay was also significantly shorter in the enriched diet group. Senkal and colleagues (11) carried out a similar prospective randomized study in surgical intensive care patients. In the early postoperative period (1 to 5 days), there was no difference in postoperative complication rates between the enriched formula group and the standard enteral diet group. However, in the subgroup of patients in whom complications occurred after the fifth postoperative day, there was a statistically significant reduction in the number of patients with late complications in the enriched diet group. Braga and colleagues (7) compared total parenteral, standard enteral and enriched enteral nutrition groups in the early postoperative period following major surgery for gastric and pancreatic cancer patients. The mean hospitalization times were similar in the two enteral groups, whereas the parenteral nutrition group had a significantly longer period in hospital. The sepsis score was significantly lower in the enriched enteral group than in both the standard enteral and total parenteral groups.

In contrast to the above mentioned series, which investigated the results of total enteral nutrition, McCarter and colleagues (16) found no significant differences in postoperative complication rates or in length of hospital stay between the patients receiving standard or enriched diets as an oral supplement to the standard hospital diet in the preoperative period. Use of oral liquid supplements did not improve lymphocyte proliferation or monocyte functions. A possible explanation for the absence of any effect of preoperative enriched supplement is that one week of preoperative enriched supplements might not be sufficient to enhance immune function. They stated that it might not be possible for preoperative supplements to improve an immune system that was already functioning at a relatively efficient level or the immunosupression encountered in the immediate postoperative period might be mediated by mechanisms that were not amenable to correction with nutrients given before operation. In the present study, immunologic measurements like lymphocyte percentage and skin tests were significantly better in the enriched supplemental diet group. In addition, no postoperative complications were recorded in this group. However, the differences in the postoperative total or infectious complications rates between the groups did not reach a significant level when two patients in CG who developed evisceration after a non-therapeutic laparotomy for unresectable tumors were excluded from the analysis.

There is still no consensus on whether pre- or post operative nutritional support is more useful. There is also a limited number of studies which examine the results of nutritional support given during both pre- and post operative periods. In the present study, a sharp decline was observed in skin test and plasma proteins on the postoperative day 1 despite preoperative nutritional support, as in several studies in which the patients were not supported preoperatively (7, 10). There has been no improvement in nutritional or immunologic parameters from preoperative day 0 to preoperative day 8 during a one-week nutritional support. However, lymphocyte percentage, skin tests, albumin, prealbumin and transferrin measurements significantly improved following a 10-day postoperative administration of enriched diet. In all four nutritional indices, postoperative day 1 values were lower in the SG than in the CG, but these indices were found to be higher in the SG at the end of the postoperative nutritional support. Braga and coworkers (9) found somewhat different results in patients perioperatively fed with supplemented enteral formulas. Preoperative supplementation with immunonutrients prevented early postoperative decrease in phagocytosis and number of circulating lymphocytes, which played a key role in the control of postoperative infections.

Among certain nutrients in enriched formulas, glutamine has some special features. Beyond this, it is the most important nontoxic nitrogen transporter, it serves

as a nontoxic carrier for ammonia, and it plays a role in the regulation of acid-base balance. Glutamine may regulate protein synthesis and provides precursors for nucleotide and protein synthesis, and, most importantly, is the major fuel for immune cells and enterocytes. Shizuka (17) showed that intragastric administration of glutamine increased small intestinal weight and mucosal brush border enzyme acitivities, whereas intravenous nutrition solution with glutamine at 20% of total amino acids had no effect. Oral glutamine also decreases translocation of enteric bacteria across the mucosal barrier (18, 19), and improves the killing bacteria (18). Demetriades and colleagues (20) reported that early postoperative enteral nutrition enriched with glutamine improved healing of experimental colonic anastomoses in rats. Moreover, glutamine-enriched enteral feeding may have an extra advantage in patients with GI cancer because it enhances the tumoricidal effectiveness of chemotherapeutic agents while reducing their morbidity in a rat model (21).

Studies like the present one which have investigated the nutritional and immunologic effects of glutamine and other specific nutrients have generally had small numbers of patients due to high cost. Sacks (22) has evaluated the clinical trials and review articles in English (1970-1997) which have examined the safety and efficacy of parenteral and enteral glutamine supplementation in catabolic patients. He has concluded that although glutamine has shown promise in a select group of catabolic patients, further studies are needed to define which patient populations derive the greatest benefit from supplemental glutamine. In our study, it was observed that the patients given enriched enteral nutrition with glutamine had improved immunologic measurements, and developed no postoperative complications. In addition, postoperative nutritional support seemed to be more effective than preoperative feeding. We think additional larger and multicenter studies will be of more benefit to show the value of glutamine supplemented nutrition in patients with GI cancer.

Correspondence author:

Hakan KULAÇOĞLU

Bahçelievler, 1.cadde, 109/5

06490, Ankara-TURKEY

References

1. Shaw-Stiffel TA, Zarny LA, Pleban WE, Rosman DD, Rudolph RA, Bernstein LH. Effect of nutrition status and other factors on length of hospital stay after major gastrointestinal surgery. Nutrition 9: 140-5, 1993.
2. Bistrian BR, Blackburn GL, Hallowell E, Heddle R. Protein status of general surgical patients. JAMA 230: 858-60, 1974.
3. Nixon DW, Heymsfield SB, Cohen AE, Kutner MH, Ansley J, Lawson DH, Rudman D. Protein-calorie undernutrition in hospitalized cancer patients. Am J Med 68: 683-90, 1980.
4. Brennan MF. Malnutrition in patients with gastrointestinal malignancy: significance and management. Dig Dis Sci 31 (Suppl 9): 77S-90S, 1986.
5. Holmes S, Dickerson JW. Malignant disease: nutritional implications of disease and treatment. Cancer Metastasis Rev 6: 357-81, 1987.
6. Kudsk KA, Minard G, Croce MA, Brown RO, Lowrey TS, Pritchard FE, Dickerson RN, Fabian TC. A randomized trial of isonitrogenous enteral diets after severe trauma: an immune-enhancing diet reduces septic complications. Ann Surg 224: 531-3, 1996.
7. Braga M, Vignali A, Gianotti L, Cestari A, Profili M, Di Carlo V. Benefits of early postoperative enteral feeding in cancer patients. Infusionsther Transfusionsmed 22: 280-4, 1995.
8. Daly JM, Weintraub FN, Shou J, Rosato E, Lucia M. Enteral nutrition during multimodality therapy in upper gastrointestinal cancer patients. Ann Surg 221: 327-38, 1995.
9. Braga M, Gianotti L, Cestari A, Vignali A, Pellegatta F, Dolci A, Di Carlo V. Gut function and immune and inflammatory responses in patients perioperatively fed with supplemented enteral formulas. Arch Surg 131: 1257-6, 1996.
10. Braga M, Vignali A, Gianotti L, Cestari A, Profili M, Di Carlo V. Immune and nutritional effects of early enteral nutrition after major abdominal operations. Eur J Surg 162: 105-12, 1996.
11. Senkal M, Mumme A, Eickhoff U, Geier B, Späth G, Wulfert D, Joosten U, Frei A, Kemen M. Early postoperative enteral immunonutrition: clinical outcome and cost-comparison analysis in surgical patients. Crit Care Med 25: 1489-96, 1997.
12. Kenler AS, Swails WS, Driscoll DF, DeMichele SJ, Daley B, Babineau TJ, Peterson MB, Bistrian BR. Early enteral feeding in postsurgical cancer patients: fish oil structured lipid-based polymeric formula versus a standard polymeric formula. Ann Surg 223: 316-33, 1996.
13. Suchner U, Senftleben U, Eckart T, Scholz MR, Beck K, Murr R, Enzenbach R, Peter K. Enteral versus parenteral nutrition: effects on gastrointestinal function and metabolism. Nutrition 12: 13-22, 1996.

14. van der Hulst RRWJ, von Meyenfeldt MF, Soeters PB. Glutamine: an essential amino acid for the gut. Nutrition 12 (suppl): S78-S81, 1996.
15. Powel-Tuck J, Jamieson CP, Bettany GE, Obeid O, Fawcett HV, Archer C, Murphy DL. A double blind, randomised, controlled trial of glutamine supplementation in parenteral nutrition. Gut 45: 82-8, 1999.
16. McCarter MD, Gentilini OD, Gomez ME, Daly JM. Preoperative oral supplement with immunonutrients in cancer patients. JPEN 22: 206-11, 1998.
17. Shizuka F, Vasupongsotorn S, Kido Y, Kishi K. Comparative effect of intravenously or intragastrically administered glutamine on small intestinal function of the rat. Tokushima J Exp Med 37: 49-57, 1990.
18. Alexander JW. Immunoenhancement via enteral nutrition. Arch Surg 128: 1242-5, 1993.
19. Zapata-Sirvent RL, Hansbrough JF, Ohara MM, Rice-Asaro M, Nyhan WL. Bacterial translocation in burned mice after administration of various diets including fiber- and glutamine-enriched enteral formulas. Crit Care Med 22: 690-6, 1994.
20. Demetriades H, Botsios D, Kazantzidou D, Sakkas L, Tsalis K, Manos K, Dadoukis I. Effect of early postoperative enteral feeding on the healing of colonic anastomoses in rats. Eur J Surg 31:57-63, 1999.
21. Klimberg VS, Nwokedi E, Hutchins LF, Pappas AA, Lang NP, Broadwater JR, Read RC, Westbrook KC. Glutamine faciliates chemotherapy while reducing toxicity. JPEN 16 (Suppl 6): 83S-87S, 1992.
22. Sacks GS. Glutamine supplementation in catabolic patients. Ann Pharmacother 33: 348-54, 1999.