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EFFECTS OF STANDARD AND / OR GLUTAMINE DIPEPTIDE AND / OR OMEGA-3 FATTY ASCID-SUPPLEMENTED PARENTERAL NUTRITION ON NEUTROPHIL FUNCTIONS, INTERLEUKIN-8 LEVEL AND LENGTH OF STAY-A DOUBLE BLIND,CONTROLLED, RANDOMISED STUDY

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# EFFECTS OF STANDARD AND/OR GLUTAMINE DIPEPTIDE AND/OR OMEGA-3 FATTY ASCID-SUPPLEMENTED PARENTERAL NUTRITION ON NEUTROPHIL FUNCTIONS, INTERLEUKIN-8 LEVEL AND LENGTH OF STAY-A DOUBLE BLIND,CONTROLLED, RANDOMISED STUDY

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## ABSTRACT

***Background and Aims*: Protein calorie malnutrition for cancer patients is related with altered cellular and humoral immunity. Standard TPN and glutamine and lipid emulsion with omega 3 fatty acids were given to colorectal cancer patients and the effects of these to neutrophil functions and IL-8 levels are compared.**

***Methods*: Consecutive 36 patients with colorectal cancer diagnosed with endoscopic biopsy and with malnutrition determined by subjective global assessment were enrolled to study. The patients are randomly divided into four groups. Standard TPN to control group, TPN with glutamine solution to S-D group, TPN with omega 3 fatty acid solution to S-O group and TPN with omega 3 fatty acids solution and glutamine to S-D-O group were given for seven days after the operation. At the preoperative, postoperative first day and 7$^{th}$ day, neutrophil phagocytosis index, neutrophil adhesivity index and IL-8 levels were determined.**

***Results*: In all groups compared to control group neutrophil phagocytosis index were increased significantly ($p<0.05$). The most increasing was in group 3. There wasn't significant difference between groups about postoperative first day neutrophil adhesiveness index ($p>0.05$). At the 7$^{th}$ day the neutrophil adhesivity index for study groups were increased compared with control group, but there was no significant differences between groups. There was no significant difference between groups for IL-8 levels.**

***Conclusions*: As a result of the study, altered cellular immunity in colorectal cancer patients with malnutrition can be corrected with omega 3 fatty acid emulsions and glutamine added to TPN so the ratio of morbidity and mortality can be decreased.**

## INTRODUCTION

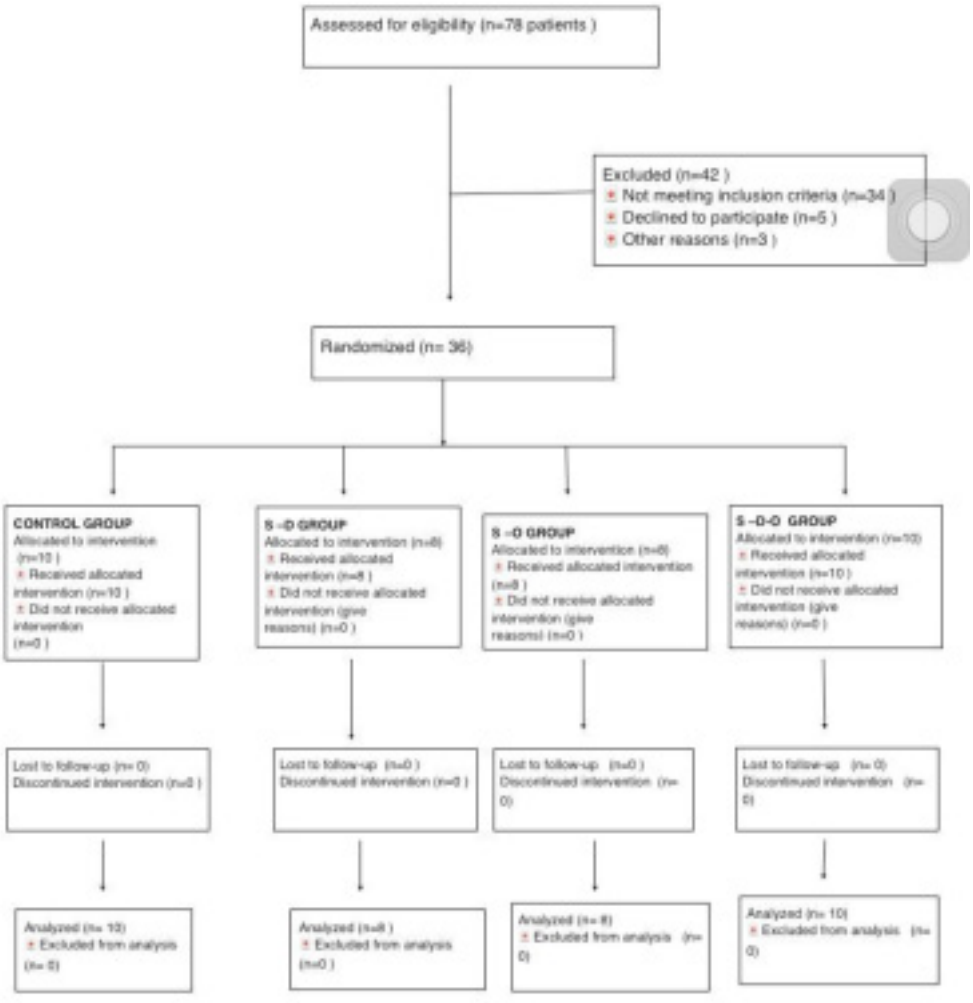
Hypercatabolism and immune suppression are frequently seen in patients with malignancy (1). Preoperative nutritional state is an important factor in determining surgical and postoperative complications because the preoperative nutritional status affects the postoperative nutritional state, immunity and inflammatory response (2). In these patients, standard parenteral nutrition may not be sufficient to maintain the immunity and provide positive or stabilised nitrogen balance (1). Preoperative and perioperative supplementation with immune-enhancing enteral nutrition has been reported to increase total lymphocytes and T lymphocytes and decrease circulating levels of interleukin 6 and tumor necrosis factor- alfa (3-7). There is a report which showed that glutamine dipeptide supplemented parenteral nutrition improved the cellular and humoral immune functions (1). We aimed to evaluate the effect of postoperative glutamine-dipeptide and / or omega 3 fatty acid supplemented parenteral nutrition on the neutrophil functions and postoperative course of patients with colorectal cancer.

## MATERIAL AND METHODS

The thirty six of 78 consecutive adult patients (25 male and 11 female) with colorectal cancer were randomly enrolled in this study. Forty two patients were not appropriate for selection criteria noticed as follow. There were five patients with ascending colon cancer, three patients with transverse colonic cancer, and eight patients with descending colonic cancer, five patients with sigmoid colonic cancer and 15 patients with rectum cancer. Patients who were included study were between 50 and 70 years old. None of the patients preoperatively suffered from serious comorbid chronic disease and received chemotherapy and radiotherapy. None of these patients were used immunosuppressive and /or immunomodulator drugs in last six months. For these patients, the operations were performed with standard and traditionally accepted methods by a senior surgeon.

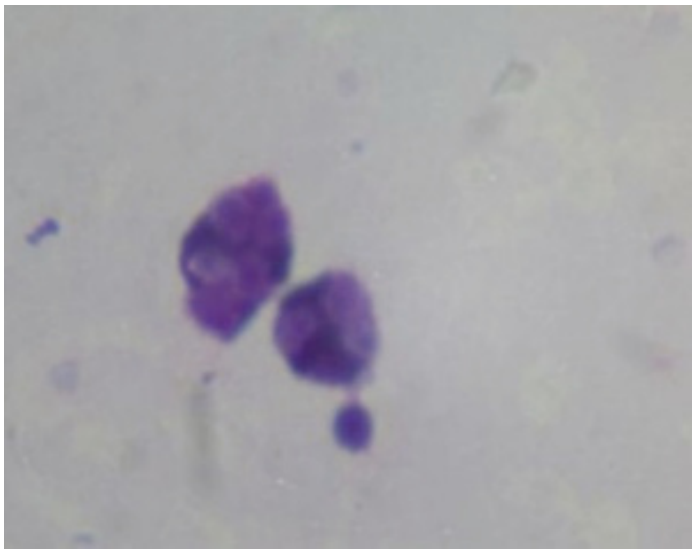
The consecutive 36 colorectal cancer patients were randomly assigned by envelope method with an independent nurse, to 4 groups of nutrition therapies as an isocaloric and iso-nitrogenous standard parenteral nutrition (control group, n=10), alanine-glutamine (aln-gln) (Dipeptiven) supplemented parenteral nutrition (S-D group, n=8), Omega-3 fatty acid (Omegaven) supplemented parenteral nutrition (S-O group, n=8) and ala-gln and omega 3 fatty ascid supplemented parenteral nutrition (S-D-O group, n=10). Neither patients nor surgeon knew which parenteral therapy was applied. This allocation to study was made by a blinded physician with explanation of study to patients who then signed informed consent form. Parenteral nutrition was started on the second postoperative day and was continued until 7th postoperative day. The patients did not receive oral or enteral nutrition during parenteral nutrition. Parenteral nutrition provided 25-30 kcal/kg/day energy and 0.15-0.20 g/kg/day nitrogen. The dose of omega 3 fatty acid supplementation was 0.1-0.2 g/kg /day and it was 0.3-0.4 g/kg/day for glutamine dipeptide supplementation. All nutrient substrates were mixed in 3L bags and infused in 24 h through a dedicated central venous line (Figure 1).

**Figure 1**
*Patient flow chart*



All patients were fasting for 10-12 h prior to surgery. Blood samples were collected on the preoperative day as well as on the first and seventh postoperative days. The total circulating white blood cell count/ mm3 was determined using an automatic cell counter. The percentage and absolute number of circulating white blood cell subsets was determined after performing a differential count of at least 100 cells/smear. Neutrophil Adhesivity Index (NAI) and Phagocytosis Index (NPI) were determined by modified methods of Brandt et al (8) and Penny et al (9) respectively (Figure 2).

**Figure 2**
*A sample of neutrophil phagocytosis*



IL-8 was assayed by the ELISA method with using IL-8/NAP-1 kit (BioSource Europe S.A. Belgium). Routine nutritional follow up of patients was made with biochemical measurements by a nutrition nurse. If any infectious complication was determined during postoperative follow up, microbiological evaluation was performed.

This study was approved by ethical committee of our institution (İAEK8/15). This study was registered under ClinicalTrials.gov Identifier no. NCT01831310. All data are expressed as mean+SD. The statistical package for Social Sciences (SPSS Inc., Chicago, USA) was used for statistical analysis. All groups were compared with each other using Kruskall Wallis Variance Analysis and Tukey test. p value of <0.05 indicated significant difference.

## RESULTS

Data of all patients were eligible for statistical analysis. Patients' demographic characteristics, including age, gender, body mass index and surgical procedures, are summarised in Table 1.

**Table 1**
*Demographic characteristics of groups*

| GROUP | S-D Group | S-O Group | S-D-O Group | Control Group |
|---|---|---|---|---|
| BMI | 24,62±3,16 | 25,62±3,93 | 27,50±4,99 | 24,60±1,78 |
| AGE | 58,0±15,6 | 63,9±17,2 | 59,9±15,1 | 56,3±14,3 |

p>0,05for all

There were no significant differences between groups at entry. No episodes of bleeding, failure of sutures, infection or death were found in the seven day observation period after surgery. There were also no significant differences for preoperative biochemical parameters such as albumin, total protein, ALT and AST levels (Table 2) neutrophil and lymphocyte counts (Table 3) among groups (p>0.05).

**Table 2**
*Preoperative total protein, albumin, AST and ALT levels for groups*

| | | | Mean±SD | |
|---|---|---|---|---|
| GROUP | S-D Group | S-O Group | S-D-O Group | Control Group |
| Total Protein | 6,56±1,09 | 6,65±0,50 | 6,33±0,65 | 6,59±0,49 |
| Albumin | 2,89±0,22 | 2,91±0,37 | 2,95±0,16 | 2,94±0,17 |
| AST | 21,62±12,44 | 16,00±4,41 | 32,80±30,83 | 22,20±8,60 |
| ALT | 23,50±12,42 | 10,00±4,66 | 41,60±37,53 | 22,70±13,50 |

p>0,05 for all

**Table 3**
*Mean neutrophil counts for groups*

| | | | Mean±SD | |
|---|---|---|---|---|
| GROUP | S-D Group | S-O Group | S-D-O Group | Control Group |
| Preoperative | 6216,25±3820,81 | 6016,25±2327,60 | 5773±3134,96 | 5773±3134,96 |
| Postoperative 1 | 8558,75±3394,86 | 9308,75±4994,64 | 6314±3081,11 | 6314±3081,11 |
| Postoperative 7 | 7525±3011,42 | 6122,50±2806,80 | 6755±2473,52 | 7159±2816,83 |

p>0.05 for all

As shown in Table 4, neutrophil phagocytosis Index (NPI) was significantly high in the S-O and S-D-O groups compared with those of control group preoperatively. On the other hand there were no significant differences among others. At postoperative first day, NPI was better in the all supplemented groups than in the control group. It was significantly high for S-D-O group when compared with other supplemented groups. NPI values have similar significance in postoperative 7$^{th}$ day when compared those of postoperative first day. NPI of S-D group and S-D-O group increased significantly on the postoperative first and seventh days as compared with the respective preoperative values; but there were no significant differentiation between postoperative first and 7$^{th}$ days.

**Table 4**
*Mean Neutrophil Phagocytosis Index for groups*

| | | | Mean±SD | |
|---|---|---|---|---|
| GROUP | S-D Group | S-O Group | S-D-O Group | Control Group |
| Preoperative | 67,61±30,18 | 50,50±18,92 | 50,60±16,01 | 28,20±12,92 |
| Postoperative 1 | 74,69±31,18 | 66,25±10,18 | 100,80±18,59 | 38,20±9,99 |
| Postoperative 7 | 82,00±24,93 | 69,00±14,97 | 107,60±13,47 | 36,67±11,07 |

Preop SO- S p=0,039, SDO- S p=0,025,
Postop 1 SD-SDO p=0,002, SD-S p=0,039, SO- SDO p=0,004, SO- S p=0,023, SDO- S p=0,000,
Postop 7 SD- SDO p=0,014, SD-S p=0,000, SO-SDO p=0,000, SO- S p= 0,02, SDO- S p=0,000

Before surgery, NAI was not significantly different in supplemented groups when compared with control group (Table 5). On the other hand there were significant differences between S-O and S-D-O group. There were no differences in NAI among groups for postoperative first day. Mean NAI of postoperative 7th day increased in supplemented groups when compared with standard TPN used control group. NAI in supplemented groups significantly increased after surgery than those of the baseline, but it was not changed in control group.

**Table 5**
*Mean Neutrophil Adhesivity Index for groups*

| | Mean±SD | | | |
|---|---|---|---|---|
| GROUP | S-D Group | S-O Group | S-D-O Group | Control Group |
| Preoperative | 1,03±2,16 | 1,15±0,19 | 1,02±6,55 | 1,03±1,49 |
| Postoperative 1 | 1,11±6,00 | 1,13±4,55 | 1,09±4,84 | 1,09±4,86 |
| Postoperative 7 | 1,37±0,10 | 1,51±0,29 | 1,44±0,21 | 1,08±4,09 |

Preop SO-SDO p=0,042,
Postop 7 SD- S p=0,01, SO- S p=0,00, SDO- S p=0,001

As seen at Table 6, preoperative levels of IL-8 in all groups were similar. It was postoperatively increased in all treatment groups. When compared, on postoperative first and 7th day there were significant increase IL-8 levels for S-D and S-D-O groups and they were significantly higher than those in control group at 7th day.

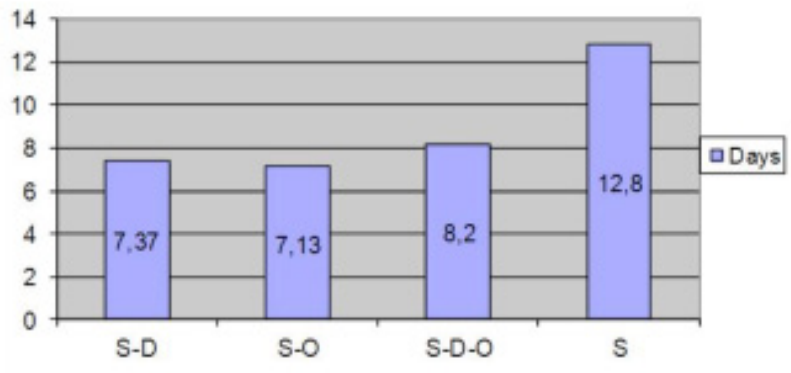
**Table 6**
*Mean Il-8 levels*

| | | | Mean±SD | |
|---|---|---|---|---|
| GRUP | S-D Group | S-O Group | S-D-O Group | Control Group |
| Preop | 1,63±4,30 | 1,53±4,10 | 3,01±9,03 | 1,74±4,40 |
| Postop 1 | 11,08±19,19 | Not Determined | 44,27±66,79 | Not Determined |
| Postop 7 | 13,27±35,11 | 23,83±58,37 | 225,63±253,75 | Not Determined |

p>0.05 for all

The length of postoperative hospital stay was similar in all supplement groups.( 7.37 ± 1.77 day in S-D group; 7.13±1.73 day in S-O group and 8.2±1.14 day S-D-O group) It was significantly short for supplement groups when compared with control group (12.48±5.43 day) (p<0.05) (Figure 3). There was no significant differences among three supplement groups (p>0.05).

**Figure 3**
*Postoperative length of hospitalization SD- S p=0.005, SO-S p=0.003, SDO-S p=0.014*



## DISCUSSION

Experiments in the 1970s and 1980s, as well as some recent studies, have shown that most of the functions of polymorphonuclear neutrophils in patients with advanced cancer were impaired or normal when compared with healthy individual (10,11). Polymorphonuclear neutrophils, as a phagocytes, play the crucial role in the host defense (11). Some studies demonstrated that cancer patients showed lymphocytopenia and neutrophilia, but normal count of monocytes and total leukocytes (11-14). These data supported hypothesis that depressed granulocyte function may contribute to an increased susceptibility to infection and may be considered as an additional factor that favors tumor dissemination (10). On the other hand, major surgery causes postoperative complications based on dysfunction of host defense mechanisms, homeostasis and inflammatory response in malnourished patients (15-19). Preoperative nutritional state is an important factor in determining surgery and predicting postoperative complications (20). Nutritional support is a potentially beneficial strategy to improve postoperative morbidity (2).

Glutamine is the most abundant amino acids in plasma and cells (21). Jing-Xiang et all reported that the nitrogen balance of patients suffering colorectal cancer was negative postoperatively with standard parenteral nutrition, while patients receiving supplemental glutamine dipeptides gained positive nitrogen balance. This results strongly indicates that glutamine improved nitrogen metabolism (1). Parenteral feeding increases the susceptibility of high-risk trauma patients to intra-abdominal abscess, suggesting an impairment in host defense mechanisms compared with individuals fed enterally (22). As known, intestinal permeability may be impaired during prolonged parenteral nutrition. Glutamine is the major fuel of mucosal and immune cells in the intestine. Glutamine supplementation has been shown to reduce the mucosal permeability and maintain normal mucosal configuration (23). The state of cellular and humoral immunosuppression was demonstrated in colorectal cancer patients (1). A clinical study implicates a significant impairment in PMN phagocytosis and peritoneal exudation involving multiple cell types. Glutamine supplementation reverses the deleterious effects of TPN on the inflammatory response and phagocytic function induced by the chemical peritonitis (24). In a pilot study, parenteral glutamine supplementation given to patients with leukemia enhanced neutrophil phagocytic function, maintains nutritional status and is cost effective (25). In this study we determined that there were significant improvement of neutrophil phagocytosis index in parenterally glutamine supplemented groups compared with standard parenteral nutrition group.

Lipid emulsions are the parenteral source of essential fatty acids. They can be infused alone or together with glucose and amino acids in malnourished patients. Polyunsaturated fatty acid supplementation may produce beneficial effects after surgery. A favorable effect of postoperative supplementation of omega-3 fatty acids on the outcomes in colorectal cancer patients undergoing radical resection was reported due to relation by lowering the magnitude of inflammatory responses and modulating the immune response (26), but the evaluations of the effects of LCT and MCT / LCT lipid emulsion infusions in animals showed no alterations of phagocytosis (27). In a recent study low dose fish oil in cancer patients receiving chemotherapy after gastrointestinal tumor removal caused to improve the function of blood neutrophils (28).

Nakamura et al (29) reported that oral administration of a supplement rich in omega 3 fatty acids for 5 days before surgery improved not only preoperative nutritional states but also preoperative and postoperative inflammatory and immune responses in patients with cancer. They observed that a remarkable decreases in interleukin-8 and polymorphonuclear leukocyte elastase in supplement group. De Baux et al (30) suggested that Il-8 level in patients with acute pancreatitis was decreased in glutamine dipeptide supplemented parenteral nutrition group when compared with standard parenteral nutrition group. In present study we did not determined any significant differentiation among groups.

In conclusion; glutamine dipeptide and/or omega 3 fatty acid supplemented postoperative parenteral nutrition improved nonspecific immunity especially neutrophil phagocytosis and adhesivity index in patients with colorectal cancer. This results let us to encourage using these supplements for colorectal patients, but the limitation of this study is number of patients, so there is necessity for larger studies with more sophisticated techniques.

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## REFERENCES


1. Jing-Xiang S, Xiao-Huang T, Lie W, Chen-Jing L. Glutamine dipeptide-supplemented parenteral nutrition in patients with colorectal cancer. *ClinNutr* 2004; **1**(suppl.):49-53.
2. Nakamura K, Moriyama Y, Kariyazono H, Hamada N, Toyohira H, Taira A, et al. Influence of preoperative nutritional state on inflammatory response after surgery. *Nutrition* 1999; **152**:834-841.
3. Barber MD. Cancer cachexia and its treatment with fish-oil– enriched nutritional supplementation. *Nutrition* 2001;**17**:751–755.
4. Senkal M, Kemen M,Homann H, 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**:115–122.
5. Braga M, Gianotti L, Vignali A, Di-Carlo V. Immunonutrition in gastric cancer surgical patients. *Nutrition* 1998;**14**:831–835.
6. 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* 1999;**23**: 314–20.
7. Tepaske R, Velthuis H, Oudemans-van Straaten HM, Heisterkamp SH, van Deventer SJ, Ince C, *et al*. Effect of preoperative oral immune-enhancing nutritional supplement on patients at high risk of infection after cardiac surgery: a randomized placebo-controlled trial. *Lancet* 2001; **358**:696 –701.
8. Brandt L. Adhesiveness to glass and phagocytic activity of neutrophilic leukocytes in myeloproliferative diseases. *Scand J Haemat* 1965; **2**:126-136.
9. Penny R, Galton DAG, Scott JT, Eisen V. Studies on neutrophil function. Br J Haemat 1966; **12**:623-632.
10. Wiezer MJ, Meijer C, Wallast-Gronewoud HP, et al. Impaired leukocyte phagocytosis in patients undergoing hemihepatectomy for liver metastases. *Liver TransplSurg* 1999; **5**:238-45.
11. Baskic D, Acimovic L, Djukic A, Djurdjevic P, Popovic S, Milicic B, et al.. Phagocytic activity and nitric oxide production of circulating polymorphonuclear leukocytes from patients with peritoneal carcinomatosis. *ActaOncol*. 2003;**42**:846-51.
12. Satomi A, Murakami S, Ishida K, Mastuki M, Hashimoto T, Sonoda M. Significance of increased neutrophils in patients with advanced colorectal cancer. *ActaOncol* 1995; **34**:69-73.
13. Ietomi K. A study on the role of granulocytes in carcinoma bearing hosts: G/L ratio as anew host indicator. *J JpnSoc Cancer Ther* 1990; **25**:662-671.
14. Garcia-Gonzalez JE, Rojas Espinosa O, Aguilar-Santelises M. Phagocytic activity of circulating polymorphonuclear leukocytes from patients with carcinoma of uterine cervix. *Rev LatinoamMicrobio*l 1992; **34**:134-141.
15. Chang H, Bistrian B. The role of cytokines in the catabolic consequences of infection and injury. *JPEN* 1998; **22**:156–166.
16. Bozzetti F, Braga M, Gianotti L, Gavazzi C, Mariani L. Postoperative enteral versus parenteral nutrition in malnourished patients with gastrointestinal cancer: a randomized multicentre trial. *Lancet* 2001; **358**:1487–1492.
17. Henriksen MG, Hansen HV, Hessov I. Early oral nutrition after elective colorectal surgery: influence of balanced analgesia and enforced mobilization. *Nutrition* 2002; **18**:263–267.
18. Lin M, 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.
19. Klein S, Kinney J, Jeejeebhoy K, Alpers D, Hellerstein M, Murray M, *et al*. Nutrition support in clinical practice: review of published data and recommendations for future research directions. National Institutes of Health, American Society for Parenteral and Enteral Nutrition, and American Society for Clinical Nutrition. *JPEN* 1997; **21**:133–156.
20. Nakamura K, Moriyama Y, Kariyazono H, Hamada N, Toyohira H, Taira A, *et al*. Influence of preoperative nutritional state on inflammatory response after surgery. *Nutrition* 1999; **152**:834–841.
21. Bergstrom J, Furst P, Noree LO, Vinnars E. Intracellular free amino acid concentration in human muscle tissue. *J. Appl. Physiol.* 1974; **36**:693-7.
22. Kudsk KA, Croce MA, Fabian TC, Minard G, Tolley EA, Poret HA, *et al.*: Enteral versus parenteral feeding: effects on septic morbidity after blunt and penetrating abdominal trauma. *Ann. Surg.* 1992; **215**:503–511.
23. Sacks GS, Kudsk KA. Maintaining mucosal immunity during parenteral feeding with surrogates to enteral nutrition. *Nutr. Clin. Pract.* 2003; **18**:483-488.
24. Ikeda S, Kudsk KA, Le T,Zarzaur BL, Johnson CD. Glutamine improves impaired cellular exudation and polymorphonuclear neutrophil phagocytosis induced by total parenteral nutrition after glycogen-induced murine peritonitis. *Shock* 2003; **19**:50-54.
25. Sornsuvit C, Komindr S, Chuncharunee S, Wanikiat P, Archararit N, SantanirandP.Pilot Study: effects of parenteral glutamine dipeptide supplementation on neutrophil functions and prevention of chemotherapy-induced side-effects i*n acute myeloid leukaemia patients*.J Int Med Res 2008; **36**:1383-91.
26. Liang B, Wang S, Ye YJ, Yang XD, Wang YL, QuJ, *et al*. Impact of postoperativeomega-3fatty acid-supplemented parenteral nutrition on clinical outcomes and immunomodulations in colorectal cancerpatients. *World J Gastroentero*l. 2008; **14**:2434-2439.
27. Waitzberg DL, Bellinati-Pires R, Yamaguchi N, Massili-Oku SM, Salgado MM, Hypolito IP, *et al*. Influence of medium chain trıglyceride-based lipid emulsion on rat polymorphonuclear cell functions. *Nutrition* 1996; **12**:93-99.

28. Bonatto SJ, Oliveira HH, Nunes EA, Pequito D, Iagher F, Coelho I, *et al*. Fish oil supplementation improves neutrophil function during cancer chemotherapy. *Lipids* 2012; **47**:383-389.
29. Nakamura K, Kariyazono H, Komokata T, Hamada N, Sakata R, Yamada K. Influence of perioperative administration of omega-3 fatty acid-enriched supplement on inflammatory and immune responses in patients undergoing major surgery for cancer. *Nutrition* 2005, **21**:639-649.
30. De baux A, O'Riordain M, Ross J, Jodozi L, Carter D. Glutamine supplemented total parenteral nutrition reduces blood mononuclear cell interleukin 8 release in severe acute pancreatitis. *Nutrition* 1998; **14**:261-265.