Original Article

The impact of perioperative enteral immunonutrition on frequent clinical outcome in patients with digestive system cancer

Wei Zhang[1], Wenbin Yang[1], Zhifeng Mo[1], Feng Nian[2], Shaomin Huang[1]

[1]The Seventh Affiliated Hospital of Sun Yat-Sen University, Shenzhen 518000, China; [2]The Third Affiliated People's Hospital of Bengbu Medical College, Bengbu 233000, China

Contributions: (I) Conception and design: W Zhang, W Yang, S Huang; (II) Administrative support: None; (III) Provision of study materials or patients: W Zhang, W Yang, Z Mo, F Nian; (IV) Collection and assembly of data: W Zhang, W Yang; (V) Data analysis and interpretation: W Zhang, Z Mo; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

Correspondence to: Shaomin Huang. The Seventh Affiliated Hospital of Sun Yat-Sen University, Shenzhen 518000, China. Email: hshaomin@163.com.

Background: Forepassed trials have indicated that perioperative enteral immunonutrition can improve the clinical outcome for patients with digestive system cancer. The purpose of this study was to evaluate the effect of perioperative enteral immunonutrition on immunity and postoperative complications in patients with digestive system cancer.

Methods: A group of 64 patients with digestive system cancer was randomly assigned for perioperative enteral immunonutrition (n=32) or standard enteral nutrition (n=32). The postoperative clinical outcome was assessed based on a clinical index, including postoperative complications, and systemic inflammatory response syndrome (SIRS) duration. Also, the postoperative cellular immunity was compared and evaluated between the two groups.

Results: The nutritional therapy of both groups were completed. The occurrence of postoperative infectious complications in the immunonutrition group (6%) was significantly (P=0.020) lower than that of the standard nutrition group (28%). The duration of SIRS in the immunonutrition group (0.77±0.91 days) was significantly shorter than that in the standard nutrition group (1.34±1.46 days) (P=0.012). The postoperative lymphocyte counts and $CD4^+$ T-cells counts significantly declined (P<0.05) in two groups. Nevertheless, the number of $CD4^+$ T-cells on preoperative day 1 and postoperative day 10 was significantly (P<0.05) higher in the immunonutrition group than in the standard nutrition group.

Conclusions: In comparison to standard enteral nutrition, perioperative enteral immunonutrition with glutamine (Gln), ω-3 fatty acids, nucleotide and arginine (Arg) improved the immune status of the patients, reduced the occurrence of postoperative infectious complications and decreased the duration of SIRS. $CD4^+$ T-cells immunity possibly played a vital role in the inflammatory response and the modulation of postoperative immunity after surgery with digestive system cancer.

Keywords: Perioperative enteral immunonutrition (EIN); cancer; immunity; complication

Received: 01 April 2019; Accepted: 14 June 2019; Published: 25 June 2019.

doi: 10.21037/dmr.2019.06.04

View this article at: http://dx.doi.org/10.21037/dmr.2019.06.04

Introduction

Patients with digestive system cancer are often inclined to malnutrition, which might worsen by surgery, chemotherapy, immunotherapy, and complication. Malnutrition is a risk factor, which was associated with immunodepression, inflammation response alteration, complications, and exaggeration of stress reaction. Thus, these patients frequently had a poor clinical outcome in several aspects, such as tumor progression, immunodepression, systemic inflammatory response syndrome (SIRS), pulmonary and wound complications, and so on.

From a nutrition standpoint, supplements of nutrition using enteral or parenteral feeding have been proposed to be a necessary adjuvant therapy of malnutrition patients. The selection of parenteral nutrition (PN) or enteral nutrition (EN) depends on each patient's gastrointestinal function and tolerance of nutrient supply patterns (1). EN is recommended over PN on account of physiological characteristics of those patients and lower costs and complications when the patient's gut function allows the case. Even though essential energy, fat, protein carbohydrate, vitamin, mineral, and so on were provided, the effect of EN was less significant than expected (2). Lately, enteral immunonutrition (EIN), including glutamine (Gln), ω-3 fatty acids, nucleotide, and arginine (Arg) has received more and more attention (3). Data indicates that perioperative EIN is possibly benefited to malnutrition patients with digestive system cancer (4,5). Most of the papers concentrate on direct postoperative impacts such as complications, postoperative mortality, and length of hospital stay. The purpose of this study was to assess the impacts of perioperative EIN on rates of postoperative infectious and noninfectious complications, postoperative cellular [lymphocyte, and white blood cell (WBC)] immunity, and SIRS in patients with digestive system cancer.

Methods

Patients and study design

From June 2017 to January 2019, 64 patients with digestive system cancer after elective curative surgery were enrolled in terms of the following inclusion and exclusion criteria. Inclusion criteria included those that had any of the following conditions: diagnosis of patients with digestive system cancer, planned radical tumor resection, nutritional status with Patient-Generated Subjective Global Assessment (PG-SGA) ≥2 points. The nutritional status of all patients was evaluated in terms of PG-SGA (6). Exclusion criteria included those that had any of the following conditions: severe malnutrition, previous abdominal radiotherapy, preoperative chemotherapy, an unresectable neoplasm, serious cardiovascular, pulmonary, hepatic or renal illness, history of immunological illness or recent immunosuppressive therapy, ongoing infection, emergency surgery, or evidence of preoperative widespread metastatic illness. All patients in this study were fully informed and signed the informed consents. This study was approved by the ethics committee of the Seventh Affiliated Hospital of Sun Yat-sen University. The ethical approval number is 2017SYSUSH-007.

Sixty-four patients were randomly assigned to either of the treatment groups: the immunonutrition group (n=32), in which internal immunonutrition was given, and the standard nutrition group (n=32), in which the patients received standard internal nutrition. All patients received internal nutrition for 7 days before the operation and 7 days since 72 hours after the operation. The patients in the standard group received standard nutrition (low-fat, oligopeptide, isocaloric, non-residue diet)，and the patients in the immunonutrition group received immunonutrition (protein rich, no-residue, an isocaloric diet including ω-3 fatty acids, Gln, and Arg) for 14 days. The diet was administered until the 10th day after surgery. During this treatment, postoperative complications were observed clinically. After the 10th day of post-operation, the immune and inflammatory reaction indices were analyzed by the WBC and the lymphocyte.

Perioperative variables

The perioperative variables are summarized in *Table 1*. TNM classification 7th edition was used for clinicopathological staging of digestive system cancer. There was no significant difference (P>0.05) between the two groups regarding gender, age, intraoperative blood loss, cancer stage, body mass index (BMI), homologous transfusion, weight loss, WBC, lymphocyte, $CD4^+$ T-cell, $CD8^+$ T-cell, and $CD4^+/CD8^+$.

Definitions of postoperative complications

Postoperative complications were recorded in terms of the following criteria:

- Respiratory system infection: abnormal chest radiograph, with positive sputum or bronchoalveolar lavage and WBC count (>12×10^9/L) and fever (temperature <38 ℃);
- SIRS: two or more of the following criteria: (I) leukocyte count >12,000/mm^3, <4,000/mm^3; (II) respiration rate >20 bpm or $PaCO_2$ <32 mmHg; (III) heart rate >90 bpm; (IV) temperature (<36 ℃ or >38 ℃).

Measurement of immunological and nutritional variables

Immunological function

The number of lymphocytes, $CD8^+$ T-cell, $CD4^+$ T-cell,

Table 1 Characteristics of patients included in two groups

Group	EIN group (n=32)	ESN group (n=32)	P value
Age (years)	62.6±11.9	62.9±10.7	0.885
Gender			0.442
Male	21	18	
female	11	14	
Stage (I/II/III)	22/6/4	17/8/7	0.418
BMI	24.65±4.23	25.12±3.85	0.526
Blood loss (mL)	408±271	382±228	0.571
weight loss (kg)	9.14±9.06	12.47±11.8	0.086
Homologous transfusion (mL)	96.2±251.0	106.0±207.0	0.816
WBC ($\times10^9$/L)	8.32±2.81	7.84±3.20	0.384
$CD4^+$ T-cell (/mm^3)	680±187	706±201	0.465
$CD8^+$ T-cell (/mm^3)	582±202	558±189	0.503
Lymphocyte ($\times10^9$/L)	2.53±1.41	2.70±1.28	0.491
$CD4^+/CD8^+$	1.17±0.33	1.27±0.28	0.076

χ^2 test, *t*-test (mean ± SD). ProD7, preoperative 7 days; WBC, white blood cell; BMI body mass index; EIN, enteral immunonutrition; ESN, enteral standard nutrition.

$CD4^+/CD8^+$ ratio of T-cell subpopulation and leukocytes were surveyed by flow cytometry on preoperative days (ProD) 7, and postoperative day (POD) 10. The $CD4^+$ T-cell count and $CD8^+$ T-cell count were measured respectively by using the CD4 FITC kit with anti-human CD4 monoclonal antibody and the CD8 FITC kit with anti-human CD8 monoclonal antibody respectively. The neutrophil is sterilizing, and phagocytosis function was measured by chemiluminescence method. The values measured at preoperative 7 days and postoperative 10 days were compared to assess the impact on surgery and nutrition support.

Statistical analysis

That statistical datum was analyzed by using SPSS 18.0. The *t*-test and the χ^2 test were respectively made use of to compare continuous and discrete variates. P<0.05 was considered to be of statistical significance.

Results

The postoperative clinical outcomes of the two groups during the period of the post-operation are shown in *Table 2*. Ten of 32 patients in the enteral standard nutrition (ESN) group required postoperative therapeutic antibiotics. However, the EIN group required significantly less: only 3 of 32 patients (P=0.030). The period of SIRS in the EIN group (0.77±0.91 days) was significantly shorter than that in the ESN group (1.34±1.46 days, P=0.012). On the contrary, the difference of length of hospital stays was no statistically significant between the two groups (P=0.580). The occurrence of postoperative infectious complications in the EIN group (2 cases) was significantly lower than that in the ESN group (P=0.020), and there was not significantly different in the postoperative noninfectious complications rate (P=1.000).

The data about cellular immunity are shown in *Table 3*. With the POD 7 and POD 10 listed, the postoperative $CD4^+$ T-cell counts on POD 10 reduced in the two groups, whereas the $CD4^+$ T-cell counts in the EIN group were significantly lower (P=0.030) compared with the ESN group. The $CD8^+$ T-cell counts on POD 10 were significantly higher in the EIN group than that in the ESN group. However, there was no significant difference (P=0.065). The serum concentrations of albumin and prealbumin on POD7 and POD 10 indicated no significant difference (P>0.05) between the EIN and ESN groups.

Table 2 Postoperative outcomes

Outcomes	EIN (n=32)	ESN (n=32)	P value
SIRS (days)	0.77±0.91	1.34±1.46	0.012
Postoperative hospitalization (days, mean ± SD)	23.7±16.5	25.1±10.5	0.580
Patients received therapeutic antibiotics, n [%]	3 [9]	10 [31]	0.030
Patients with infectious complications, n [%]	2 [6]	9 [28]	0.020
Respiratory system infection, n [%]	1 [3]	2 [6]	
Infection of incisional wound or effusion	1 [3]	2 [6]	
Catheter infection	0	1 [3]	
Abdominal cavity empyema or effusion	0	4 [13]	
Patients with noninfectious complications, n [%]	4 [13]	4 [13]	1.000
Intestinal obstruction	1 [3]	0	
Cardiac dysfunction	0	1 [3]	
Bleeding	1 [3]	0	
Edematous of anastomosis	2 [6]	3 [9]	

χ^2 test, *t*-test (mean ± SD). SIRS, systemic inflammatory response syndrome; EIN, enteral immunonutrition; ESN, enteral standard nutrition.

Table 3 Comparison of postoperative cellular immunity

Group	POD 10 (mean ± SD)		P value
	EIN (n=60)	ESN (n=60)	
WBC ($\times10^9$/L)	11.4±4.3	12.1±4.7	0.396
Lymphocyte function			
Lymphocyte (/mm^3)	2.30±0.65	2.50±0.56	0.073
CD8$^+$ T-cell (/mm^3)	312±81	339±78	0.065
CD4$^+$ T-cell (/mm^3)	427±68	456±76	0.030
CD4$^+$/CD8$^+$	1.36±0.38	1.34±0.47	0.798

POD, postoperative day; WBC, white blood cell.

Discussion

Patients with digestive system cancer frequently suffer from perioperative malnutrition in connection with the suppression of immunological functions (7). The immune suppression gives rise to anastomotic trouble, infectious complications, and postoperative metastasis (8,9). Immunonutrition has been shown to improve the clinical outcomes for several kinds of patients, such as malnutrition for trauma and critical illness, and those who are receiving treatment in an intensive care unit or after specific surgery, for instance, liver, pancreatic and gastroesophageal resection (10-12). In several clinical trials, the administration of supplemented diets after the operation did not prevent the early postoperative changes of cytokine profiles, phagocytotic ability, immunoglobulin levels, lymphocyte mitogenesis, and the number of activated T and B cells (13). On the contrary, preoperative oral supplementation was found to validly improve the postoperative inflammatory responses and immunity in patients with cancer (14). Moreover, previous researches have shown that preoperative immunonutrition supplement for 7 days provides perioperative benefits, therefore this study was conducted using a 14-day perioperative immunonutrition program.

Recent clinical trials have shown that the provision of immunonutrient, including Gln, ω-3 fatty acids, dietary nucleotides, and Arg, restores normal homeostasis postoperatively and reduces proinflammatory mediators, for instance, TNF-a and IL-6 (13). These results were completely consistent with our data. ω-3 fatty acids derived from fish oil, develop anti-inflammatory and immunomodulatory properties (15). Arg is known to be a promoter to T-cells, which proliferate when stimulated by mitogen or cytokines (16). There is one of the well-known influences of Arg on immune cells, which mediated by the L-arginine-nitric oxide pathway (17).

From this study, there were no statistically significant differences in postoperative hospitalization and the occurrence of postoperative noninfectious complications

between both groups. There was no significant difference in total lymphocytes counts and $CD8^+$ T-cell and $CD4^+$/$CD8^+$ at POD 10 between the two groups. Patients treated with perioperative immunonutrition showed a significantly lower occurrence of infectious complications compared with patients treated with standard nutrition. Furthermore, the duration of SIRS after the operation was significantly shorter in the EIN group compared with the ESN group. The analysis of perioperative cellular immunity showed that maintaining the $CD4^+$ T-cell counts in the EIN group was likely to bring about a few clinical benefits. The patients in the EIN group required less postoperative therapeutic antibiotics compared with the ESN group. Hence, it is possible that perioperative immunonutrition effectively improves the postoperative inflammatory responses and immunity after the operation.

Conclusions

This study indicated that perioperative EIN containing Gln, ω-3 fatty acids, nucleotide and Arg in patients with digestive system cancer reduced the occurrence of postoperative infectious complications and shortened the duration of SIRS by improving the cellular immunity on account of maintaining the $CD4^+$ T-cell levels.

Acknowledgments

Funding: None.

Footnote

Provenance and Peer Review: This article was commissioned by the Guest Editors (Changhua Zhang and Liang Li) for the series "Nutritional Support for Digestive Surgery" published in *Digestive Medicine Research*. The article has undergone external peer review.

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/dmr.2019.06.04). The series "Nutritional Support for Digestive Surgery" was commissioned by the editorial office without any funding or sponsorship. The authors have no other conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All patients in this study were fully informed and signed the informed consents. This study was approved by the ethics committee of the Seventh Affiliated Hospital of Sun Yat-sen University. The ethical approval number is 2017SYSUSH-007. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013).

References

1. Akbulut G. New perspective for nutritional support of cancer patients: Enteral/parenteral nutrition. Exp Ther Med 2011;2:675-84.
2. Bachmann J, Müller T, Schröder A, et al. Influence of an elevated nutrition risk score (NRS) on survival in patients following gastrectomy for gastric cancer. Med Oncol 2015;32:204.
3. Braga M, Gianotti L, Nespoli L, et al. Nutritional approach in malnourished surgical patients: a prospective randomized study. Arch Surg 2002;137:174-80.
4. Klek S, Kulig J, Sierzega M, et al. The impact of immunostimulating nutrition on infectious complications after upper gastrointestinal surgery: a prospective, randomized, clinical trial. Ann Surg 2008;248:212-20.
5. Maruyama T, Mimura K, Izawa S, et al. Immunonutritional diet modulates natural killer cell activation and Th17 cell distribution in patients with gastric and esophageal cancer. Nutrition 2011;27:146-52.
6. Dzieniszewski J, Jarosz M, Szczygieł B, et al. Nutritional status of patients hospitalised in Poland. Eur J Clin Nutr 2005;59:552-60.
7. Xu J, Zhong Y, Jing D, et al. Preoperative enteral immunonutrition improves postoperative outcome in patients with gastrointestinal cancer. World J Surg 2006;30:1284-9.
8. Lundy J, Lovett EJ 3rd, Wolinsky SM, et al. Immune impairment and metastatic tumor growth: the need for an immunorestorative drug as an adjunct to surgery. Cancer

1979;43:945-51.
9. Christou NV, Meakins JL, Gordon J, et al. The delayed hypersensitivity response and host resistance in surgical patients. 20 years later. Ann Surg 1995;222:534-46; discussion 546-8.
10. Daly JM, Lieberman MD, Goldfine J, et al. Enteral nutrition with supplemental arginine, RNA, and omega-3 fatty acids in patients after operation: immunologic, metabolic, and clinical outcome. Surgery 1992;112:56-67.
11. Atkinson S, Sieffert E, Bihari D. A prospective, randomized, double-blind, controlled clinical trial of enteral immunonutrition in the critically ill. Guy's Hospital Intensive Care Group. Crit Care Med 1998;26:1164-72.
12. Gianotti L, Braga M, Gentilini O, et al. Artificial nutrition after pancreaticoduodenectomy. Pancreas 2000;21:344-51.
13. Senkal M, Kemen M, Homann HH, et al. 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.
14. Braga M, Gianotti L, Vignali A, et al. Preoperative oral arginine and n-3 fatty acid supplementation improves the immunometabolic host response and outcome after colorectal resection for cancer. Surgery 2002;132:805-14.
15. Kinsella JE, Lokesh B, Broughton S, et al. Dietary polyunsaturated fatty acids and eicosanoids: potential effects on the modulation of inflammatory and immune cells: an overview. Nutrition 1990;6:24-44; discussion 59-62.
16. Reynolds JV, Daly JM, Zhang S, et al. Immunomodulatory mechanisms of arginine. Surgery 1988;104:142-51.
17. Mansouri MT, Naghizadeh B, Ghorbanzadeh B, et al. Venlafaxine prevents morphine antinociceptive tolerance: The role of neuroinflammation and the l-arginine-nitric oxide pathway. Exp Neurol 2018;303:134-41.

doi: 10.21037/dmr.2019.06.04
Cite this article as: Zhang W, Yang W, Mo Z, Nian F, Huang S. The impact of perioperative enteral immunonutrition on frequent clinical outcome in patients with digestive system cancer. Dig Med Res 2019;2:11.