JBUON 2019; 24(3): 1113-1119
ISSN: 1107-0625, online ISSN: 2241-6293 • www.jbuon.com
Email: editorial_office@jbuon.com

ORIGINAL ARTICLE

Effects of neoadjuvant chemotherapy combined with enteral nutrition on perioperative immunity, inflammation and intestinal flora in gastric cancer patients

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Summary

Purpose: *To investigate the effects of neoadjuvant chemotherapy combined with enteral nutrition on perioperative immunity, inflammation and intestinal flora in gastric cancer patients.*

Methods: *A total of 96 gastric cancer patients scheduled to undergo operation were selected and randomly divided into the observation group (n=48) and the control group (n=48). The patients in the control group were treated with neoadjuvant chemotherapy before operation, while those in the observation group received enteral nutrition before operation based on the treatment in the control group. The changes in immune indexes, inflammatory indexes and intestinal flora were compared between the two groups.*

Results: *After treatment, the levels of serum interleukin-2 (IL-2), IL-6, IL-10 and C-reactive protein (CRP) elevated gradually, while the level of serum tumor necrosis factor-alpha (TNF-a) lowered gradually in both groups (p<0.05). The indexes of nutritional status in the control group declined gradually after operation, and the levels of nutritional indexes, T cell subsets and immunoglobulins in the observation group were significantly higher than those in the control group (p<0.05). In the observation group, after operation, the levels of Bifidobacterium and Lactobacillus rose gradually, but those of Escherichia coli and Enterococcus exhibited progressive decline (p<0.05).*

Conclusions: *Neoadjuvant chemotherapy combined with enteral nutrition can markedly relieve the perioperative inflammatory responses, improve the body immunity and maintain the structure of intestinal flora in gastric cancer patients, so it has certain clinical application value.*

Key words: *enteral nutrition, gastric cancer, immune function, inflammatory factor, intestinal flora, neoadjuvant chemotherapy*

Introduction

In recent years, the incidence rate of malignant diseases is rising year by year due to the influence of people's living habits and surrounding environment. Gastrointestinal tumors take a great proportion in the known human tumors, among which gastric cancer has the highest incidence rate, ranking fourth in the world [1]. According to surveys, gastric cancer mostly occurs in middle-aged and elderly patients aged over 50 years and its incidence varies according to gender, i.e. the prevalence rate of gastric cancer in women is about twice as high than in men. About 1 million individuals are definitely diagnosed with gastric cancer, and approximately 700,000 die of the disease every year [2].

Studies have shown that factors such as eating habits, genetic factors, precancerous lesions, regional environment and Helicobacter pylori infection are closely correlated with the occurrence of gastric cancer. Patients may have early signs, such as nausea and vomiting, but no typical specific

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Received: 20/11/2018; Accepted: 28/12/2018

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symptoms. Therefore, it is very difficult to achieve early diagnosis, and most gastric cancer patients are already in advanced stage when diagnosed clinically [3].

Preoperative neoadjuvant chemotherapy is a treatment method for gastric cancer with favorable efficacy, which can improve the overall survival rate and the one-stage resection rate [4]. However, chemotherapy will lead to bone marrow suppression, loss of appetite nausea, vomiting and other adverse reactions in patients, decrease the patient's tolerance to operation and aggravate low immune function and malnutrition [5]. In recent years, the postoperative nutritional status can be significantly ameliorated and the operative effect can be notably improved in gastric cancer patients undergoing enteral nutrition combined with neoadjuvant chemotherapy before operation [6]. Therefore, the effects of neoadjuvant chemotherapy combined with enteral nutrition on perioperative immunity, inflammation and intestinal flora of gastric cancer patients were investigated and discussed in this paper.

Methods

General data

A total of 96 gastric cancer patients scheduled to undergo selective operation in the Department of General Surgery of our hospital from February 2017 to February 2018 were selected as the research objects and then randomly divided into the observation group (n=48) and the control group (n=48). The general data, including age, gender, site of lesion, type of operation, grade of differentiation and TNM stage, were not significantly different between the two groups of patients, and they were comparable (p>0.05) (Table 1).

TNM staging methods

T stage is subdivided into Tis (tumor cells are located in the mucosa), T1 (tumor cells are located below and above the mucosa), T2 (tumor cells infiltrate into the serosa or muscularis), T3 (tumor cells penetrate the serosa) and T4 (tumor cells expand from the cavity to the duodenum and esophagus or invade into adjacent tissues and structures). At least 15 lymph nodes are taken from the specimens for pathological analysis, and the N stage is subdivided into N0 (no lymph node metastasis), N1 (1-6 regional lymph node metastases pathologically confirmed), N2 (7-15 regional lymph node metastases) and N3 (more than 15 regional lymph node metastases). The M stage is subdivided into M0 (no distant metastasis confirmed by pathology), and M1 (lymph node metastases behind the abdominal aorta, mesentery and pancreas) [7]. Stage I includes T1N0M0, stage II includes T2N0M0, T3N0M0, T1N1M0 and T2N1M0, stage III includes T3N1M0 and T4N(any)M0, and stage IV includes T(any)N(any)M1 [8].

Inclusion and exclusion criteria

Inclusion criteria: 1) patients definitely diagnosed with gastric cancer through cytological and histopathological examinations; 2) patients with a nutrition risk score of not less than 3 points [9]; 3) patients with tolerance to general anesthesia and laparotomy; 4) patients with indications of nutritional support. Exclusion cri-

Table 1. Comparisons of baseline characteristics between the two groups of patients (n=48)

Characteristics	*Control group n (%)*	*Observation group n (%)*	*t/x*	*p*
Male/female (n)	30/18	28/20		
Age (years)	39-70	40-70	-	-
Average age (years) mean±SD	52.15±6.74	51.86±6.83	0.209	0.417
Site of lesion	-	-	-	-
Gastric fundus	19 (39.58)	20 (41.67)	0.066	0.978
Gastric body	13 (27.08)	12 (25.00)		
Gastric antrum	16 (33.33)	16 (33.33)		
Type of operation	-	-	-	-
Proximal gastrectomy	12 (25.00)	13 (27.08)	0.005	0.998
Distal gastrectomy	16 (33.33)	14 (29.17)		
Total gastrectomy	20 (41.67)	21 (43.75)		
Differentiation	-	-	-	-
Mucinous adenocarcinoma	11 (22.92)	10 (20.83)	0.173	0.917
Poorly differentiated adenocarcinoma	17 (35.42)	16 (33.33)		
Moderately differentiated adenocarcinoma	20 (41.67)	22 (45.83)		
TNM stage [n (%)]	-	-	-	-
I-II	28 (58.33)	30 (62.50)	0.174	0.676
III-IV	20 (41.67)	18 (37.50)		

teria: 1) patients with contraindications to parenteral nutrition; 2) patients who received treatments with glucocorticoid, immunodepressant or antibiotics before operation; 3) patients with diabetes mellitus, cardiovascular and cerebrovascular diseases or severe infection; 4) pregnant or breast-feeding women; 5) patients complicated with mental diseases; and 6) patients with poor compliance or withdrawal midway.

This research was approved by the Medical Ethics Committee of Weifang People's Hospital, and patients and their families agreed with and cooperated in this research and signed informed consent.

Methods

The patients in the control group were treated with FOLFOX4 neoadjuvant chemotherapy [10], as follows: 400 mg/m^2 fluorouracil, 200 mg/m^2 calcium folinate and 85 mg/m^2 oxaliplatin (intravenous injection) and 600 mg/m^2 fluorouracil (intravenous infusion for 44 hrs). The treatment was given every 2 weeks for 2 courses in total. The patients in the observation group received treatment with enteral nutrition, in which 500 ml nutrition preparations containing ω-3 fatty acid, low sugars and high fatty acids were administered orally. The enteral nutrition was conducted for 2 courses (7 consecutive days for each course).

Observation indexes

1) Measurement of inflammatory factor levels: 5 ml fasting venous blood was drawn from every patient in the morning of d1 before operation and d1 and 7 after operation, respectively, which was centrifuged using a centrifuge [Ortho BioVue, Johnson & Johnson (Shanghai) Medical Company] with a centrifuge radius of 10.5 cm at 3,000 rpm for 10 min. Then the supernatant was taken and preserved in a refrigerator at -75°C. Enzyme-linked immunosorbent assay (ELISA) was performed to measure the levels of serum tumor necrosis factor-alpha (TNF-α), interleukin-2 (IL-2), IL-6 and IL-10 in strict accordance with the instructions of the kits purchased from Qiyi Biological Technology Co., Ltd. (Shanghai, China). A full-automatic biochemistry analyzer (BS-800 type, Roche, Basel, Switzerland) was used to determine the level of serum C-reactive protein (CRP) in the patients. 2) Measurement of levels of serum T cell subsets: 5 ml fasting venous blood was collected from the patients before treatment and added with ethylenediaminetetraacetic acid for anticoagulation. Then the levels of cluster of differentiation 4 $(CD4)^+$, $CD4^+/CD8^+$ and $CD8^+$ in the peripheral blood was measured by virtue of a flow cytometer (BD FACSCalibur 342975 type, BD, Franklin Lakes, NJ, USA). 3) Measurement of immunoglobulin levels: The immune turbidimetry was adopted to determine the levels of serum immunoglobulin A (IgA), IgG and IgM. 4) The content of total protein, albumin, prealbumin and transferrin on d1 before operation and d1 and 7 after operation in the two groups of patients was observed and recorded. 5) Detection of intestinal flora [11]: On d1 before operation and d1 and 7 after operation, 4-6 g fresh feces were collected separately from the patients after enema, which was assessed within 30 min. The medium plate was selected according to the characteristics and requirements of anaerobic bacteria and aerobic bacteria, and the Bifidobacterium, Lactobacillus, Escherichia coli and Enterococcus were cultured, identified and calculated in strict accordance with the growth environment of bacteria. The log CFU/g (logarithm of bacterial counts in each gram of feces) was utilized to express the bacterial level.

Statistics

SPSS 19.0 software (SPSS Inc., Chicago, IL, USA) was used for data processing. The quantitative data were presented as mean±SD, and evaluated by t-test. One-way analysis of variance (ANOVA) was utilized for comparison at multiple time periods. The percentage data was and evaluated by chi-square test. $P<0.05$ suggested that the difference was statistically significant.

Results

Comparison of nutritional status before and after operation between the two groups of patients

The indexes of nutritional status in the control group decreased gradually after operation, and were remarkably lower than those in the obser-

Table 2. Comparison of nutritional status before and after operation between the two groups of patients

Group	*Time, days (d)*	*Total protein (g/L)*	*Albumin (g/L)*	*Prealbumin (mg/L)*	*Transferrin (g/L)*
Control group	d 1 before operation	68.02±6.23	35.35±3.26	2.42±0.26	2.59±0.46
	d 1 after operation	62.36±5.75	33.23±3.02	2.33±0.22	2.43±0.56
	D 7 after operation	59.26±5.23	31.02±2.85	2.10±0.46	2.12±0.47
	F-test (ANOVA)	11.236	19.637	13.254	18.657
	p	0.025	0.002	0.016	0.009
Observation group	d 1 before operation	69.01±6.31	35.26±3.18	2.45±0.36	2.57±0.48
	d 1 after operation	66.82±6.05*	34.89±3.20*	2.41±0.37*	2.48±0.51*
	d 7 after operation	65.86±5.99*	35.33±3.02*	2.39±0.33*	2.52±0.52*
	F-test (ANOVA)	3.254	2.567	1.854	1.226
	p	0.069	0.096	0.153	0.215

p*<0.05 *vs.* control group

vation group in the same time period, displaying statistically significant difference (p<0.05). There was no statistically significant difference in the indexes of nutritional status in the observation group (p>0.05;Table 2).

Comparisons of serum IL-2, IL-6 and IL-10 levels before and after operation between the two groups of patients

After treatment, the serum levels of IL-2, IL-6 and IL-10 elevated gradually in both groups, and the elevations in those indexes were more prominent in the control group (p<0.05;Table 3).

Comparisons of serum TNF-a and CRP levels before and after operation between the two groups of patients

After treatment, the level of serum TNF-α declined gradually, while the serum CRP level rose gradually in both groups, and more evident improvement in those indexes was observed in the control group (p<0.05;Table 4).

Comparison of levels of T cell subsets before and after operation between the two groups of patients

The levels of T cell subsets in the control group decreased gradually, and they were markedly higher in the observation group than those in the control group in the same time period (p<0.05). The differences in the levels of T cell subsets in the observation group were not statistically significant before and after operation (p>0.05; Table 5).

Comparison of immunoglobulin levels before and after operation between the two groups of patients

The immunoglobulin levels in the control group declined gradually after operation, and they were obviously higher in the observation group than those in the control group in the same time period (p<0.05). There was no statistically significant difference in the immunoglobulin levels in observation group before and after operation (p>0.05;Table 6).

Table 3. Comparisons of serum IL-2, IL-6 and IL-10 levels before and after operation between the two groups of patients

	Time, days (d)	*IL-2 (ng/L)*	*IL-6 (ng/L)*	*IL-10 (ng/L)*
Control group	d 1 before operation	44.32±7.15	271.56±61.33	53.25±7.52
	d 1 after operation	51.63±8.23	270.39±56.39	48.33±6.36
	d 7 after operation	55.69±8.62	258.32±50.36	45.37±6.02
	F-test (ANOVA)	24.568	20.134	35.698
	p	<0.001	<0.001	<0.001
Observation group	d 1 before operation	44.36±5.63	281.66±65.33	52.25±7.20
	d 1 after operation	50.69±8.33#	265.29±61.59#	43.64±5.98#
	d 7 after operation	52.87±9.68#	251.37±58.74#	34.69±5.10#
	F-test (ANOVA)	18.365	34.698	33.512
	p	<0.001	<0.001	<0.001

p#<0.05 *vs.* control group

Table 4. Comparisons of serum TNF-α and CRP levels before and after operation between the two groups of patients

	Time, days (d)	*TNF-a (pg/mL)*	*CRP (mg/L)*
Control group	d 1 before operation	141.23±20.39	130.25±15.32
	d 1 after operation	136.52±27.84	141.52±29.69
	d 7 after operation	139.35±28.63	147.92±30.54
	F-test (ANOVA)	21.036	22.571
	p	<0.001	<0.001
Observation group	d 1 before operation	137.85±21.36	128.32±15.53
	d 1 after operation	132.36±16.85@	136.84±16.20@
	d 7 after operation	129.32±18.52@	139.32±11.63@
	F-test (ANOVA)	15.367	18.852
	p	<0.001	<0.001

p@<0.05 *vs.* the control group

Comparison of composition of intestinal flora before and after operation between the two groups of patients

In the observation group, the levels of Bifidobacterium and Lactobacillus rose gradually, and those of Escherichia coli and Enterococcus declined gradually after operation. Moreover, the improvement in the above-mentioned indexes was more apparent in the control group (p<0.05). The difference in the composition of intestinal flora in the control group was not significant before and after operation (p>0.05;Table 7).

Table 5. Comparisons of levels of T cell subsets before and after operation between the two groups of patients (mean±SD)

	Time, days (d)	*$CD4^+$*	*$CD8^+$*	*$CD4^+/CD8^+$*
Control group	d 1 before operation	42.35±6.85	25.74±7.53	1.82±0.67
	d 1 after operation	33.26±8.74	23.14±6.85	1.61±0.81
	d 7 after operation	31.54±6.39	22.12±6.23	1.45±0.74
	F-test (ANOVA)	14.356	12.857	15.689
	P	<0.001	<0.001	<0.001
Observation group	d 1 before operation	42.65±7.36	25.66±7.65	1.90±0.78
	d 1 after operation	43.22±7.65[a]	25.01±7.52[a]	1.84±0.75[a]
	d 7 after operation	43.21±7.72[a]	24.89±7.45[a]	1.82±0.69[a]
	F-test (ANOVA)	3.586	1.325	2.563
	p	0.258	0.684	0.457

p^a<0.05 *vs.* control group

Table 6. Comparison of immunoglobulin levels before and after operation between the two groups of patients (mean±SD)

	Time, days (d)	*IgG (g/L)*	*IgA (g/L)*	*IgM (g/L)*
Control group	d 1 before operation	12.03±1.58	1.85±0.78	1.12±0.14
	d 1 after operation	9.32±1.67	1.52±0.21	0.72±0.13
	7 d after operation	8.56±1.42	1.16±0.18	0.61±0.09
	F-test (ANOVA)	16.856	18.352	13.652
	P	<0.001	<0.001	<0.001
Observation group	d 1 before operation	12.15±1.62	1.87±0.17	1.09±0.16
	d 1 after operation	11.02±1.59[b]	1.93±0.35[b]	1.12±0.14[b]
	d 7 after operation	12.28±1.58[b]	1.82±0.25[b]	1.17±0.35[b]
	F-test (ANOVA)	0.325	1.026	3.521
	p	0.785	0.236	0.137

p^b<0.05 *vs.* control group

Table 7. Comparison of structure of intestinal flora before and after operation between the two groups of patients (ln/g) (mean±SD)

Group	*Time, days (d)*	*Bifidobacterium*	*Lactobacillus*	*Escherichia coli*	*Enterococcus*
Control group	d 1 before operation	3.86±1.12	4.21±1.56	9.83±1.23	6.25±1.45
	d 1 after operation	3.96±1.05	4.52±1.63	9.54±1.31	6.53±1.24
	d 7 after operation	4.12±0.35	4.69±1.55	9.96±1.01	6.75±1.53
	F-test (ANOVA)	1.325	0.698	2.598	3.963
	p	0.159	0.365	0.086	0.072
Observation group	d 1 before operation	3.23±0.74	4.53±0.52	10.98±2.32	6.89±1.26
	d 1 after operation	4.25±1.02[c]	5.69±1.23[c]	8.19±1.86[c]	5.66±1.02[c]
	d 7 after operation	6.59±1.25[c]	7.42±1.86[c]	7.53±1.35[c]	5.01±0.82[c]
	F-test (ANOVA)	22.361	25.654	19.852	13.251
	p	<0.001	<0.001	<0.001	<0.001

p^c<0.05 *vs.* control group

Discussion

Studies have indicated that although surgical treatments have certain efficacy on gastric cancer. Those treatments will change the structure of the digestive tract to some extent. In addition, the application of anesthetic drugs during operation can also impair the body's immune function in various degrees [12]. The surgical trauma-associated stress responses will induce certain inflammatory responses, releasing CRP, IL-2, IL-6, TNF-α and other inflammatory factors. Therefore, providing the patients, especially those with malnutrition or whose nutrition is difficult to be satisfied by general diet, with immune support has some clinical significance. If the patients are not treated in time, the body recovery ability will be reduced, infections will be triggered, the disease will even aggravate, and the length of hospital stay will be prolonged [13]. According to the related guidelines formulated by the American Society for Parenteral and Enteral Nutrition in 2011 [14], giving critically ill patients relevant enteral nutrition can effectively ameliorate the systemic inflammatory responses and increase their autoimmunity. It is also pointed out that preoperative nutritional therapy has favorable effects on the patients.

The enteral nutrition preparations are capable of stimulating the blood circulation in the abdominal organs to some extent, improving blood flow in the gastrointestinal mucosa and accelerating the recovery of gastrointestinal function [15]. Miyata et al. [16] studied and found that enteral nutrition combined with neoadjuvant chemotherapy exerts prominent effects on decreasing the proliferation of tumor cells, killing more tumor cells and improving the efficiency of chemotherapy. The inflammatory responses caused by surgical treatments can stimulate the tumor stromal cells to produce inflammatory factors such as IL-10 and IL-6, of which IL-6 mainly induces angiogenesis and tissue remodeling in the body, and IL-10 can inhibit anti-tumor immune responses to some extent and promote the deterioration of tumor [17]. In addition, IL-10 is able to make CD8 and CD4 transform into regulatory T cells in the case of tumor, playing a vital role in the process of tumor immune escape. However, the TNF-α produced by activated macrophages and mast cells possesses certain anti-tumor effects. Moreover, CD4/CD8, CD8 and CD4 are sensitivity indexes that reflect the immune level in the body, and the higher the levels of CD4/CD8 and CD4 are, the stronger the immunity will be [18]. In this paper, the changes in the inflammatory factors and indexes of immune function in the patients receiving neoadjuvant chemotherapy combined with enteral nutrition may be caused by a rich variety of components in the enteral nutrition solution, including nucleotides, fatty acids and amino acids. Among them, glutamine can preferably promote the synthesis and secretion of cytokines and repair the epithelium of the digestive tract, thus increasing the immune function of macrophages [19]. Moreover, ω-3 fatty acid can accelerate the degradation of triglycerides in the body to some degree and improve the cardiac function. At the same time, it can repress the generation of TNF-α, CD8 and interferon in the body, reduce the synthesis and secretion of inflammatory mediators and regulate the body immunity [20]. Besides, arginine in the nutrition solution is also able to regulate macrophages and T lymphocytes to a certain extent, influence the inflammatory responses in gastric cancer patients, lower the content of serum TNF-α, increase the synthesis and secretion of IgG, IgA, IgM, etc., and enhance the body immunity. For patients with malnutrition, the supplement of arginine is conducive to maintaining positive nitrogen balance in the body and promoting cell proliferation and early healing of operative wound [21]. With regard to the variations in intestinal flora in this paper, the possible reason is that the enteral nutrition solution can be easily absorbed and utilized by the small intestine, thus stimulating the intestine to secret the digestive juice, certainly enhancing intestinal peristalsis, maintaining and promoting recovery of intestinal mucosa function, inhibiting the intestinal endotoxin to enter the blood, preventing the translocation of intestinal flora to some degree, reducing the degree of inflammatory responses in the body, decreasing the stimulation on related blood vessels and sustaining relatively stable intestinal flora.

Conclusions

In conclusion, neoadjuvant chemotherapy combined with enteral nutrition for gastric cancer patients can markedly reduce the degree of perioperative inflammatory responses, improve the body immunity and maintain the structure of intestinal flora, so it has certain clinical application value.

Conflict of interests

The authors declare no conflict of interests.

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