



Effect of fast-track surgery on inflammatory response and immune function in patients with laparoscopic distal gastrectomy

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Received: 5 May 2018 / Accepted: 5 February 2019 / Published online: 25 February 2019
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Summary

Introduction Enhanced recovery after surgery can reduce immunosuppression and inflammation in patients with laparoscopic distal gastrectomy

Objective The aim of this study was to investigate the effect of fast-track surgery on inflammatory response and immune function in patients with laparoscopic radical gastrectomy.

Methods A total of 244 patients undergoing laparoscopic radical gastrectomy for gastric cancer from January 2014 to December 2017 were collected. The patients were divided into fast-track surgery (FTS) and traditional groups. The inflammatory index, immune index, and postoperative complications were measured before and after the operation.

Materials and methods There was no significant difference in immune index between the two groups on the day before operation and one day after operation, all $P > 0.05$. On POD3 and POD6, the expression of CD3+, CD4+, CD4+/CD8+, IgG, IgM, and IgA in the FTS group was higher than that in the traditional group and the difference was statistically significant ($P < 0.05$). There was no significant difference in inflammation index between the two groups on the day before operation; on POD1, POD3, and POD6, the expression of IL-6, TNF- α , and CRP in the FTS group was lower than in the traditional group and the difference was statistically significant ($P < 0.05$). The total postoperative complications in the FTS group were significantly lower than those in the traditional group and the difference was statistically significant ($P < 0.05$).

Results Fast-track surgery can effectively reduce the degree of postoperative inflammatory reaction and the incidence of postoperative complications compared with the traditional group and has a smaller impact on the body's immune function, which is worthy of promotion in clinical practice.

Keywords Gastric cancer · Surgery · Inflammatory reactions · Immune function · Laparoscope

Introduction

Fast-track surgery (FTS) is also known as enhanced recovery after surgery (ERAS); FTS has been applied to gastric cancer surgery for nearly 10 years and mainly adopts various active and effective measures during the perioperative period to reduce the patient's stress response to surgery and reduce the occurrence of postoperative complications [1]. During this period, many studies have compared FTS with traditional perioperative care. The results show that FTS can accelerate the recovery of body functions after gastric cancer surgery; reduce complications, diastolic angina, and pulmonary infections; and also better protect the function of various organs of the human body [2]. In addition, the application of FTS during gastric cancer surgery can effectively shorten the postoperative hospital stay, reduce the cost of surgery/hospitalization, and improve the utilization of hospital resources [3]. Khorgami Z et al. [4] found that immunosuppression and postoperative inflammation may increase postoperative infection and tumor cell metastasis. Studies by Esteban M B et al. [5] have shown that inflammation and immune status in patients with gastric cancer are closely related to the occurrence of postoperative complications. A recent study reported that the use of FTS can protect the immune function of patients after surgery and reduce

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Table 1 Normal information

	FTS group (n= 126)	Traditional group (n= 118)	t	P-value
<i>Gender</i>	–	–	2.292	0.130
Men	72	56	–	–
Women	54	62	–	–
<i>Age (years, mean ± SD)</i>	58.44 ± 12.49	62.33 ± 10.83	–0.706	0.490
<i>TNM stage</i>	–	–	0.636	0.731
I	41	43	–	–
II	56	52	–	–
III	29	23	–	–
<i>Degree of differentiation</i>	–	–	2.124	0.346
Good	53	47	–	–
Moderate	50	56	–	–
Poor	23	15	–	–
<i>Histological type</i>	–	–	0.394	0.942
Adenocarcinoma	73	68	–	–
Mucinous adenocarcinoma	42	40	–	–
Signet ring cell carcinoma	8	6	–	–
Other	3	4	–	–
<i>Operation time (min)</i>	143.26 ± 23.28	152.30 ± 26.45	–0.770	0.452
<i>Bleeding volume</i>	–	–	1.168	0.280
≥300 ml	48	53	–	–
<300 ml	78	65	–	–
<i>BMI (kg/m²)</i>	20.48 ± 1.75	21.57 ± 2.11	–1.192	0.251

FTS group Fast-track surgery group

inflammation [6]. Therefore, for patients with gastric cancer undergoing surgery, it is very important to maintain the balance of the immune system and control inflammation. These factors directly affect the long-term prognosis of cancer patients [7]. We conducted a retrospective clinical study to investigate the differences in inflammatory response and humoral immunity after surgery for gastric cancer between FTS and traditional perioperative care.

Objective

The aim of this study was to analyze the effect of accelerated rehabilitation surgery on immune function and inflammatory response after laparoscopic distal gastrectomy.

Materials and methods

A retrospective non-randomized method was used to collect 244 patients undergoing laparoscopic radical gastrectomy for gastric cancer from January 2014 to December 2017 in our hospital. 244 patients were divided into FTS and traditional groups. There was no significant difference in normal information between the two groups (all $P > 0.05$; Table 1).

Inclusion and exclusion criteria

inclusion criteria: (1) imaging examination: abdominal enhanced CT diagnosis of gastric cancer; (2) endoscopy: gastroscopy diagnosis of gastric cancer; (3) pathological examination: gastric endoscopic partial biopsy for gastric cancer. Exclusion criteria: (1) there are multiple epigastric surgeries and it is estimated that there are extensive and dense adhesions in the abdominal cavity; (2) there is distant metastasis or celiac metastasis; (3) open surgery; (4) total gas-

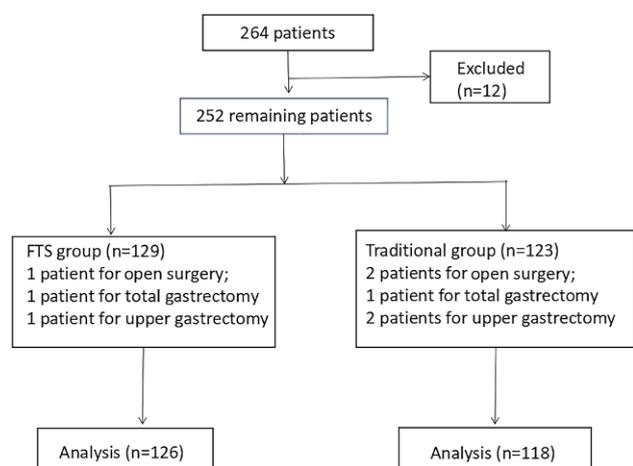
**Fig. 1** Inclusion and exclusion criteria

Table 2 Two groups of patient treatment methods

Treatment measures	FTS group (n= 126)	Traditional group (n= 118)
<i>Preoperative</i>		
Mission	Inform patients and their families of the type of surgery and preoperative and postoperative cooperation, good communication with patients reduces preoperative anxiety	None
Intestinal preparation	No mechanical bowel preparation	Mechanical bowel preparation (10% magnesium sulfate [10 mL], 2 times, before surgery)
Diet preparation	Drink 10% glucose solution 1000 ml at 10 pm the day before surgery; preoperative 2–3 h; drink 10% glucose solution 1000 ml	Fasting for 12 h, no drinking water for 4 h
<i>Intraoperative</i>		
Stomach tube	The stomach tube is not routinely placed and the stomach tube is usually removed during surgery	Remove after normal diet
Insulation	Insulating blanket is used during operation and the temperature is maintained at 37 ± 0.5 °C	None
Abdominal drainage tube	Drainage tube is not placed regularly. If it needs to be placed, it is usually retracted on the first postoperative day and pulled out in 2 to 3 days	Routine placement, pull out after a week
Anesthesia management	General anesthesia combined with epidural anesthesia (T6–T12)	General anesthesia
<i>Postoperative</i>		
Postoperative pain management	Use of epidural catheter (0.125% bupivacaine and fentanyl [2.5 µg/mL])	Intravenous injection of diclofenac or morphine
Urinary management	Usually removed within 24 h after surgery	Usually removed 3 days after surgery
Eating	8 h after surgery, 5% GS, 50 ml/time, twice a day, no discomfort, then start enteral nutrition in the next day	Don't until bowel venting
Mobilization	Encourage patients to ambulate early	At patient's will

trectomy or upper gastrectomy; (5) cardiopulmonary dysfunction, unable to tolerate general anesthesia and pneumoperitoneum. Fig. 1.

Treatment

The perioperative treatment methods of the two groups of patients are shown in Table 2.

Observation indicators

Fasting peripheral venous blood was taken on Pre1 and on POD1, POD3, and POD6 to compare the levels of CD3+, CD4+, CD4+/CD8+, IgG, IgM, IgA, IL-6, TNF- α , and CRP in peripheral blood on Pre1 and POD1, POD3, and POD6. Flow cytometry was used to measure T lymphocyte subsets (CD3 +, CD4 +, CD4 + / CD8 +), enzyme-linked immunosorbent assay (ELISA) was used to determine the concentration of IgG, IgM, IgA, IL-6 and TNF-a, and immunoturbidimetry was

Table 3 Changes of lymphocyte subsets before and after surgery in two groups

Lymphocyte subsets	FTS group (n= 126)	Traditional group (n= 118)	t	P-value
<i>CD3 (%)</i>				
Pre1	63.03 \pm 9.43	68.50 \pm 6.68	-1.420	0.175
POD1	56.33 \pm 5.63	55.56 \pm 8.52	0.228	0.822
POD3	58.33 \pm 5.17	51.78 \pm 5.40	2.629	0.018
POD4	62.56 \pm 6.64	55.58 \pm 7.16	2.144	0.048
<i>CD4 (%)</i>				
Pre1	30.42 \pm 4.89	29.49 \pm 5.53	0.379	0.710
POD1	27.46 \pm 2.60	26.20 \pm 2.06	1.136	0.273
POD3	26.79 \pm 3.03	23.34 \pm 2.63	2.576	0.020
POD4	29.01 \pm 3.83	25.16 \pm 2.97	2.386	0.030
<i>CD4/CD8</i>				
Pre1	1.57 \pm 0.22	1.46 \pm 0.30	0.885	0.389
POD1	1.34 \pm 0.21	1.27 \pm 0.18	0.774	0.450
POD3	1.27 \pm 0.12	1.04 \pm 0.17	3.223	0.005
POD4	1.49 \pm 0.24	1.20 \pm 0.22	2.660	0.017

Table 4 Changes of preoperative and postoperative immunoglobulin in two groups of patients

Immunoglobulin	FTS group (n= 126)	Traditional group (n= 118)	t	P-value
<i>IgA (g/L)</i>				
Pre1	2.18 ± 0.25	2.07 ± 0.19	1.057	0.306
POD1	1.83 ± 0.33	1.72 ± 0.24	-0.841	0.413
POD3	1.73 ± 0.18	1.53 ± 0.20	2.228	0.041
POD4	1.87 ± 0.16	1.62 ± 0.23	2.602	0.019
<i>IgM (g/L)</i>				
Pre1	1.47 ± 0.37	1.36 ± 0.25	0.691	0.499
POD1	0.99 ± 0.28	0.87 ± 0.20	1.076	0.298
POD3	0.94 ± 0.16	0.70 ± 0.27	2.345	0.032
POD4	1.30 ± 0.19	1.02 ± 0.21	2.911	0.010
<i>IgG (g/L)</i>				
Pre1	14.19 ± 1.22	13.67 ± 1.32	0.870	0.397
POD1	11.33 ± 2.12	10.67 ± 1.94	0.696	0.496
POD3	10.20 ± 1.44	8.22 ± 1.48	2.877	0.011
POD4	12.58 ± 1.29	10.13 ± 1.50	3.715	0.002

used to determine the concentration of CRP. Postoperative complications of the two groups were recorded.

Statistical methods

SPSS 22.0 (IBM, USA) statistical software was used for data analysis. Measured data were expressed as mean ± standard deviation ($\bar{x} \pm s$), and count data were compared using χ^2 test. The comparison of the two independent samples used t-tests with two independent samples and was statistically significant at $P < 0.05$.

Results

Changes of lymphocyte subsets before and after surgery in two groups

There was no significant difference in CD3+, CD4+, and CD4+/CD8+ levels in the peripheral blood be-

tween the two groups on Pre1 and POD1 (both $P > 0.05$). On POD1, POD3, and POD6, the CD3+, CD4+, and CD4+/CD8+ values decreased in the two groups compared with Pre1. The expression of CD3+, CD4+, and CD4+/CD8+ on POD3 and POD6 were higher in the FTS group than in the traditional group, and the difference was statistically significant ($P < 0.05$). Table 3.

Changes of preoperative and postoperative immunoglobulin in two groups of patients

There was no significant difference in IgG, IgM, and IgA levels between the two groups of patients on Pre1 and POD1, both $P > 0.05$. On POD1, POD3, and POD6, the expression of immunoglobulin IgG, IgM, and IgA in the peripheral blood of both groups decreased compared with the day before surgery. In the FTS group, the expression of IgG, IgM, and IgA in the peripheral

Table 5 Comparison of inflammatory factors in two groups of patients

Inflammatory factors	FTS group (n= 126)	Traditional group (n= 118)	t	P-value
<i>CRP (mg/L)</i>				
Pre1	3.50 ± 0.71	3.44 ± 0.53	0.189	0.852
POD1	59.41 ± 10.72	72.91 ± 8.78	-2.923	0.010
POD3	29.86 ± 8.67	39.31 ± 8.65	-2.316	0.034
POD6	9.73 ± 4.05	16.37 ± 5.41	-2.944	0.010
<i>IL-6 (ng/L)</i>				
Pre1	9.33 ± 1.58	8.11 ± 1.45	1.798	0.107
POD1	59.19 ± 9.21	79.87 ± 12.01	-4.100	0.001
POD3	19.14 ± 8.59	27.69 ± 6.69	-2.354	0.032
POD6	10.21 ± 4.64	15.56 ± 4.72	-2.423	0.028
<i>TNF-α (ng/L)</i>				
Pre1	111.74 ± 11.90	119.22 ± 9.89	1.449	0.167
POD1	150.98 ± 10.28	165.24 ± 16.08	-2.242	0.039
POD3	125.06 ± 15.63	147.56 ± 17.99	-2.832	0.012
POD6	107.96 ± 15.98	123.44 ± 13.45	-2.224	0.041

Table 6 Comparison of postoperative complications between the two groups

Postoperative complications	FTS group (n= 126)	Traditional group (n= 118)	χ^2	P-value
Complications	–	–	9.490	0.002
Yes	8	23	–	–
No	118	95	–	–
Anastomotic bleeding	1	3	0.326	0.568
Anastomotic leakage	1	2	0.003	0.954
Wound infection	2	6	1.377	0.241
Pulmonary infection	1	4	0.245	0.621
Stomach cramps	1	3	0.326	0.568
Urinary retention	2	5	0.714	0.398

blood was higher on POD3 and POD6 than in the traditional group. The difference was statistically significant ($P < 0.05$). Table 4.

Comparison of inflammatory factors in two groups of patients

There was no significant difference in CRP, IL-6, and TNF- α levels in peripheral blood between the two groups on Pre1, all $P > 0.05$. The expression of CRP, IL-6, and TNF- α in the peripheral blood of the two groups was increased on POD1, POD3, and POD6 compared with Pre1. Expression of CRP, IL-6, and TNF- α in the peripheral blood on POD1, POD3, and POD6 was lower in the FTS group than in the traditional group, and the difference was statistically significant ($P < 0.05$). Table 5.

Comparison of postoperative complications between the two groups

The number of postoperative complications in the FTS group was significantly lower than that in the traditional group, with a statistically significant difference ($P < 0.05$). There was no significant difference in single complications such as anastomotic bleeding, anastomotic leakage, wound infection, pulmonary infection, stomach cramps, and urinary retention, all $P > 0.05$. Table 6.

Discussion

In 2001, Wilmore and Kehlet first proposed standardized management of patients undergoing major surgery to reduce postoperative stress and organ dysfunction, shorten full recovery time, and reduce postoperative complications. At present, ERAS is widely used in colorectal cancer, urology, and gynecology, and has shown good results and improved patient outcomes [8]. In 2014, a consensus guideline for implementation of the ERAS plan after radical gastrectomy was published. Although the items included have different levels of recommendation and evidence, its purpose is to provide a theoretical and

evidence-based basis for the application of ERAS in the perioperative period of gastric cancer [9].

Fang F et al. [10] confirmed that ERAS also has a great advantage in gastric cancer, especially in accelerating short-term recovery, reducing postoperative complications, shortening hospital stay, and improving quality of life. Makuuchi R et al. [11] found that the average postoperative complication rate after elective gastric cancer surgery was between 25 and 35%. The length of hospital stay after laparoscopic surgery was as long as 14 days, and after conventional open surgery was as long as 20 days. However, hospitalization time and complications were significantly reduced after perioperative use of an FTS intervention. A randomized controlled study in Italy found that postoperative complication rates in gastric cancer were as high as 45%. The study believes that postoperative high complications are related to the patient's own characteristics, as patients with total gastrectomy, age over 65 years, gender, and comorbidity are risk factors for postoperative complications of gastric cancer. These factors cannot be corrected, and moderate and severe malnutrition are common factors for postoperative complications and predictors of poor prognosis in gastric cancer patients. At the same time, malnutrition is one of the few factors that surgeons can correct and is an important aspect of the ERAS plan; therefore, the study considers that the core of the implementation of ERAS is how to improve the patient's malnutrition early in the context of reducing surgical stress [12]. Mingjie X et al. [13] found that the important step of ERAS implementation is minimally invasive surgery, because minimally invasive surgery can reduce postoperative stress and inflammatory response and improve respiratory function. In South Korea, the average age of 20% of patients with gastric cancer is more than 70 years old. Because of potential complications and low physiological reserves, elderly patients often show a greater complication risk and longer postoperative recovery period after surgery. Perioperative ERAS management of elderly patients revealed that the incidence of postoperative complications in elderly patients was significantly reduced and hospitalization time was shortened [14]. Other recent prospective clinical studies have demonstrated that

the multimodal approach to perioperative care includes shorter preoperative and postoperative hunger times, more aggressive pain management, and avoidance of peritoneal drainage and preoperative mechanical bowel preparation. These can restore surgical patients faster, reduce the incidence of postoperative complications, shorten the postoperative course of treatment, and reduce hospital stay time [15]. Related studies have found that a multimodal approach to perioperative pathophysiology can improve physical performance and significantly reduce subjective psychological sensations (pain and fatigue) [16]. The surgical process and related inflammatory factors can inhibit the body's immune function, while surgical stress activates the sympathetic nervous system and the hypothalamus–pituitary–adrenal (HPA) axis and induces neuroendocrine responses, promoting the release of hormones such as catecholamines (norepinephrine and epinephrine), adrenocorticotrophic hormone, and cortisol, which can inhibit pro-inflammatory T cell responses [17].

Immunoglobulins and complement are two important elements of globulin. Immunoglobulins present in blood and extracellular fluids play a major role in the immune response against infectious pathogens. The complement system is a key component of the innate immune system and plays an important role in the adaptive immunity of T cells and B cells, helping to eliminate pathogens [18]. T cells also play an important role in anti-tumor immunity, although antigen-specific cytotoxic CD8+ T cells are essential for controlling tumor growth. However, over the past decade, we have found that the importance of CD4+ T cells in the coordinated immune response has increased significantly. CD4+ T cells are present in different subpopulations, such as T helper (Th)1, Th2, and Th17 cells, and regulatory T cells (Treg), which play an opposing role in regulating the immune response to tumor cells [19]. Bu J et al. [20] found that surgery can promote inflammation in both the conventional group and FTS group; however, cellular immunity differs in outcomes in both patient groups, however, the results of cellular immunity are different in the two patient groups, like circulating T cells, Th cells, and NK cells are higher in the FTS group than those in the conventional group. B cells play a role in humoral immunity in humans. Chen S et al. [21] found that IgG, IgA, and IgM levels were significantly higher in the ERAS group than in the non-ERAS group. We found that the levels of IgG, IgA, IgM, CD3, CD4, and CD4/CD8 in patients with postoperative gastric cancer in the FTS group were significantly higher than those in the control group on the third and sixth postoperative days. The difference was statistically significant, the result is consistent with Bu J and Chen S. The results showed that ERAS had little effect on the immune function of patients with gastric cancer. The immune function of non-ERAS patients decreased significantly after surgery.

CRP is a non-specific acute-phase protein produced after trauma and inflammation. Elevated serum CRP levels are associated with trauma and stress. Therefore, postoperative CRP levels may reflect the degree of trauma after perioperative management and surgical procedures [22]. IL-6 is produced and activated by monocytes, macrophages, and endothelial cells under surgical trauma and stress conditions and is positively correlated with wound severity [23]. TNF- α is not only produced by tumor cells, but one study found that most monocytes can also produce TNF- α , which mainly mediates inflammation, and its effect is similar to IL-6 [24]. Our study found that the levels of serum CRP, IL-6, and TNF- α in patients with FTS were much lower than those in traditional perioperative care patients, indicating that ERAS can reduce the patients' surgical trauma and stress response.

In terms of overall complications, the overall complications of FTS are significantly lower than in routine care. The reason is that FTS promotes minimally invasive techniques, reduces intraoperative trauma and postoperative stress, promotes early oral intake, and improves nutritional status. Encourage early out-of-bed activity and restore physical function. These measures can promote early recovery of patients and reduce postoperative complications. Tanaka R et al. [25] reported that the postoperative complications in the FTS group were significantly lower than those in the control group, the results of this study were consistent with our results.

In conclusion, FTS can effectively inhibit the postoperative release of inflammatory mediators and provide good postoperative immune protection, reducing perioperative trauma and postoperative complications. However, due to the small number of cases collected in this study, its clinical efficacy remains to be verified by large scale, randomized, double-blind trials.

Conclusion

In our opinion, ERAS can reduce the inhibition of immune function and inflammation response in patients with gastric cancer.

Acknowledgements This work was supported by Science and Technology Planning Project of Zhejiang Province (No.2017F30045), Traditional Chinese Medicine Science and Technology Planning Project (No.2018ZZ004).

Compliance with ethical guidelines

Conflict of interest Q. Hu, T. He, Y. Sun, F. Wang, and J. Wu declare that they have no competing interests.

Ethical standards All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1975 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent was obtained from all individual participants included in the study.

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