Int J Clin Exp Med 2020;13(8):6065-6073
www.ijcem.com /ISSN:1940-5901/IJCEM0111737

Original Article

Effect of enteral nutrition support on the curative effect and immune system in patients with rectal cancer during fast track surgery

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Received April 1, 2020; Accepted May 11, 2020; Epub August 15, 2020; Published August 30, 2020

Abstract: Objective: To investigate the effect of enteral nutrition support on the curative rate and immune system in patients with rectal cancer during fast track surgery. Methods: Seventy-six patients with rectal cancer who received fast track surgery (FTS) intervention were divided into the enteral group (n=38) and parenteral group (n=38) by a randomized method. Patients in the enteral group received enteral nutrition support and patients in the parenteral group received parenteral nutrition support. The differences in clinical indicators, nutrition status and immunity of patients one week before surgery as well as 1st day and 7th day after surgery between the two groups were analyzed. Results: The levels of general clinical indicators in the enteral group were lower than those in the parenteral group (all P<0.01). There were no significant differences in levels of nutritional indicators, lymphocytes, neutrophils, $CD4^+/CD8^+$, immunoglobulin, C-reactive protein (CRP) and tumor necrosis factor α (TNF-α) before surgery between the two groups (all P>0.05). Compared with the parenteral group, there were higher levels of nutrition indicators, lymphocytes and $CD4^+/CD8^+$, but lower levels of neutrophils in the enteral group at different times after surgery (all P<0.05). There were no significant differences in levels of immunoglobulin and CRP on the 1st day after surgery between the two groups (P>0.05). Compared with the parenteral group, there were higher levels of immunoglobulins, but lower levels of CRP in the enteral group on the 7th day after surgery (all P<0.01). The levels of TNF-α in the enteral group were lower than those in the parenteral group on the 1st day and 7th day after surgery (all P<0.01). The incidence of adverse reactions in the enteral group (42.11%, 16 cases) was lower than that in the parenteral group (60.53%, 23 cases; P<0.05). Conclusion: Enteral nutrition is safer than parenteral nutrition in rectal cancer patients during FTS, as it can accelerate peristalsis, reduce inflammation and improve the immune function of these patients.

Keywords: Rectal cancer, fast track surgery, nutritional support, immune system, nutritional indicators, inflammation

Introduction

Rectal cancer is a type of malignant tumor of the digestive system with high incidence. The main lesion site of rectal cancer is at the junction of rectum and sigmoid colon. The damaged rectal tissues can develop into rectal cancer and in the early stage, there are no symptoms [1]. The incidence of rectal cancer in China has accounted for about 70% of colorectal diseases. The development of rectal cancer is related to diet and the external environment, and a high-fat diet will speed up the process [2].

At present, fast track surgery (FTS) is believed to play a role in improving the complications of patients and accelerating the recovery during the perioperative period with the development of diagnosis and understanding of rectal cancer. FTS is a series of optimized protocols adopted in the perioperative phase according to evidence-based medicine to reduce or avoid stress and complications after surgery and to accelerate postoperative recovery of patients. FTS is widely applied in clinical surgical treatment and has become a main way to provide high-quality health care for patients [3].

Nutritional oncology is an emerging area of research in recent years, which can evaluate the nutritional status and risks of tumor patients and increase the practicability of anti-tumor therapy by improving the nutritional status of tumor patients [4]. Studies have shown that improving the nutritional status of patients with rectal cancer can improve the prognosis and contribute to implementation of anti-tumor therapy [5]. Enteral nutrition, which means nutrients are given directly through the digestive tract of patients, may be an effective method in nutritional oncology. However, there is little research about the comparison of the clinical effect of enteral nutrition and parenteral nutrition in patients with rectal cancer during FTS. Our study aims to investigate the effect of enteral nutrition and parenteral nutrition on the recovery of patients with rectal cancer during FTS.

Materials and methods

General materials

Seventy-six patients with rectal cancer were admitted to Ninghai First Hospital from June 2018 to July 2019. They all received FTS and were divided into an enteral group (n=38) and parenteral group (n=38) by random draw. This study was approved by the Ethics Committee of Ninghai First Hospital and all patients signed an informed consent.

Criteria for inclusion and exclusion

Inclusion criteria were: Patients with rectal cancer diagnosed by pathological or cytological detection according to diagnostic criteria for rectal cancer issued by the WHO [6]; patients without radiotherapy or chemotherapy; patients with a score of 'B' in patient-generated subjective global assessment (PG-SGA); patients without history of other abdominal surgery.

Exclusion criteria were: 1) Patients with severe organ dysfunction and cognitive impairment; 2) Patients with enteral nutritional intolerance.

Methods of FTS

Patients in both groups all received FTS. Before surgery, patients were told the about knowledge relating to rectal cancer. And psychological guidance was given to patients to improve their nervous and anxious moods. The patients fasted for 8 hours before surgery and an oral liquid diet was administered 3 hours before surgery. No patient received mechanical bowel preparation. Patients were kept warm during the perioperative period. No drainage tube was placed after surgery. Antibiotics, antemetics and patient-controlled analgesia were administrated. Patients were encouraged to get out of bed to carry out normal activities.

Protocols of nutrition support

Enteral group: Supportan Liqd (Fresenius Kabi China Huarui Pharmaceutical Co., Ltd., 200 mL) was taken orally from 7 d before surgery to 8 h before surgery at a doge of 104.6-125.52 kJ (25-30 kcal) * kg^{-1} * d^{-1}. Normal saline (100 mL) was given 24 hours after surgery. Nutrison Fibre (Nutricia Pharmaceutical (Wuxi, China) Co., Ltd., 0.75 kcal/mL * 500 mL) was given from the second day by intravenous drip at 20-60 mL/h. The dose was 250 mL on the first day, 500 mL on the second day, 750 mL on the third day, 1,000 mL on the fourth day, 1,500 mL on the fifth day. Then, 250 mL of Glucose Solution (Double Crane Pharmaceutical (Anhui, China) Co., Ltd., 10 g * 250 mL) was added if the energy of patients was not enough. After first gas exhaust, the patients were given a liquid diet, semi-liquid diet and general food in that order and nutritional supply was reduced.

Parenteral group: The patients received a normal diet before surgery and were fasted after surgery, and 250-500 mL of compound Amino Acid Injection (China Cisen Pharmaceutical Co., Ltd., 250 mL) and 400 mL of Glucose Solution (Double Crane Pharmaceutical Co., Ltd., Anhui, China, 10 g * 250 mL) were postoperatively given with total Calories of 30 kcal/(kg·d). After first gas exhaust, the patients were given a liquid diet, semi-liquid diet and general food in that order and nutritional supply was reduced.

The total energy of patients in the two groups was controlled at 1,025 kJ. The extubation and food intake were performed on the 6th day and nutritional supply was withdrawn on the 8th day.

Outcome measures

General clinical indicators: The time of first gas exhaust, defecation and bowel sounds of

Table 1. General materials

Group	n	Gender (case)		Average age (year)	Average weight (kg)	ASA grading (case)		
		Male	Female			I	II	III
Enteral group	38	25	13	59.4±6.9	70.25±2.12	4	31	3
Parenteral group	38	27	11	60.1±5.8	69.73±2.38	6	30	2
χ^2/t		0.244		0.501	0.987	0.616		
P		0.621		0.618	0.327	0.734		

patients in the two groups after surgery were observed and recorded.

Nutritional indicators: About 10 mL of venous blood of all patients was collected on the 7th day before surgery as well as 1st and 7th day after surgery respectively. The levels of total serum protein (TP, biuret method, Item Number: YZB/Su 0352-2006, Boeing biotechnology (Nanjing) Co., Ltd.), serum albumin (ALB, bromocresol green method, Item Number: TY01-252B, Shanghai Lichen Trading Co., Ltd.) and prealbumin (PA, immunoturbidimetry, Item Number: YZB/USA 0235-2009, Shanghai Rongsheng Biotechnology Co., Ltd.) were detected according to kit instruction. The absorbance of samples was detected by Japanese 7170 biological detector.

Immune indicators: About 4 mL of venous blood from all patients was collected on the 7th day before surgery as well as 1st and 7th day after surgery to detect the levels of neutrophils, lymphocytes and $CD4^+/CD8^+$. Briefly, the blood sample was collected in two tubes with dipotassium ethylene diamine tetraacetic acid (EDKA-K2, Shanghai Lianshuo Biotechnology Co., Ltd.). Each sample containing about 3000 cells was detected by flow cytometry (Jiangsu Beckman Coulter, Type: CytoFLEX).

Immunoglobulin: About 2 mL of venous blood from all patients was collected on the 7th day before surgery as well as 1st and 7th day after surgery. The levels of immunoglobulin A, immunoglobulin G and immunoglobulin M were detected by kits from Weifang Kanghua Biotechnology Co., LTD (WT6057, turbidimetry). The detections were performed strictly according to the kit instructions.

Inflammatory factors: About 10 mL of venous blood from all patients was collected on the 7th day before surgery as well as 1st and 7th day after surgery. The levels of C-reactive protein (CRP, latex-enhanced immunoturbidimetry) and tumor necrosis factor α (TNF-α, double-antibody sandwich ELISA) were detected by kits from Shanghai Kanglang Biotechnology Co., Ltd. (KLC001.4896T) and Qiyi biotechnology (Shanghai) Co., Ltd. (QY-H10038), respectively. The detections were performed strictly according to the kit instructions.

Adverse reactions: The adverse reactions of patients in the two groups such as abdominal distension, gastrointestinal reaction and infection were observed and recorded during the therapy.

Statistical analysis

SPSS 22.0 was used to analyze the research data of the two groups. The measurement data were expressed by $\bar{x} \pm s$. Repeated measures analysis of variance was adopted to compare the data at different time points and t test was adopted to compare the data between the two groups. The enumeration data were expressed by n (%) and comparison between the two groups were performed by χ^2 test. $P<0.05$ was considered statistically significant.

Results

Comparison of general materials

There was no significant difference in sex, age and other general data between the two groups ($P>0.05$, **Table 1**).

Comparison of general clinical indicators

The postoperative bowel sound recovery time, first gas exhaust time, first defecation time and postoperative hospital stay in the enteral group were all less than those in the parenteral group ($t_{bowel}=5.276$, $P<0.01$; $t_{exhaust}=14.860$, $P<0.001$; $t_{defecation}=8.527$, $P<0.001$; $t_{hospital}=7.406$, $P<0.001$). See **Figure 1**; **Table 2**.

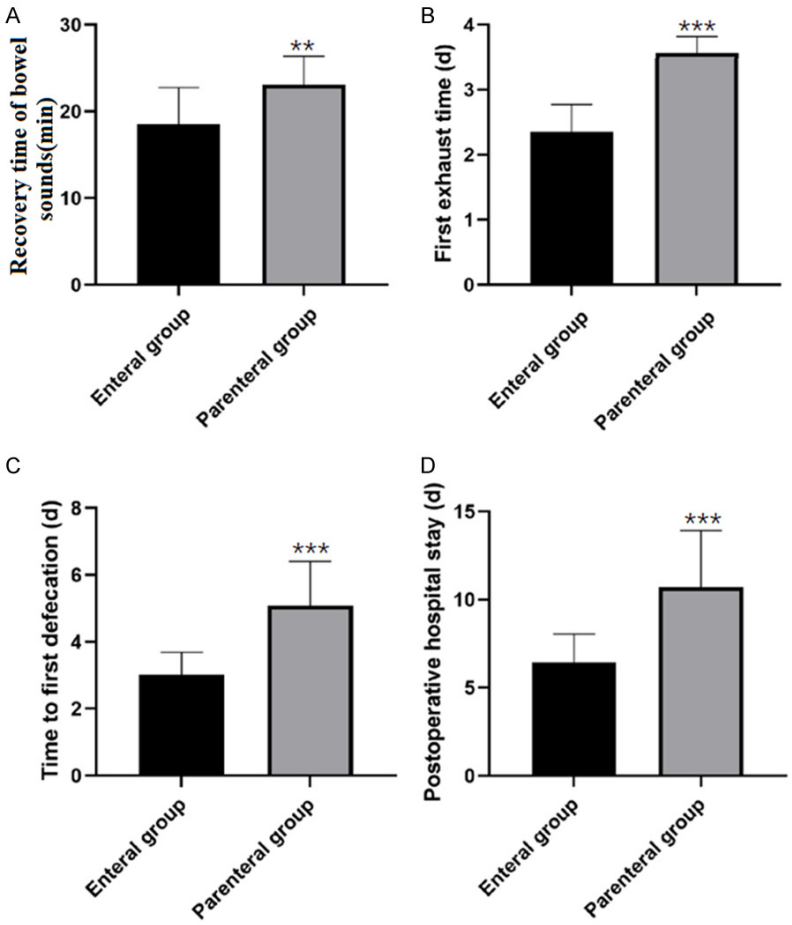

Figure 1. Comparison of clinical general indicators. A: Recovery time of bowel sounds; B: First exhaust time; C: Time of first defecation; D: Postoperative hospital stay. **P<0.01, compared with enteral group; ***P<0.001, compared with enteral group.

Comparison of nutritional indicators

There was no significant difference in nutritional indicators on the 7th day before surgery between the two groups (all P>0.05). The nutritional indicators were all higher at different times after surgery in the enteral group than those in the parenteral group (all P<0.05, **Table 3**).

Comparison of immune indicators

There was no significant difference in levels of lymphocytes, neutrophils and $CD4^+/CD8^+$ on the 7th day before surgery between the two groups (all P>0.05). Compared with the parenteral group, there were higher levels of lymphocytes and $CD4^+/CD8^+$, but lower levels of neutrophils on the 1st and 7th day after surgery in the enteral group (all P<0.05). See **Table 4**.

Comparison of immunoglobulins

There was no significant difference in levels of immunoglobulins on the 7th day before surgery and 1st day after surgery between the two groups (all P>0.05). The levels of immunoglobulins on the 7th day after surgery in the enteral group were all higher than those in the parenteral group (all P<0.01). See **Table 5**.

Comparison of inflammatory factors

There was no significant difference in levels of CRP and TNF-α on the 7th day before surgery between the two groups (P>0.05). Compared with the parenteral group, there was no significant difference of levels of CRP (P>0.05), but lower levels of TNF-α on the 1st day after surgery in the enteral group (P<0.01). The levels of CRP and TNF-α on the 7th day after surgery in the enteral group were lower than those in the parenteral group (all P<0.001). See **Table 6**.

Comparison of adverse reactions

The incidence of adverse reactions in the enteral group (42.11%, 16 cases) was lower than that in the parenteral group (60.53%, 23 cases; P<0.05). See **Table 7**.

Discussion

Based on the theory of FTS, scientific intervention in patients with rectal cancer has become a research hot spot, which can improve the safety of patients during the perioperative period, reduce surgical stress and accelerate recovery. The traditional clinical treatment cannot satisfy the demand of patients with rectal cancer as they are often complicated with mal-

Table 2. Comparison of general clinical indicators

Group	n	Bowel recovery time (min)	First exhaust time (d)	First defecation time (d)	Postoperative hospital stay (d)
Enteral group	38	18.50±4.25	2.35±0.42	3.02±0.67	6.40±1.64
Parenteral group	38	23.09±3.27	3.58±0.29	5.08±1.33	10.72±3.20
t		5.276	14.860	8.527	7.406
P		0.001	<0.001	<0.001	<0.001

Table 3. Analysis of nutritional indicators of patients

Nutritional indicators		7 d before surgery	1 d after surgery	7 d after surgery	F	P
TP (g/L)	Enteral group	62.55±3.36	64.25±5.89	62.30±5.86[a]	2.545	0.026
	Parenteral group	63.02±3.15	62.45±3.86	59.39±6.05	7.059	0.001
t		0.629	2.576	3.128		
P		0.531	0.019	0.006		
ALB (g/L)	Enteral group	32.25±3.10	34.19±2.38	38.56±3.21[a]	19.600	<0.001
	Parenteral group	33.04±2.68	31.87±1.91	33.49±2.36	2.369	0.105
t		0.771	3.488	5.090		
P		0.446	0.002	0.001		
PA (mg/L)	Enteral group	205.21±17.76	244.15±22.64	221.37±17.33[#,a]	16.280	<0.001
	Parenteral group	204.56±18.31	210.49±22.03	192.46±15.54[#,a]	3.816	0.029
t		0.102	4.262	4.968		
P		0.919	0.002	0.001		

Note: [#]P<0.05 compared with 7 d before surgery; [a]P<0.05 compared with 1 d after surgery. TP: total serum protein; ALB: serum albumin; PA: prealbumin.

Table 4. Analysis of immune indicators of patients

Immune indicators		7 d before surgery	1 d after surgery	7 d after surgery	F	P
Lymphocyte ($\times10^9$/L)	Enteral group	2.18±0.24	1.55±0.29	1.67±0.54[#,c]	29.440	<0.001
	Parenteral group	2.20±0.19	0.95±0.21	1.13±0.39[#,c]	224.102	<0.001
t		0.403	10.330	4.997		
P		0.688	<0.001	0.004		
Neutrophil ($\times10^9$/L)	Enteral group	6.25±0.95	12.11±1.38[#]	13.48±1.50[#,c]	330.528	<0.001
	Parenteral group	6.23±0.96	13.87±1.55[#]	14.40±1.66[#,c]	391.962	<0.001
t		0.091	5.288	2.527		
P		0.928	0.004	0.013		
$CD4^+/CD8^+$	Enteral group	1.60±0.25	1.27±0.15[#]	1.40±0.34[#,c]	15.705	<0.001
	Parenteral group	1.63±0.18	1.14±0.18[#]	1.20±0.21[#,c]	74.780	<0.001
t		0.600	3.420	3.085		
P		0.550	0.001	0.003		

Note: [#]P<0.05 compared with 7 d before surgery; [c]P<0.05 compared with 1 d after surgery.

nutrition. Surgery increases the inflammation and stress responses while aggravate malnutrition, which then will induce complications. Therefore, nutritional support in patients with rectal cancer during the perioperative period is important to accelerate the postoperative recovery of patients [7].

The time of first gas exhaust and defecation of patients with rectal cancer after surgery indicate the degree of improvement of gastrointestinal function. The earlier the defecation after surgery the more beneficial it is for inhibiting intestinal bacteria breeding and reducing the absorption of endotoxins. Bowel sounds are

Table 5. Comparison of immunoglobulins

Immunoglobulins	Group	7 d before surgery	1 d after surgery	7 d after surgery	F	P
Immunoglobulin G (g/L)	Enteral group	11.34±2.25	10.85±1.68	10.67±2.44	0.991	0.345
	Parenteral group	11.18±2.39	10.45±1.21[#]	9.11±1.33[#,c]	14.050	<0.001
t		0.301	1.191	3.460		
P		0.765	0.237	0.009		
Immunoglobulin A (g/L)	Enteral group	2.35±0.29	2.21±0.45	2.68±0.33[#,c]	16.790	<0.001
	Parenteral group	2.38±0.27	2.10±0.26[#]	2.11±0.28[#,c]	13.140	<0.001
t		0.432	1.305	8.119		
P		0.642	0.196	<0.001		
Immunoglobulin M (g/L)	Enteral group	1.44±0.63	1.52±0.23	1.55±0.27	0.705	0.496
	Parenteral group	1.42±0.58	1.44±0.31	1.28±0.34	1.581	0.210
t		0.144	1.278	3.834		
P		0.886	0.205	<0.001		

Note: [#]P<0.05 compared with 7 d before surgery; [c]P<0.001 compared with 1 d after surgery.

Table 6. Comparison of inflammatory factors

Inflammatory factors		7 d before surgery	1 d after surgery	7 d after surgery	f	P
CRP (mg/L)	Enteral group	35.74±20.25	35.64±19.58	28.76±11.04	1.991	0.141
	Parenteral group	36.17±19.49	35.31±18.29	50.13±13.53[b]	8.791	0.008
t		0.094	0.076	7.544		
P		0.925	0.939	<0.001		
TNF-α (ng/L)	Enteral group	247.55±28.49	229.72±33.40[#]	185.61±20.43[#,b]	49.430	<0.001
	Parenteral group	248.31±27.20	250.12±13.44	220.70±22.42[#,b]	21.780	<0.001
t		0.119	3.493	7.133		
P		0.906	0.008	<0.001		

Note: [#]P<0.05 compared with 7 d before surgery; [b]P<0.01 compared with 1 day after surgery. CRP: C-reactive protein; TNF-α: tumor necrosis factor α.

Table 7. Comparison of adverse reactions (n, %)

Group	n	Abdominal distention	Diarrhea	Gastrointestinal reaction	Intestinal Obstruction	Infection	Incidence
Enteral group	38	3 (7.89)	5 (13.16)	7 (18.42)	2 (5.26)	2 (5.26)	16 (42.11%)
Parenteral group	38	8 (21.05)	7 (18.42)	6 (15.79)	3 (7.89)	5 (13.16)	23 (60.53%)
χ^2							4.772
P							0.029

caused by intestinal movement and the occurrence is the premise of gastrointestinal function recovery of patients with rectal cancer after surgery [8, 9]. In our study, we found the time of bowel sound recovery, first gas exhaust and first defecation of patients in the enteral group were all less than those in the parenteral group, suggesting that enteral nutrition is more beneficial for accelerating the recovery of patients and reducing the hospital stay. Oral nutritional preparation can increase the blood flow of the gastrointestinal portal vein, reduce gastrointestinal disorders and improve the recovery of intestinal mucosa function of patients with rectal cancer. Ma Yanmei et al. also found that enteral nutrition intervention is more helpful for improving the gastrointestinal function of patients with rectal cancer after surgery, speeding up food intake and promoting recovery [10]. Therefore, the effect of enteral

nutrition on recovery of patients with rectal cancer after surgery is better on the basis of fast track surgery.

PA, ALB and TF are all nutritional indicators. ALB is an important indicator to evaluate the prognosis of patients with rectal cancer. TF is mainly composed of ferritin. The low level of PA predicts malnutrition in patients [11, 12]. Our study found that the levels of these nutritional indicators on the 1st and 7th day after surgery in the enteral group were all higher than those in the parenteral group, indicating that enteral nutrition can directly improve the nutritional status of patients with rectal cancer. The reason may be that the enteral nutrition is consistent with the characteristics of intestinal absorption function, thus food can be absorbed better [13]. Gong Hua et al. found that enteral nutrition could improve the function of intestinal mucosa, inhibit the growth of bacteria and enhance the nutritional status in patients with rectal cancer [14]. These findings are similar to the results of our study. Therefore, enteral nutrition can directly improve the nutritional status of patients with rectal cancer over parenteral nutrition on the basis of fast track surgery.

In our study, the levels of lymphocytes, neutrophils and $CD4^+/CD8^+$ after surgery of patients with rectal cancer in the enteral group were higher than those in the parenteral group. The results suggest that enteral nutrition support on patients with rectal cancer can increase their immune function. Surgical anesthesia and trauma may lead to immunosuppression in patients, which is related to postoperative adverse events [15]. At present, studies have found that immunosuppression can promote the growth of cancer cells and increase the probability of cancer spread. Nevertheless, enteral nutrition can reduce the occurrence of immunosuppression in patients with rectal cancer [16, 17].

The immune defense system plays an important role in resisting tumor escape. Our study also found that the levels of IgA, IgG and IGM on the 7th day after surgery in the enteral group were higher than those in the parenteral group, which suggests that enteral nutrition can reduce the occurrence of immune function decline. Wang et al. reported that enteral nutrition could restore the levels of immunoglobulins of patients with rectal cancer after surgery and they thought it was related to the regulation of B cell function [18]. From the above results, it can be concluded that enteral nutrition promotes the immune function recovery of patients with rectal cancer during FTS.

CRP indicates the sensibility to stress of the body. High level of CRP indicates a severe degree of surgical trauma. TNF-α can induce chronic inflammation and metabolic imbalance, and plays an important role in diseases. Our results showed that the levels of CRP and TNF-α on the 7th day after surgery of patients in the enteral group were significantly lower than those in the parenteral group, which suggests enteral nutrition can improve the stress response and suppress the inflammation [19]. Yang et al. reported similar results. They found that enteral nutrition support was beneficial for reducing inflammation and response to stress [20, 21]. In addition, the incidence of adverse reactions of patients in the enteral group was lower than that in the parenteral group. All these results suggest enteral nutrition during FTS can accelerate metabolism, reduce abdominal distension and infection and accelerate recovery of patients with rectal cancer.

However, our study has certain limitations. Because of the limited foundation and other problems, we did not carry out a comprehensive medical examination of all subjects, so we cannot exclude the influence of other factors. Additionally, due to the short study time and insufficient sample size, the results may have some deviations. Moreover, this study only used one kind of medicine for treatment. Therefore, a study with more experimental methods should be conducted to provide more evidence for application of enteral nutrition in the treatment of rectal cancer during FTS.

In conclusion, enteral nutrition is safer than parenteral nutrition in patients with rectal cancer during FTS, which can accelerate intestinal peristalsis, reduce inflammation and improve immune function. Enteral nutrition is worth promoting.

Acknowledgements

This work was supported by the Science and Technology Foundation of Ninghai County, China (201711H010034).

Disclosure of conflict of interest

None.

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