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ORIGINAL ARTICLE

Observation of clinical efficacy of application of enhanced recovery after surgery in perioperative period on esophageal carcinoma patients

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Summary

Purpose: *To observe the clinical efficacy of the application of enhanced recovery after surgery (ERAS) in the perioperative period of esophageal carcinoma patients.*

Methods: *A total of 114 patients who were admitted to Affiliated Hospital of Jining Medical University for surgical treatment of esophageal carcinoma between June 2012 and June 2016 were enrolled and randomly divided into the intervention group and the regular group according to the difference of management procedures during the perioperative period. ERAS was carried out in 57 patients in the intervention group, while conventional management procedures were applied in 57 patients in the regular group. Thereafter, compared were the fluctuations in nutritional indicators and immunological indicators, postoperative complications, time to recovery of gastrointestinal function, length of stay (LOS) in hospital and cost of patients between the two groups.*

Results: *Seven days post-operation in the intervention group, the evaluation indexes of nutrition status, including total protein (TP), albumin (ALB), prealbumin (PA) and transferrin (TF), and of immunological functions, including immunoglobulin G (IgG), immunoglobulin A (IgA), immunoglobulin M (IgM) and total blood lymphocyte count (TLC), were significantly higher than those in the regular group. As for postoperative complications, the incidence rate of the intervention group was remarkably lower than that of the regular group; the recovery time of gastrointestinal function in the intervention group was shorter than that in the regular group; the LOS in the intervention group was also shorter than that in the regular group; the in-hospital cost in the intervention group was also lower than that in the regular group. All differences above were statistically significant ($p<0.05$).*

Conclusion: *During the perioperative period of esophageal carcinoma patients, ERAS should be fully applied to sustain the good status, and promote the recovery of immunological functions and gastrointestinal functions; at the same time, ERAS also reduces the incidence rate of postoperative complications, LOS and in-hospital cost, and we maintain that ERAS should be performed in clinical practice.*

Key words: *ERAS, esophageal carcinoma, perioperative management*

Introduction

Esophageal carcinoma, as one of the most common malignant tumors in the world, ranks 5th among all malignant tumors in China according to 2014 World Cancer Report of WHO. The incidence of esophageal cancer in China accounted for half of the world and the mortality rate is as high as 4.9% [1]. Comprehensive treatment, with surgical treatment as the major method, remains the preferred therapeutic procedure with promising efficacy in esophageal carcinoma patients that could be subjected to surgical treatment. Most of the esophageal carcinoma patients suffer from

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declined cellular immune functions, malnutrition, poor cardiac and pulmonary functions [2]. In addition, due to severe surgical trauma and the upper gastrointestinal tract remodeling on physiological functions, patients are usually tormented by slow recovery after operation, frequent onset of complications, long LOS and high hospital costs [3]. Thus, how to improve the treatment efficacy, reduce complications and alleviate the pain has made the treatment and nursing care in the perioperative period more important. In recent years, ERAS has provided a new platform and pattern for performing surgical treatment, so as to maximally improve the physiological and psychological trauma of patients and reduce the stress responses and complications in the perioperative period [4]. The application of ERAS is frequently reported in surgery of colorectal cancer, but scarcely seen in esophageal cancer. Thus, in this study, we assessed the efficacy of ERAS on esophageal cancer patients in the perioperative period, and the detailed information is reported below.

Methods

Patient data

In this study, a total of 114 patients with complete clinical data who were admitted to the affiliated Hospital of Jining Medical University between June 2012 and June 2016 for surgical treatment of esophageal carcinoma confirmed by endoscopy and pathological examination were enrolled.

Inclusion criteria

Patients with primary esophageal carcinoma, having never received any treatment before this study and with no other malignant tumors.

Exclusion criteria

Patients with history of metabolic diseases, such as diabetes mellitus, severe heart, lung, liver or kidney problems, or severe malnutrition.

To eliminate the bias of surgical method on the results of study, we selected patients whose lesions were located in median or median-lower esophagus, and performed the Ivor-Lewis subtotal esophageal resection with median incisions in the upper abdomen and posterior-lateral incision in right chest. According to the differences in the management in the perioperative period, patients were randomly divided into the intervention group (57 patients with ERAS in the perioperative period) and the regular group (57 patients with conventional management in the perioperative period). In the intervention group there were 18 males and 39 females with an average age of 66.89±13.45 years and an average weight of 53.03±9.16 kg. Forty of them had squamous cell carcinoma, while the remaining 17 patients had adeno-squamous carcinoma. The regular group consisted of 19 males and 38 females with an average age of 67.01±12.78 years and an average weight of 52.98±9.27 kg. Thirty-nine had squamous cell carcinoma and 18 adeno-squamous carcinoma. Comparison of the patient general clinical characteristics in the two groups showed no statistically significant difference ($p>0.05$) and the baseline data were comparable. This study had been approved by the Ethics Committee of the affiliated Hospital of Jining Medical University, and all enrolled patients signed written informed consent and actively cooperate with the preoperative preparation (Tables 1 and 2).

Research methods

Management protocol in the perioperative period

In strict accordance with the micro-invasive principle, we carried out the operations, in which 57 patients in the intervention group accepted the ERAS management during the perioperative period, and the remaining 57 patients in the regular group underwent conventional management in the perioperative period. Detailed information on the specific protocols is listed in Table 2.

Recording the general clinical data

General clinical data, including gender, age, weight (when measuring weight, patients were required to be fasted in unlined clothes without shoes and hats), pathological type, surgical method, complications, duration of postoperative ventilation, LOS and hospital cost.

Table 1. Clinicopathological characteristics in the two groups

Characteristics	*Intervention group (n=57) n*	*Regular group (n=57) n*	t/x^2	*p value*
Gender (n)			1.769	0.168
Female	39	38	38	
Male	18	19	19	
Age (years) (mean±SD)	66.89±13.45	67.01±12.78	1.912	0.089
Weight (kg) (mean±SD)	53.03±9.16	52.98±9.27	1.325	0.123
Pathological type (n)			2.126	0.073
Adenosquamous carcinoma	17	18		
Squamous carcinoma	40	39		

Table 2. Management protocols in the perioperative period of patients in the two groups

Management protocol in the perioperative period	*Intervention group*	*Regular group*
Preoperative education	Preoperative education should be prepared sufficiently and specifically for the following aspects: exercise and nutrient support for maintaining the functions of organs before operation, rational drug administration before operation, ameliorating the patient tension and fear and other aspects conducive patients to cooperating for surgery physically and emotionally.	Routine introduction of the Notice of Admission
Fasting before surgery	2 or 3 days before operation, patients were required to take liquid diet that mainly consisted of the enteral nutritional suspension, and the evening before surgery, patients took only 500 mL of carbohydrate solution without any bowel preparation, and received the energy mixture via intravenous injection in the morning of the operation day.	Routine fasting overnight
Anesthetic protocol	Patients received combined intravenous-inhalation anesthesia anesthesia with anesthetics of rapid metabolism and short half-life.	Conventional anesthesia
Management of body temperature	Heat preservation was carried out through infusion and flushing with warm liquid and heating bed; after operation, analgesia was performed by application of self-controled analgesic pump in combination with non-steroid anti-inflammatory drugs.	No special measures for heat preservation and opioid drugs for analgesia.
Prophylaxis of deep venous thrombosis in lower limbs	After operation, patients were transfered to the wards, were administered subcutaneously low molecular weight heparin sodium every night and antithrombotic pressure pump for one week, and immediately after the recovery of anesthesia, patients were required to use the ankle pump for exercise.	Routine subcutaneous injection of low molecular weight heparin sodium every night for one week.
Postoperative alimentation method	Early enteral nutrition (EEN).	Routine nutrient support.
Time of leaving bed	Patients received intraoperative intubation of drainage tube in certain cases, and left bed after removal of the urethral catheter in an early stage after operation and extubation of chest drainage tube 2 or 3 days after operation.	One week after operation.

Monitoring indexes

One day before operation, and days 1 and 7 after operation, 3 to 5 mL fasting blood was drawn from the elbow vein of patients, and was preserved in a refrigerator after being treated with anti-coagulant and centrifugation. all of the indexes relating to the patient nutrition status, including TP, ALB, PA and TF, and those indicators relating to assessment of immunological functions, such as IgG, IgA, IgM and TLC, were evaluated.

Statistics

SPSS 20.0 software (SPSS Inc., Chicago, IL, USA) was used to record and analyze the data. Qualitative data were presented in number of cases (rate), and Fisher's exact test or chi-square test were performed for comparisons. Quantitative data in normal distribution were expressed in mean±standard deviation, and *t* test was carried out for comparisons. P<0.05 suggested that the difference was statistically significant.

Results

Comparison of the changes in nutrient indicators between the two groups

No statistically significant difference in the nutrient indicators was found between one day before and one day after the operation between the two groups (p>0.05). Seven days after the operation, improvement in TP, ALB, PA and TF levels in the intervention group was statistically significant compared with the regular group (p<0.05; Table 3).

Comparison of the changes in immunological indicators between the two groups

No statistically significant difference was found in the immunological parameters between one day before and one day after the op-

eration (p>0.05). On day 7 after the operation, improvement in IgG, IgA, IgM and TLC levels in the intervention group was statistically significant compared with the regular group (p<0.05; Table 4).

Comparison of the incidence of postoperative complications between the two groups

No perioperative death, major complications or anastomotic fistula were identified in all of the patients. In the regular group, 16 patients developed complications (4 with gastrointestinal symptoms, including nausea, vomiting, and diarrhea), 4 with respiratory system infections, 2 with deep vein thrombosis, 2 with incisional infection, 1 with infection of the urinary tract, 2 with pleural effusion and 1 with incomplete bowel obstruction). In the intervention group, there were 6 patients with complications (2 patients with gastrointestinal symptoms, including nausea, vomiting, and diarrhea , 2 with respiratory system infection, 1 with incisional infection and 1 with pleural effusion. The incidence rate of complications in the intervention group was significantly lower than in the regular group (p<0.05). After symptomatic treatment, recovery of all complications was achieved. In the intervention and the regular group, the recovery time of gastrointestinal function was 52.26±6.58 and 79.35±5.34 hrs respectively, LOS was 9.47±2.65 and 13.52±4.67 days, with statistical difference favoring the intervention group (p<0.05; Table 5).

Table 3. Comparison of the changes in nutrient parameters between the two groups (mean±SD)

Nutrient parameters	Intervention group			Regular group		
	On day 1before operation	*On day 1 after operation*	*On day 7 after operation*	*On day 1 before operation*	*On day 1 after operation*	*On day 7 after operation*
TP (g/l)	68.25±4.23	50.93±4.91	68.42±3.82*	68.30±4.18	50.36±3.97	60.87±4.65
ALB (g/l)	43.80±2.34	32.65±3.26	41.64±3.86*	43.78±2.26	29.47±4.93	33.21±5.17
PA (mg/l)	319.57±21.47	260.76±20.88	288.74±25.52*	319.03±17.92	254.81±21.45	212.62±30.75
TF (mg/l)	2815±182	2016±124	2479±196*	2810±193	1931±132	2011±143

For abbreviations see text. * Compared with the regular group, p<0.05.

Table 4. Comparison of the changes in immunological parameters between the two groups (mean±SD)

Immunological parameters	Intervention group			Regular group		
	On day 1 before operation	*On day 1 after operation*	*On day 7 after operation*	*On day 1 before operation*	*On day 1 after operation*	*On day 7 after operation*
IgG (g/l)	9.51±0.92	7.32±1.05	8.93±1.67*	9.49±0.81	7.06±0.94	7.79±1.08
IgA (g/l)	3.15±0.23	2.14±0.12	3.04±0.75*	3.13±0.27	2.01±0.24	2.48±0.56
IgM (g/l)	1.72±0.22	1.03±0.14	1.71±0.23*	1.73±0.20	0.92±0.21	1.53±0.10
TLC ($\times 10^9$/l)	1.21±0.42	0.82±0.18	1.19±0.13*	1.20±0.43	0.81±0.16	1.10±0.13

For abbreviations see text. * Compared with the regular group, p<0.05.

Table 5. Comparison of the incidence of postoperative complications between the two groups

Complications	*Control group (n=57) n*	*Regular group (n=57) n*	*t/x²*	*p value*
Incidence rate of complications	10.53% (6/57)	28.07% (16/57)	4.769	0.003
Gastrointestinal symptoms	2	4		
Infection of respiratory system	2	4		
Deep vein thrombosis	0	2		
Incisional infection	1	2		
Urinary tract infection	0	1		
Pleural exudation	1	2		
Incomplete bowel obstruction	0	1		
Recovery time of gastrointestinal functions (hrs)*	52.26±6.58	79.35±5.34	3.129	0.009
LOS (days)*	9.47±2.65	13.52±4.67	6.253	0.000

LOS: length of hospital stay. * mean±SD

Comparison of the in-hospital cost between the two groups

The average in-hospital cost of patients in the intervention and the regular group was 10^3 euro (2.70±0.50) and 10^3 euro (4.04±0.92), suggesting that the cost in the intervention group was obviously higher compared with the regular group ($p<0.05$; Figure 1).

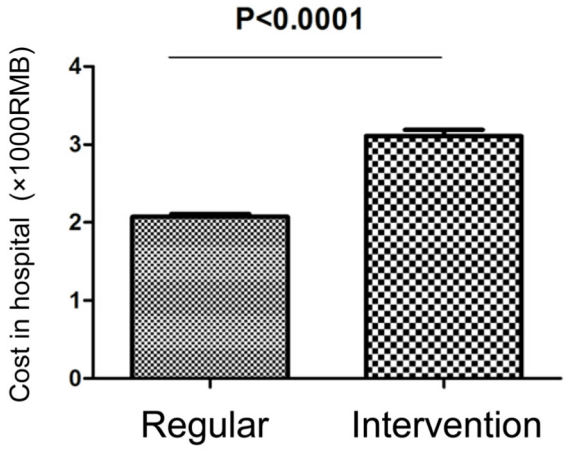

Figure 1. Comparison of the cost in hospital between the two groups. The in-hospital cost of patients in the intervention group was obviously higher than that in the regular group, and the difference was statistically significant ($p<0.0001$).

Discussion

Esophageal carcinoma derives from abnormal hyperplasia of esophageal squamous epithelium or glandular epithelium, and ranks 8th among all malignant tumors in the world [5]. From 1988 to 2008, the incidence rate of esophageal carcinoma was increased by about 50% worldwide [6]. Malnutrition, or even cachexia, are frequently seen in patients with malignant tumors [7]. Thus, perioperative management is extremely important for esophageal carcinoma patients. In recent years, once being presented, ERAS has attracted wide attention by surgeons, and has been gradually applied in multiple disciplines, such as general surgery, orthopedics and gynecology. In Europe, expert consensus has already been established over the application of ERAS in colorectal resection [8]. Based on evidence-based medicine, ERAS can reduce the postoperative complications, shorten the LOS in hospital and promote the postoperative recovery.

The level of some proteins is the major indicator reflecting the nutrient status, including ALB, PA, TF and fibronectin. In recent years, PA has become a protein attracting much attention due to its short half-life, promising specificity and close association with the nutrient status and prognosis of patients [9], so, thus, can serve as a reliable indicator for evaluating the nutrient status of patients. In this study, PA was also selected as one of nutrient indicators for evaluation of nutrition. The results of this study suggested that in the intervention group, significant improvement was attained in the nutrient indicators (TP, ALB, PA and TF) and immunological indicators (IgG, IgA, IgM and TLC) 7 days after the operation. In the intervention group the incidence rate of postoperative complications was relatively lower, the recovery time of gastrointestinal function was also better, both LOS and the in-hospital cost were reduced, and the differences in comparison with the regular group were statistically significant ($p<0.05$). All these imply that the application of ERAS in the perioperative management of esophageal carcinoma is safe and feasible with fewer postoperative complications, shorter LOS, lower in-hospital cost and less pain, and at the same time, patients can sustain a better nutrient status, which can promote the recovery of immunological and gastrointestinal functions, thus maintaining the patients in better status for the following comprehensive treatment.

Different from the conventional management, novel measures applied in ERAS including preoperative education and fasting, anesthetic procedure, management of body temperature, prophylaxis of deep vein thrombosis in the lower limbs, and postoperative nutrition support, are established on evidence-based medicine to reduce the trauma and stress response in the perioperative period, thereby accelerating the recovery of patients who were subjected to surgery [10]. Currently, the most promising success of ERAS has been observed in colorectal resections, and patients can be discharged within 2 or 3 days after colorectal surgery [11]. However, the discharge criteria are the same as the conventional criteria, including the semiliquid diet, painlessness or intestine exhaust.

The idea of ERAS in the intervention group should be promoted in the preoperative education. With sufficient preoperative education, not only could patients' negative feelings (such as fear and tension) be ameliorated, but also the exercise of organ functions , the nutrient support and rational medication before surgery would help patients stay in good psychological and physiological status to prepare for surgery [12]. Different from the conventional bowel preparation requiring fasting for a long time, patients in the intervention group only had liquid diet, mainly consisting of enteral nutrients 2 or 3 days before operation. Patients were given 500 mL carbohydrate solution at midnight before surgery and intravenous injection of energy mixture in the morning on the day of

operation, which could reduce the consumption of nutrients and loss of fluid and electrolyte due to long-lasting operation. Cerfolio et al. believed that superior to the conventional management protocol, the bowel preparation through oral administration of enteral nutrients suspension for esophageal carcinoma patients before surgery can facilitate the recovery of gastrointestinal function of patients after surgery, shorten the in-hospital LOS and, more importantly, reduce the risk of inhalation of countercurrent anesthetics [13]. One should be aware that intraoperative hypotension of patients is usually caused by the administration of anesthetics, for which usually are preferred vasoconstrictive drugs for boosting the pressure to reduce the cardiopulmonary burden of patients, instead of tremendous fluid infusion, control infusion or excessive supplementation of sodium-containing solutions [14].

Early enteral nutrition (EEN) has been widely recognized as the preferred postoperative nutritional support method for patients who have been subjected to gastrointestinal surgery [15-17]. EEN refers to enteral nutritional support 6 to 24 hrs after surgery [18]. Research has shown that after abdominal surgery, patients present slow recovery of stomach and colon functions, while the function of small intestine can be recovered within 6 to 12 hrs after surgery, which is the theoretical evidence for performing EEN [19]. Moreover, EEN is more suitable for sustaining the physiological condition with comprehensive nutritional support and few complications, thus ameliorating the functions of organs in a safe and effective way [20,21]. Performing nutritional support through enteral nutrition in an early stage benefits the growth of intestinal mucosal epithelium, avoiding thus the mucosal atrophy and maintaining the function of mechanical barriers. In addition, it can also induce the secretion of IgA from intestinal cells; besides, it can keep the integrity of immune barrier to prevent migration of the flora, which is good for the growth of normal intestinal flora and sustaining the natural barrier of intestine. Additionally, it can protect the chemical barrier of mucosa through promoting the secretion of gastrin and gastric acid in the stomach, thereby accelerating the recovery of gastrointestinal functions [22]. Moreover, it can activate the secretion of digestive fluids, hormones and enzymes to mobilize the stomach and intestine and constriction of gall bladder, increase the visceral blood, thereby reducing the incidence of complications in the liver and gall bladder. Thus, in this study, EEN was given to patients after surgery, through which the transition from enteral nutrition to diet was completed successfully.

After operation, extubation and off-bed activity in an early stage are also the key factors to facilitate the rapid recovery; in clinical practice, extubation is suggested for patients receiving drainage liquid of less than 200 mL within 24 hrs [23]. Postoperatively, patients in the intervention group were transferred to the wards and were administered subcutaneously low molecular weight heparin sodium every night and antithrombotic pressure pump for one week [23], and immediately after the recovery from anesthesia, patients were required to use the ankle pump for exercise. Finally, no deep vein thrombosis was identified in any patient, suggesting that these measures can avoid the risk of vein thrombosis in lower limbs.

Emphasizing the multidisciplinary collaboration among the departments of anesthesia, pain management and surgery, ERAS has spread the new technology and ideas over the perioperative management of patients before, during and after operation to reduce the stress response to surgery, maintain the nutrient status, promote the recovery of immunological and gastrointestinal functions and reduce the incidence rate and mortality rate of postoperative complications. Thus, ERAS should be accepted in clinical practice for its significant benefits.

We acknowledge, however, that this study is limited by single-center patient and the small sample size, and therefore more significant results are expected in future multi-center large-sample studies.

Conflict of interests

The authors declare no conflict of interests.

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