

Effect of early enteral nutrition on postoperative nutritional status and immune function in elderly patients with esophageal cancer or cardiac cancer

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Objective: To explore the effect of early enteral nutrition (EN) on postoperative nutritional status, intestinal permeability, and immune function in elderly patients with esophageal cancer or cardiac cancer.

Methods: A total of 96 patients with esophageal cancer or cardiac cancer who underwent surgical treatment in our hospital from June 2007 to December 2010 were enrolled in this study. They were divided into EN group (n=50) and parenteral nutrition (PN) group (n=46) based on the nutrition support modes. The body weight, time to first flatus/defecation, average hospital stay, complications and mortality after the surgery as well as the liver function indicators were recorded and analyzed. Peripheral blood samples were collected on the days 1, 4 and 7 after surgery. The plasma diamine oxidase (DAO) activity and D-lactate level were determined to assess the intestinal permeability. The plasma endotoxin levels were determined using dynamic turbidimetric assay to assess the protective effect of EN on intestinal mucosal barrier. The postoperative blood levels of inflammatory cytokines and immunoglobulins were determined using enzyme-linked immunosorbent assay (ELISA).

Results: After the surgery, the time to first flatus/defecation, average hospital stay, and complications were significantly less in the EN group than those in the PN group ($P<0.05$), whereas the EN group had significantly higher albumin levels than the PN group ($P<0.05$). On the 7th postoperative day, the DAO activity, D-lactate level and endotoxin contents were significantly lower in the EN group than those in the PN group (all $P<0.05$). In addition, the EN group had significantly higher IgA, IgG, IgM, and CD4 levels than the PN group ($P<0.05$) but significantly lower IL-2, IL-6, and TNF- α levels ($P<0.05$).

Conclusions: In elderly patients with esophageal cancer or cardiac cancer, early EN after surgery can effectively improve the nutritional status, protect intestinal mucosal barrier (by reducing plasma endotoxins), and enhance the immune function

Key Words: Enteral nutrition; nutritional status; intestinal permeability; endotoxin; immune function



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Introduction

Esophageal cancer is one of the common malignant tumors in the digestive system, and China has the highest incidence and mortality rate of esophageal cancer all over the world (1). The death toll from esophageal cancer in China reaches 150,000; unfortunately, the incidence is still increasing annually, particularly in the elderly, who account for 50% of the esophageal cancer cases (2). Currently surgery is still the best way for treatment of esophageal cancer. (3) Patients with cardiac cancer tend to have varying degrees of malnutrition because of the reduced food intake due to difficulty swallowing, preoperative diet restrictions, and nutrition consumption by tumors. Meanwhile, the surgeries for esophageal and cardiac cancers are highly invasive and often take a long time, inducing a strong stress response in human body. Therefore, postoperative catabolism hyperthyroidism may occur, which is characterized by obvious negative nitrogen balance, hypoproteinemia, and hyperglycemia, resulting in further malnutrition (4). The situation is even worse in the elderly patients with esophageal cancer or cardiac cancer. Zhu *et al.* found that the incidence of perioperative malnutrition among these patients reached 20-80%. Therefore, it is particularly important to investigate the postoperative nutritional status in elderly patients with esophageal cancer or cardiac cancer.

The surgical trauma (caused by intestinal ischemia or intestinal paralysis) and lack of the intestinal stimulation and nutrition after the surgery (due to fasting) can increase the atrophy, damage and permeability of intestinal mucosa; as a result, the gut bacteria and endotoxins can easily migrate and enter the blood stream. For patients with esophageal cancer or cardiac cancer, their nutritional status will be worsened after surgeries, along with the decrease of the cellular and humoral immunity (5).

Clinically, nutritional support, particularly enteral nutrition (EN), is applied to facilitate the improvement of nutritional status, restoration of immune function, and protection of intestinal mucosal barrier after the surgeries. In our current randomized and controlled study, we explored the effect of early EN on postoperative nutritional status, intestinal permeability, and immune function in elderly patients with esophageal cancer or cardiac cancer. Also, we investigated the effect of EN on the intestinal barrier function to identify the correlation of intestinal bacterial translocation with postoperative infections in cardiac surgery. By studying the influences of postoperative early EN on the intestinal barrier function

and immune function in elderly patients with esophageal cancer or cardiac cancer, we tried to verify the role of EN in improving the intestinal bacterial translocation and enterogenic infections.

Materials and methods

Subjects and grouping

A total of 96 patients with esophageal cancer or cardiac cancer who underwent surgical treatment in our hospital from June 2007 to December 2010 were enrolled in this study. They were divided into EN group [n=50; 34 males and 16 females, aged 65-79 years (mean: 68.9 years)] and parenteral nutrition (PN) group [n=46; 26 males and 20 females, aged 65-78 years (mean: 67.5 years)] based on the nutrition support modes. Patients with diabetes, cirrhosis, and/or other chronic comorbidities were ruled out. The two groups showed no significant difference in terms of gender, age, site of lesion, surgical approach, and pathologic stage (all $P>0.05$).

Nutritional supports

EN group: The anesthetist and surgeon cooperated closely during the surgery. Under the guidance of the surgeon, duodenal feeding tube was nasally placed at 20-30 cm away from distal Treitz ligament. On the first postoperative day (day 1), the patients were provided with routine peripheral intravenous infusion of glucose solution (2,000-2,500 mL) plus potassium chloride; furthermore, the 30 °C normal saline (250 mL) was instilled via the nasal-intestinal tube. At day 2, the patients were perfused with Peptisorb (NUTRICIA, Netherland) 500 mL at a constant speed (30-50 mL/h). The dose was gradually increased according to the patients' subjective feeling and tolerance. At day 2, the patients were tube-fed with Peptisorb 500 mL plus Nutrison Fibre (NUTRICIA, Netherland) 500 mL at a speed of 50-60 mL/h. At day 3, the patients were tube-fed with 1,500-2,000 mL of the products at a speed of 80-100 mL/h, reaching the full dose. The full dosage was provided in the following four days. The total amount of nutrient solution was calculated based on the total daily energy intake (125.52 kJ). During the perfusion, the tube was flushed every four hours to maintain it unobstructed. Fluid warmer was applied to maintain the nutrient solution at a temperature of 38-42 °C. The initially insufficient fluid and heat were supplemented intravenously.

PN group: PN was provided using a standard three-liter package containing compound amino acid, long-chain fat emulsion, glucose, vitamins, electrolytes, and trace elements via the central vein after the surgery. Based on a total daily energy of 125.52 kJ (30 kcal)/kg, the carbohydrate:fat calorie percentage ratio was set at 2:1. PN was applied for 8-10 d. The patients in both groups were provided with liquid diet at day 8, semi-liquid diet at day 10, and ordinary diet at day 12.

Clinical observations and laboratory tests

The body weight, total serum protein, serum albumin, hemoglobin, liver function, lymphocytes 7 days before and after surgery as well as anal exhaust/defecation time, average hospital stay, complications, and mortality after the surgery were recorded for patients in both groups.

Effect of EN on intestinal permeability

Blood samples were collected on the days 1, 4 and 7 after surgery. Diamine oxidase (DAO) activity was determined by measuring the oxidation of o-dianisidine dihydrochloride, and D-lactic acid was detected using modified spectrophotometry. The plasma DAO kit and the agent kit for the semi-quantitative assay of lactic acid were purchased from Sigma-Aldrich Company.

Determination of plasma endotoxin levels

The working standard endotoxin (WSE) was diluted 10 times using water for bacterial endotoxins test, yielding a series of endotoxin concentrations of 2.0, 0.2, and 0.02 EU/mL. After adding 0.1 mL of each solution into a reaction tube already containing 0.1 mL limulus amoebocyte lysate, the solution was mixed evenly. Then, the samples were inserted into the EDS-99 Bacterial Endotoxin Dynamic Testing System, and the endotoxin level in each sample was detected for three times.

Venous blood samples (1.0-2.0 mL; after anticoagulation) were collected before and after surgery. The blood sample was slowly placed into sterile centrifuge tubes, which was then closed to avoid contamination. After the sample was centrifuged at 3,000 r/min for 40 min, plasma was isolated and harvested, and stored in ice water bath for further determination. The plasma was pre-treated, and endotoxin standard curve was prepared, and the plasma bacterial

endotoxin level was determined.

Effect of EN on the immune function

Blood immunoglobulins (IgA, IgG and IgM), cytokines (IL-2 and IL-6), and tumor necrosis factor (TNF- α) before surgery and 1 day and 7 days after surgery were determined using enzyme linked immunosorbent assay (ELISA). T lymphocyte subsets (CD4, CD8 and CD4/CD8) were determined using flow cytometry. The IgA, IgG, and IgM detection kits were purchased from Shanghai Sangon Biological Engineering Technology And Service Co., Ltd. The reagent kits for the determination of IL-2, IL-6 and TNF- were purchased from Jingmei Biological Engineering Co., Ltd.

Statistical analysis

All measurement data are presented as $\bar{x} \pm s$. The intergroup difference was compared using *t*-test. All the statistical analysis was performed using SPSS 13.0 software (SPSS Inc., Chicago, IL, USA), and $P < 0.05$ was regarded as statistically significant.

Results

Effect of early EN on postoperative nutritional status in elderly patients with esophageal cancer or cardiac cancer

The postoperative body weight and liver function parameters were within the normal range. Serum albumin was significantly higher in the EN group than that in the PN group ($P < 0.05$). The results are shown in *Table 1*. Also, as shown in *Table 2*, compared with the PN group, the EN group had significantly shorter time to first flatus/defecation and mean hospital stay, lower incidences of complications, and lower mortality ($P < 0.05$).

Effect of early EN on postoperative intestinal permeability in elderly patients with esophageal cancer or cardiac cancer

The effect of early EN on postoperative intestinal permeability in elderly patients with esophageal cancer or cardiac cancer was assessed based on the blood DAO and D-lactic acid levels. As shown in *Table 3*, the DAO and D-lactic acid levels showed no significant differences between these two groups at day 4; at day 7, however, the EN group had significantly lower DAO and D-lactic acid levels than the PN group ($P < 0.05$).

Table 1 Nutritional status and liver function before and after surgery in PN group and EN group

Indicators	PN group (n=46)		EN group (n=50)	
	Before surgery	Day 7 after surgery	Before surgery	Day 7 after surgery
Body weight (kg)	65.1±9.6	61.9±8.4	66.1±10.2	62.3±9.2
Serum total protein (g/L)	57.8±5.1	54.7±6.5	58.1±5.7	54.1±6.9
Serum albumin (g/L)	34.7±5.5	31.8±4.1	35.2±4.2	33.2±5.5*
Hemoglobin (g/L)	121.8±40.3	109.6±28.9	123.7±41.6	112.3±30.5
Lymphocyte count (10 ⁹ /L)	1.6±0.4	1.4±0.4	1.8±1.1	1.5±0.8
Aspartate aminotransferase (U/L)	33.1±5.4	41.2±2.7	33.6±5.3	31.5±5.8
Alanine aminotransferase (U/L)	32.3±2.8	46.1±2.1	33.5±3.2	35.2±3.7
Serum total bilirubin (μmol/L)	18.1±1.4	22.9±2.9	18.2±1.5	16.1±2.3
Serum conjugated bilirubin (μmol/L)	10.8±2.3	11.6±1.7	10.3±2.1	5.6±2.3

*P<0.05, compared with the PN group

Table 2 Comparison of time to first flatus/defecation, mean hospital stay, complications, and mortality between PN group and EN group

Group	n	Time to first flatus (h)	Time to first defecation (h)	Mean hospital stay (d)	Complications				Mortality
					ARDS	ARF	AHF	Stress ulcer	
PN group	46	70.6±21.9	83.4±13.8	14.3±2.1	8.5	6.9	4.8	11.2	1.7
EN group	50	52.7±17.8*	66.1±8.1*	10.3±2*	2.6*	1.5*	1.4*	0**	1.5

*, P<0.05, compared with the PN group; **, P<0.01, compared with the PN group; ARDS, acute respiratory distress syndrome; ARF, acute renal failure; AHF, acute heart failure

Table 3 Blood DAO and D-lactic acid levels in PN group and EN group

Detection time	PN group (n=46)		EN group (n=50)	
	D-lactic acid level (μg/mL)	DAO (mg/mL)	D-lactic acid level (μg/mL)	DAO (mg/mL)
Day 1 after surgery	12.9±10.8	87.6±70.7	13.6±10.7	92.5±69.1
Day 4 after surgery	41.5±26.9	123.9±92.3	40.6±27.3	117.4±106.2
Day 7 after surgery	37.1±10.7	124.4±39.5	31.2±8.9*	80.3±37.4*

*, P<0.05, compared with the PN group

Table 4 Blood endotoxin levels in PN group and EN group

Detection time	Plasma endotoxin levels (EU/mL)	
	PN group (n=46)	EN group (n=50)
Before surgery	0.09±0.07	0.08±0.07
Day 4 after surgery	0.31±0.11	0.22±0.09
Day 7 after surgery	0.34±0.12	0.17±0.06*

*, P<0.05, compared with the PN group

Effect of early EN on intestinal mucosal barrier in elderly patients with esophageal cancer or cardiac cancer

The effect of early EN on intestinal mucosal barrier in elderly patients with esophageal cancer or cardiac cancer was assessed based on the endotoxins in both groups. The endotoxin levels showed no significant differences between these two groups at day 4; at day 7, however, the EN group had significantly lower endotoxin levels than the PN group (P<0.05) (Table 4).

Table 5 Changes of immune indicators in PN group and EN group

	PN group (n=46)			EN group (n=50)		
	Before surgery	Day 1 after surgery	Day 7 after surgery	Before surgery	Day 1 after surgery	Day 7 after surgery
IgA (g/L)	2.34±0.79	1.92±0.54	2.67±0.92	2.45±0.61	1.93±0.61	3.09±0.95*
IgG (g/L)	9.79±1.41	9.15±1.16	12.03±1.32	10.01±1.39	9.23±1.27	13.27±1.33*
IgM (g/L)	1.40±0.35	0.99±0.43	1.45±0.39	1.42±0.31	0.97±0.52	1.73±0.42*
CD4 (%)	42.03±14.37	33.79±8.41	40.81±7.38	42.19±10.98	33.46±6.03	47.89±7.01*
CD8 (%)	25.31±4.43	23.46±6.72	23.29±4.63	24.99±6.15	23.57±7.01	23.07±4.12
CD4/CD8	1.66±0.61	1.44±0.51	1.75±0.47	1.68±0.52	1.42±0.49	2.07±0.52*
IL-2 (pg/mL)	281.12±74.95	279.13±59.01	316.69±63.38	279.93±75.57	281.34±72.17	359.48±66.19*
IL-6 (pg/mL)	269.83±109.49	537.29±103.81	489.09±89.32	273.74±119.09	543.92±104.32	411.15±109.41*
TNF- α (pg/mL)	283.23±46.12	387.05±119.13	438.46±99.17	286.01±49.83	372.01±117.59	321.69±85.64*

*, P<0.05, compared with the PN group

Effect of early EN on postoperative immune function in elderly patients with esophageal cancer or cardiac cancer

The immune function was low in both groups before surgery and 1 day after surgery, showing no significant difference. At day 7 after surgery, the immune function indicators increased in both groups. In the EN group, the immune globulins (IgA, IgG and IgM), T lymphocyte subsets (CD4 and CD4/CD8), and IL-2 were significantly higher than those in the PN group (P<0.05), whereas IL-6 and TNF- α were significantly lower (P<0.05). The results are shown in *Table 5*.

Discussion

Esophageal cancer is a common malignant tumor of the gastrointestinal tract. Before surgery, patients often already have poor nutritional status and low immune function; the surgical trauma and the further decreased immune function after surgery will make the residual tumor cells easily escape from immune surveillance and result in the early relapse of tumors (6). It has been found that the incidence of postoperative infections is about 10% in patients with cardiac cancer, which is remarkably higher than those of other tumors (e.g., lung cancer). In fact, infection is the leading cause of postoperative death among cardiac cancer patients (7). Therefore, it is critically important to improve the postoperative nutritional status and restore the immune function in patients with esophageal cancer or cardiac cancer (8). EN has been well recognized as an economical, safe, and effective nutritional support method that complies with the physiological state, helps to maintain the digestive

tract morphology and function, operates in a simple way, and has few complications. Therefore, it can effectively regulate the restoration of intestinal mucosa (9). In our current study, the postoperative body weight and liver function parameters were within the normal range in both EN group and PN group. Serum albumin was significantly higher in the EN group than that in the PN group (P<0.05). Also, compared with the PN group, the EN group had significantly shorter time to first flatus/defecation and mean hospital stay, lower incidences of complications, and lower mortality (P<0.05). Obviously, early EN is helpful to improve the nutritional status in the elderly patients with esophageal cancer or cardiac cancer, shorten the postoperative recovery phase, and reduce the complications.

The surgical trauma (caused by intestinal ischemia or intestinal paralysis) and lack of the intestinal stimulation and nutrition after the surgery (due to fasting) can increase the atrophy, damage, and permeability of intestinal mucosa; as a result, the gut bacteria and endotoxins can easily migrate and enter the blood stream (8,10). This may result in many hazards: the bacteria and endotoxins can cause enterogenic systemic infection; meanwhile, the bacterial toxins also stimulate the monocytes, macrophages and other tissue cells to release a variety of proinflammatory cytokines (e.g., IL-1, IL-6, and TNF- α) (11,12) and reduce the release of the protective anti-inflammatory cytokines (e.g., IL-2, IL-4, and IL-10) (13). The excessive release of proinflammatory cytokines and inhibition of anti-inflammatory cytokines will unavoidably trigger excessive inflammatory response, resulting in systemic inflammatory response syndrome (SIRS) and multiple organ dysfunction syndrome (MODS)

(14,15). In recent years, the intestinal function has been applied as a major indicator for the prognosis of critically ill patients. Gut is regarded as a central organ after surgical stress; also, among the intestinal mucosal barrier functions, immune barrier plays an important role (16). A recent study has found that the postoperative gastrointestinal paralysis mainly occurs in the stomach and colon; the functions of small intestine often return normal 6-12 h after the surgery, which supports the early application of EN after surgery for cardiac cancer (17).

In our current study, the DAO and D-lactic acid levels showed no significant differences between these two groups at day 4; at day 7, however, the EN group had significantly lower DAO and D-lactic acid levels than the PN group ($P<0.05$). Therefore, the early EN can help to reduce the postoperative intestinal permeability and protect the intestinal mucosal barrier in elderly patients with esophageal cancer or cardiac cancer. Quite a few elderly patients with esophageal cancer or cardiac cancer have suffered from eating disorder for a long period of time, and therefore intestinal mucosal barrier dysfunction is highly possible among these patients. In addition, the surgical trauma and postoperative fasting (for about one week) further increase the intestinal mucosal barrier dysfunction. EN is helpful to maintain the integrity of the structure and function of intestinal mucosal cells, protect the intestinal mucosal barrier (18), remarkably decrease enterogenic infection, and prevent the intestinal mucosal atrophy. Meanwhile, EN has more comprehensive and reasonable nutrients; compared with PE, it is physiologically more compatible, and more flexible, safe and affordable (19).

The normal human intestinal mucosal barrier is composed of intestinal mucosal epithelium, normal intestinal flora, intestinal secretions, and intestinal immune cells (20). The intact intestinal barrier can effectively block the translocation of intestinal parasitic fungi and their toxins from the gut to other tissues and organs and thus prevent the invasion of endogenous microorganisms and their toxins. The permeability of the intestinal mucosa increases when the integrity of the intestinal mucosal barrier is damaged; as a result, the bacteria and toxins originally in the gut will pass through the damaged intestinal mucosa, resulting in bacterial translocation and endotoxemia; after having entered the blood stream, the bacteria and their toxins will in turn exert their effects on the intestinal mucosa, further aggravating the damage of intestinal mucosal barrier and increasing the permeability of the intestinal mucosa. Such a vicious circle may cause SIRS,

MODS, and, ultimately, death (21). In our current study, the endotoxin levels showed no significant difference between these two groups at day 4; at day 7, however, the EN group had significantly lower endotoxin levels than the PN group ($P<0.05$). Therefore, the early EN can help to lower the postoperative endotoxin levels and protect the intestinal mucosal barrier in elderly patients with esophageal cancer or cardiac cancer.

TNF- α is one of the key factors leading to inflammatory reaction. It is an endogenous cytokine produced by activated monocyte-macrophage system (22). IL-2 is one of the most important lymphokines in the immune network, reflecting the change of IL-2 level and thus the immune response in human body (23). IL-6 is known to be a major mediator of the acute-phase response. It can stimulate the liver to synthesize C-reactive protein (CRP), enhance inflammatory reaction by promoting B cell differentiation and antibody formation, and assist the T cells to produce the expressions of IL-2 and its receptor (24). In our current study, the immune function was low in both groups before surgery and 1 day after surgery, showing no significant difference. At day 7 after surgery, the immune function indicators increased in both groups. In the EN group, the immune globulins (IgA, IgG and IgM), T lymphocyte subsets (CD4 and CD4/CD8), and IL-2 were significantly higher than those in the PN group ($P<0.05$), whereas IL-6 and TNF- α were significantly lower ($P<0.05$). Therefore, the early EN is helpful to improve the immune function in elderly patients with esophageal cancer or cardiac cancer.

In summary, in elderly patients with esophageal cancer or cardiac cancer, early EN after surgery can effectively improve the nutritional status, protect intestinal mucosal barrier (by reducing plasma endotoxins), and enhance the immune function.

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