Clinical effects of total protein and short peptide enteral nutrition during recovery after radical gastrectomy

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ABSTRACT

Background and Objectives: Enteral nutrition (EN) plays a vital role in promoting the recovery of patients after surgery. This study aims to clarify the effects of total protein enteral nutrition (TPEN) and short peptide enteral nutrition (SPEN) on the recovery of patients after radical gastrectomy. **Methods and Study Design:** Patients underwent radical gastrectomy were randomly divided into a TPEN (n=60) or SPEN group (n=60). These two kinds of EN were fed 24 hours after radical gastrectomy with increasing dose from 10 kcal/kg to maximal 25 kcal/kg on postoperative day (POD) 5 and with the maximal dose in following days. Supplemental parenteral nutrition was given for replenishing energy deficits. The tube feeding was discontinued when oral intake increased to sixty percent of the target requirements. The postoperative recovery was evaluated on POD 1 and POD 7. **Results:** On POD 7, the serum prealbumin (transthyretin) was higher in the TPEN than the SPEN group (p<0.001). The patients in the TPEN group had a higher incidence of abdominal distension (p=0.043), but had a lower incidence of diarrhea (p=0.016) compared to the SPEN group. The anal exhaust time of patients in the TPEN group was postponed (p=0.020), but the postoperative hospitalization time (p=0.005) and total hospitalization time (p=0.027) were shortened compared to the SPEN group. No significant differences were observed between the two groups in any other indicators. **Conclusions:** SPEN is suitable for early and TPEN for later stage recovery after radical gastrectomy.

Key Words: enteral nutrition, total protein, short peptide, radical gastrectomy, clinical effect

INTRODUCTION

Gastric cancer is one of the common malignant tumors in digestive system, with considerably high morbidity and mortality.[1] Recently, radical gastrectomy remains to be the most reliable treatment of gastric cancer. However, 65%~85% gastric cancer patients are in malnutrition, higher than any other tumors, which contributes to the increased risk of perioperative morbidity and mortality.[2,3] A variety of factors caused by tumors are involved in perioperative malnutrition, including decreased appetite, early satiety, physical obstruction of gastrointestinal tract, malabsorption and nutrient consumption, metabolic disturbance, as well as tissue destruction.[4,5] Because of the trauma caused by surgery, patients are in a hypermetabolic and hypercatabolic state. The insulin resistance and nutrition deficiency in patients after the surgery will further result in severe postoperative metabolic disorders.

Nutritional therapy is the cornerstone of postoperative recovery, but it is still challenging to select appropriate nutrition for clinical applications. Compared with parenteral nutrition, enteral nutrition (EN) is less expensive and has fewer complications. Thus, EN is recommended for patients after gastrointestinal surgery because it can greatly maintain and recover the structure and function of the intestinal mucosa by regulating metabolism, enhancing immunity, and reducing postoperative complication.[6-8]

Total protein enteral nutrition (TPEN) and short peptide enteral nutrition (SPEN) are commonly used in clinical practice. Appropriate arrangement of EN by physicians can increase therapeutic efficacy, and decrease the financial expense of adverse events during the postoperative recovery of patients. However, it is still unknown how to give proper EN for patients after surgery, e.g. radical gastrectomy. Therefore, our study aims to observe the clinical effects in cancer patients after gastrointestinal surgery by administrating either TPEN or SPEN, and thus create an optimal EN scheme.

MATERIALS AND METHODS

Study design

A randomized and controlled study was performed to evaluate the efficacy of TPEN or SPEN on the recovery of patients after radical gastrectomy. The informed consent was made with the participants before the study and the whole study was approved by the Ethics Committee of Jiangsu Cancer Hospital.

Participants

A total of 142 patients with pathologically confirmed gastric cancer and received radical gastrectomy were recruited from Jiangsu Cancer Hospital from January to October in 2017.

All candidates had never suffered any situation including 1) acute malnutrition; 2) preoperative chemotherapy or radiotherapy; 3) severe cardiopulmonary, hepatic or renal dysfunction; 4) severe gastrointestinal dysfunction; 5) percutaneous endoscopic gastrostomy or percutaneous endoscopic jejunostomy preoperatively; 6) metabolic disorders, including diabetes mellitus, hyperthyroidism and hyperlipidemia; 7) urological or psychiatric diseases and could not cooperate on research. 22 cases were excluded, among which eight patients had metabolic disorders, 12 patients encountered preoperative chemotherapy, and two patients were accompanied with acute gastrointestinal obstruction. Finally, 120 participants were involved in this study.

Study protocol

In the study, nasointestinal tubes were placed in all the patients during the radical gastrectomy. Normal saline was given through the nasointestinal tubes 12 hours after the operation. Then early EN was fed through the nasointestinal tubes 24 hours after the surgery. The participants were randomly given either TPEN (TPEN group, n=60) or SPEN (SPEN group, n=60) with an increasing dose from 10 kcal/kg to 25 kcal/kg until the maximal dose on postoperative day (POD) 5 and with the maximal dose in the following days. Supplemental parenteral nutrition was given to make sure that all the patients were received 25-30 kcal/kg of energy and 1.5 g/kg of protein per day. The infusion velocity and temperature of EN were adjusted through feeding pump. Patients started oral nutritional supplement (ONS) on POD 6, and tube feeding was stopped when ONS and food intake increased to sixty percent of the target requirements. The study protocol is shown in Figure 1.

Data collection

Clinical variables were examined and recorded, including age, sex, body mass index (BMI), postoperative hospitalization time and total hospitalization time. Surgical parameters included operative time, extent of gastrectomy, intraoperative bleeding and anal exhaust time. On POD 1 and POD 7, the nutrition indexes and immune indexes were tested and documented, including total protein, serum albumin, serum prealbumin (transthyretin), hemoglobin, T lymphocyte subsets (CD3, CD4, CD8, CD4/CD8) and blood immunoglobulins (IgA, IgG, IgM).

Gastrointestinal problems including abdominal distension, diarrhea and constipation were assessed according to patients' information and symptoms. Pulmonary infection was diagnosed based on lung radiographic findings, deterioration of neutrophil count, C-reactive protein, procalcitonin, as well as positive active surveillance culture. All postoperative complications were evaluated according to the Clavien-Dindo classification and the complications not lower than grade II were considered positive. [9]

Statistical analyses

Statistical analysis of all the data was conducted using Statistical Product and Service Solutions (SPSS, Version 24.0). Count data were presented as percentage and compared using Chi-square test or Fisher's exact test. After ensuring the normality of data, independent sample t-test or Welch's approximate t-test was used for testing the difference between the TPEN group and the SPEN group and the data were presented as mean ± standard deviation

(SD). Whereas, if the data were abnormally distributed, they were presented as median with interquartile range [25th-75th percentile] and Mann-Whitney U test was used for testing the difference between the TPEN group and the SPEN group. The significance level for all the tests was $\alpha = 0.05$.

RESULTS

Patient characteristics

The clinical characteristics of all the patients recruited are shown in the Table 1. There were no significant differences in the age, sex, operative time, intraoperative bleeding, and extent of gastrectomy of patients between the TPEN group and the SPEN group ($p>0.05$).

Nutrition indexes of patients

Preoperatively, there were no significant differences in total protein, serum albumin, hemoglobin or BMI of patients between the TPEN and the SPEN groups ($p>0.05$). During the study period, there were also no significant differences between the two groups in terms of total protein, serum albumin, hemoglobin and BMI ($p>0.05$) (Table 2). While there were no significant differences in serum prealbumin between two groups in preoperatively or POD 1, the serum prealbumin was higher in the TPEN group than in the SPEN group on POD 7 ($p<0.001$) (Figure 2).

Immune indexes of patients

During the study period, there were no statistical differences with regard to CD3, CD4, CD8, CD4/CD8, IgA, IgM and IgG between the TPEN and SPEN groups ($p>0.05$) (Table 3).

Postoperative complications, gastrointestinal function recovery and other conditions of patients

The patients in the TPEN group had a significantly higher incidence of abdominal distension ($p=0.043$) and lower incidence of diarrhea ($p=0.016$) than did patients in the SPEN group (Table 4). The anal exhaust time of patients in the TPEN group was later than that in the SPEN group ($p=0.020$), but the postoperative hospitalization ($p=0.005$) and total hospitalization times ($p=0.027$) were shorter than those in the SPEN group. The incidences of constipation and pulmonary infection were not significantly different between the groups ($p>0.05$).

DISCUSSION

Gastric cancer is one of the most common malignant tumors of alimentary tract. Most of the patients are malnourished in preoperatively due to inadequate food intake and tumor activity.[10] The trauma, inflammation and fasting after surgery contribute to hypermetabolic and hypercatabolic states, which can lead to metabolic disorders, electrolyte loss and nutrient deficiency in surgical patients. Numerous studies have shown that EN support after gastrointestinal surgery improves the nutritional status and reduces complications.[11,12] Therefore, nutritional program choice after radical gastrectomy is strategic. We found no significant differences in baseline and intrastudy characteristics between the TPEN and SPEN groups. However, TPEN improved nutritional status and shortened hospitalization time, while SPEN promoted intestinal function recovery.

Serum albumin, serum prealbumin (transthyretin) and hemoglobin are commonly used as nutrition indicators. Serum albumin and hemoglobin have long half-lives, and can be affected by fever, fluid imbalance and other factors during the postoperative period, which makes it difficult to deduce nutrition-specific and timely changes from these proteins. Compared to serum albumin, serum prealbumin has a lower molecular mass and shorter half-life (only 2 to 3 days).[13,14] In addition, as an acute phase reaction protein, serum prealbumin responds quickly with high sensitivity, specificity and timeliness. Thus, serum prealbumin is preferred as a meaningful nutritional indicator, because it can reflect the dynamic nutritional status. Serum prealbumin in the TPEN group was higher than in the SPEN group on POD-7. This can be explained by the better tolerance of isotonic or near isotonic TPEN. The ratio of carbohydrate, lipid and protein of TPEN is compatible with dietary standards. The long-term use of SPEN, with its low fat content, may lead to a deficiency of essential fatty acids with its adverse metabolic consequences. Our findings indicate that TPEN, more so than SPEN, can better improve postoperative nutrition.

Gastrointestinal dysfunction is a common postoperative complication. Abdominal exposure can damage the intestinal mucosal barrier and intestinal peristaltic function, and such injury is positively correlated with the time of abdominal exposure.[15,16] Sympathetic excitation, vagus inhibition and gastrointestinal hormone disorder caused by gastrointestinal surgery may impair gastrointestinal function. Anesthesia and analgesia inhibit intestinal transit or at least reduce peristaltic activity.[17] In this stusy, the anal exhaust time of SPEN patients was shorter than that their TPEN counterparts, attributable to short peptide effects the in digestive system. The short peptides can serve as energy substrates for the intestinal mucosal epithelial cells and thus promote intestinal mucosal tissue integrity.[18] Moreover, elemental short peptide

absorption is direct, without digestion, which facilitates intestinal mucosal nourishment and promotes the recovery of intestinal barrier function. Therefore, SPEN is probably the better choice for intestinal function restoration in the early postoperative period, allowing patients to resume oral intake earlier.

However, the incidence of diarrhea in the SPEN group was higher, but that of abdominal distension lower than in the TPEN group. These differences may be partly ascribed to how the feeds manage the increased intestinal mucosal barrier permeability during the postoperative period. The osmotic pressure of the short peptide formula is high, enabling much liquid to enter the enteric cavity and generate pressure differences with malabsorption, and a higher incidence of diarrhea and dehydration. EN should begin with a low concentration and low volume to minimise diarrhea. TPEN must be digested before absorption and utilization; a large residue stays in the gut. The TPEN residue can expand the intestine, increase intestinal wall tension, and cause abdominal distention, whereas SPEN is easily absorbed with less residue and side effects. The postoperative and total hospitalization times for the SPEN group were longer than those for the TPEN group. The length of hospital stay not only depends on the resumption of gastrointestinal function and improved nutritional status, but on the differential gastrointestinal tolerance of the two kinds of EN. SPEN may restore intestinal function earlier, but with diarrhea which may cause fluid and electrolyte loss and intestinal disorder, so prolonging hospitalization time.[19,20] Meanwhile, TPEN improves the patient net nutrition state better, given a digestive tract is broken ,reconstructed and undergoing repair throughout the postoperative period, with loss of digestive function and decreased absorptive capacity of intestinal villi. The relative advantages and disadvantages of TPEN and SPEN in this setting after radical gastrectomy are summarized in Table 5.

Conclusions

The effects of TPEN and SPEN have been evaluated with a focus on postoperative recovery after gastrectomy. The selection of EN highly relies on the recovery stage of surgical operations. In the early postoperative period, pre-digested formula may be preferred because of poor gastrointestinal motility and less secretion of gastrointestinal hormones. After intestinal function is restored, TPEN can improve nutritional status, reduce the postoperative complications and lessen hospital stay time. Thus, SPEN is suitable for early postoperative nutritional management and TPEN for the later postoperative Verification and refinement of this protocol is encouraged.

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AUTHOR DISCLOSURE

The authors declare no conflict of interest.

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Table 1. Demographic and clinical characteristics of patients

Parameters	TPEN group	SPEN group	*p*
Age	60.25±8.83	63.03±9.13	0.090
Sex (%)			0.544
Male	45 (75.00)	41 (68.33)	
Female	15 (25.00)	19 (31.67)	
Operative time (h)	3.24±1.15	3.29±0.90	0.810
intraoperative bleeding (mL)	144.0±97.6	158.6±150.8	0.584
Extent of gastrectomy (%)			0.704
Subtotal	37 (61.67)	40 (66.67)	
Total	23 (38.33)	20 (33.33)	

TPEN: total protein enteral nutrition; SPEN: short peptide enteral nutrition.
Values are means±SD or number of patients (%).

Table 2. Nutrition status of patients before and after surgery

Nutrition indexes	TPEN group	SPEN group	*p*
Total protein (g/L)			
Preoperative	57.04±4.68	57.42±5.12	0.555
POD 1	68.68±6.62	69.68±7.00	0.495
POD 7	63.37±6.16	64.10±5.46	0.449
Serum albumin (g/L)			
Preoperative	43.35±4.38	43.91±3.74	0.420
POD 1	35.50±3.53	36.32±3.64	0.171
POD 7	37.54±3.53	38.06±3.62	0.390
Hemoglobin (g/L)			
Preoperative	139.00 (128.00~151.00)	136.50 (125.50~149.00)	0.474
POD 1	134.00 (120.00~142.00)	124.00 (112.00~133.00)	0.060
POD 7	125.00 (111.00~132.00)	121.00 (108.00~130.00)	0.372
BMI (kg/m2)			
Preoperative	24.17±2.26	24.41±3.52	0.545
POD 1	24.07±2.29	24.25±3.42	0.723
POD 7	23.47±2.23	23.93±3.32	0.382

TPEN: total protein enteral nutrition; SPEN: short peptide enteral nutrition; POD: postoperative day.
Values are means±SD or range [25th-75th percentile].

Table 3. Immune status of patients before and after surgery

Immune indexes	TPEN group	SPEN group	*p*
CD3 (%)			
Preoperative	63.16±9.77	59.96±10.75	0.133
POD 1	53.40±11.98	54.55±13.17	0.658
POD 7	65.31±10.50	63.85±9.24	0.470
CD4 (%)			
Preoperative	42.43±7.79	39.94±9.19	0.158
POD 1	34.07±8.31	34.92±10.88	0.670
POD 7	43.96±8.95	43.90±10.49	0.973
CD8 (%)			
Preoperative	15.65 (12.34~20.48)	17.12 (12.14~23.70)	0.830
POD 1	14.09 (9.42~17.99)	14.88 (10.59~21.70)	0.233
POD 7	21.66 (15.60~37.94)	18.30 (13.40~38.89)	0.624
CD4/CD8			
Preoperative	2.68 (1.89~3.49)	2.57 (1.57~3.61)	0.481
POD 1	2.29 (1.81~3.51)	2.22 (1.39~3.50)	0.401
POD 7	2.01 (1.26~2.67)	1.65 (1.00~3.50)	0.807
IgA (g/L)			
Preoperative	2.31 (1.60~2.79)	2.13 (1.42~2.63)	0.785
POD 1	1.87 (1.49~2.31)	1.78 (1.29~2.19)	0.235
POD 7	2.01 (1.26~2.67)	2.12 (1.47~2.68)	0.442
IgM (g/L)			
Preoperative	0.86 (0.52~1.24)	0.84 (0.55~1.42)	0.148
POD 1	0.61 (0.39~0.92)	0.72 (0.39~1.07)	0.337
POD 7	1.69 (0.99~1.97)	1.40 (0.91~2.33)	0.884
IgG (g/L)			
Preoperative	10.40±3.01	10.59±2.40	0.735
POD 1	8.92±1.75	8.35±1.87	0.135
POD 7	10.17±2.53	9.42±2.19	0.134

TPEN: total protein enteral nutrition; SPEN: short peptide enteral nutrition; POD: postoperative day.
Values are means±SD or range [25th-75th percentile].

Table 4. Postoperative complications and recovery of patients

	TPEN group	SPEN group	*p*
Abdominal distension (%)	17 (28.33)	8 (18.33)	0.043*
Diarrhea (%)	4 (6.67)	12 (20.00)	0.016*
Constipation (%)	18 (30.00)	17 (28.33)	0.841
Pulmonary infection (%)	1 (0.00%)	5 (10.00%)	0.209
Anal exhaust time (h)	67.84 (63.00~88.17)	65.50 (61.25~73.00)	0.020*
Postoperative hospitalization time (d)	11.00 (10.00~12.00)	12.00 (10.00~14.00)	0.005*
Total hospitalization time (d)	17.00 (15.00~19.00)	19.00 (16.00~21.00)	0.027*

TPEN: total protein enteral nutrition; SPEN: short peptide enteral nutrition.
Values are range [25th-75th percentile] or number of patients (%).
*Compared TPEN group with SPEN group, $p<0.05$.

Table 5. Advantages and disadvantages of TPEN and SPEN in patients after radical gastrectomy

Types of EN	Advantages	Disadvantages
TPEN	The isotonic or near isotonic TPEN is well tolerated; The nutritional components are close to the dietary standard; It not only improves tnutritional status, but also shortens hospital stay.	It needs to be digested in the gut before absorption and utilization; Large amounts of digested residues are left in the gut, thus causing abdominal distention.
SPEN	It can promote the development of intestinal mucosal tissue. It can be easily absorbed and utilized with less digestive enzymes and has less residue.	It may lead to higher incidence rate of diarrhea and dehydration because of high osmotic pressure; It may lead to deficiency of essential fatty acids, with low fat.

EN: enteral nutrition; TPEN: total protein enteral nutrition; SPEN: short peptide enteral nutrition.

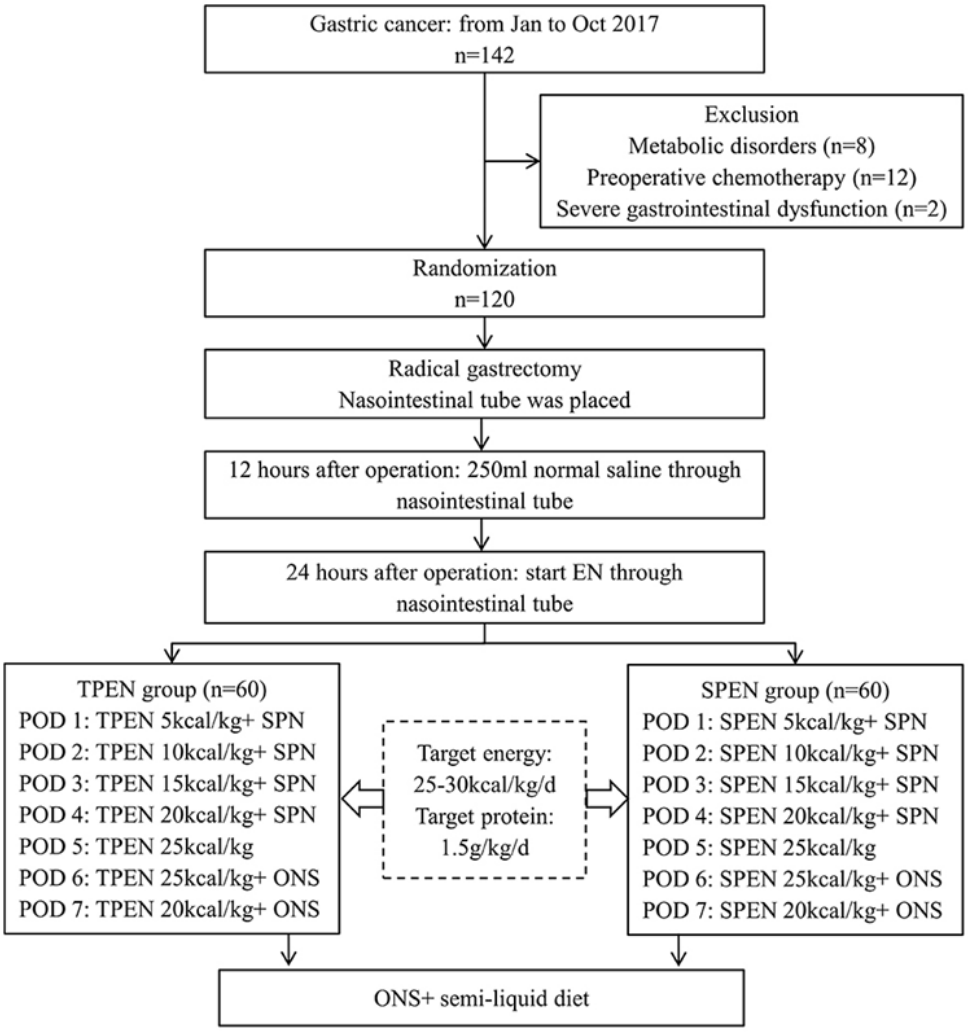

Figure 1. The flow chart of the study. EN: enteral nutrition; TPEN: total protein enteral nutrition; SPEN: short peptide enteral nutrition; SPN: supplemental parenteral nutrition; ONS: oral nutritional supplement.

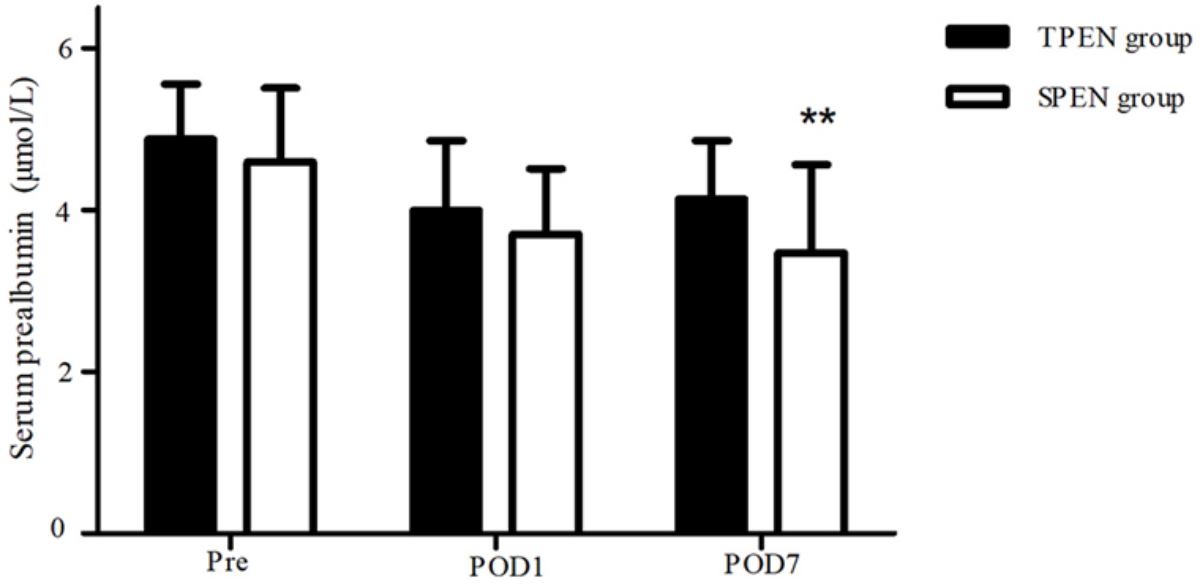

Figure 2. Serum prealbumin of patients preoperatively and postoperatively. Pre: preoperation; POD: postoperative day; TPEN: total protein enteral nutrition; SPEN: short peptide enteral nutrition. **Compared with the TPEN group, $p<0.001$.