Early enteral infusion of traditional Chinese medicine preparation can effectively promote the recovery of gastrointestinal function after esophageal cancer surgery

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ABSTRACT

Objective: To evaluate the effectiveness and safety of the enteral infusion of traditional Chinese medicine (TCM) preparation in promoting the recovery of gastrointestinal function in patients who have received surgery for esophageal cancer.

Methods: Of patients who received surgeries for their esophageal cancers in the Sun Yat-Sen University Cancer Center from October 2009 to July 2011, 100 patients were enrolled and randomly divided into TCM group (n=50) and control group (n=50): in the TCM group, 200 ml home-made TCM preparation was administered via the enteral feeding tube after the enteral nutrition was provided once daily one day after surgery. In the control group, 200 ml normal saline was administered via the enteral feeding tube after the enteral nutrition was provided one day after surgery. Both groups were infused until the gastrointestinal function returned normal. The time to first audible bowel sounds, bowel sound recovery time, time to first flatus, time to first stool, and abdominal symptom score were compared between these two groups.

Results: The time to first audible bowel sounds, bowel sound recovery time, time to first flatus, and time to first stool were 34.68±6.92 h, 60.56±9.188 h, 58.52±8.986 h, and 90.38±15.379 h in the TCM group and 43.04±8.214 h, 68.72±10.180 h, 64.64±10.198 h, and 99.28±15.456 h in the control group ($p=0.002$, $p=0.005$, $p<0.001$, $p<0.001$, respectively).

Conclusions: Early enteral injection of TCM preparation via the enteral feeding tube can effectively and safely promote the recovery of gastrointestinal function after esophageal cancer surgery.

KEY WORDS Esophageal cancer; Surgery; Gastrointestinal function; Traditional Chinese Medicine

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Introduction

Esophageal cancer is a common malignancy (1-2). Every year, about 200,000 people die worldwide from esophageal cancer, making it the sixth most common cause of death from cancer (3-4). Patients with esophageal cancer in China accounted for more than 50% of the world, ranking the No. 4 cause of death of tumor (5).

Surgery is the main treatment of esophageal cancer. However, as an invasive approach, surgery is often accompanied by a variety of complications such as delayed gastrointestinal emptying; the latter mainly includes functional dyspepsia such as bloating, belching, nausea, and vomiting (6-8). The delayed gastrointestinal emptying may be explained by the following reasons (6-8): (i) During the esophageal cancer surgery, removal of the tumor will inevitably cause the injury or disconnection of the vagas nerve; once the stomach loses normal regulations from the vagus nerve, ectopic pacemaker can occur and cause tachygastria, resulting in retroperistalsis and finally causing 'stomach paralysis' or gastric stagnation. (ii) Surgery can activate the inhibitory sympathetic reflex system through a variety of pathways; the activated sympathetic nerve fibers can suppress the gastric motility by inhibiting the excitatory neurons in the

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gastrointestinal plexus; meanwhile, the catecholamines released from its endings can directly bind to the receptors a and b on the gastric smooth muscle cells and thus inhibit the contraction of smooth muscle cells. (iii) After the stomach moves into the thoracic cavity, its anatomical structure and physiological function changes, and the positive pressure inside the stomach and the negative pressure in the thoracic cavity form differential pressure. (iv) The gastrointestinal peptide hormones change after surgery. (v) the use of narcotic drugs during surgery may also influence the gastrointestinal function. And, (vi) esophageal cancer patients are often elderly with diabetes, thyroid dysfunction, and other diseases, which also increase the incidence of delayed gastrointestinal emptying after surgery.

The clinical symptoms are usually mild in most patients and can spontaneously resolve within 3-5 days. However, in some patients they can last 2-3 weeks or longer, and gastroparesis may occur in severe cases (about 3%). The early recovery of gastrointestinal function not only promotes the postoperative rehabilitation, shortens hospital stay, and reduces the financial burden of patients, but also helps to improve the food situation, reduce clinical symptoms, and improve patients' quality of life. Therefore, how to promote recovery of gastrointestinal function after surgery for esophageal cancer has became a hot research topic.

The current management for the recovery of gastrointestinal function after surgery for esophageal cancer, mainly based on modern Western medicine (6-8), includes: routine postoperative indwelling stomach tube; continuous gastrointestinal decompression; fasting; postoperative nutritional support; supplementation of sufficient calories, protein, vitamins and trace elements; infusion of whole blood, plasma, or albumin to correct the negative nitrogen balance, when appropriate; gastric lavage with a warm saltwater solution; and, use of prokinetic agents. However, even after the above treatment, there is still a high percentage of patients may experience delated gastrointestinal emptying or even gastroparesis. Furthermore, the conventional Western medicine-based therapies are often blamed for their high costs, frequent complications, and limited effectiveness. Therefore, the role of TCM in promoting the recovery of gastrointestinal function after surgery for esophageal cancer has increasingly been studied by Chinese researchers. Most TCM-based preparations have mild side effects and low costs. More importantly, TCM-based therapies (including traditional Chinese medicine, acupuncture, and physiotherapy) have been found to be effective in promoting the recovery of gastrointestinal function in both animal experiments and clinical studies. However, most currently available studies are based on personal experiences with small sample size, and few randomized controlled studies on the clinical application of TCM in this aspect have been published.

In our current study, by adopting a prospective randomized controlled clinical trial, we tried to compare the effectiveness and safety of TCM/Western medicine-based therapies with those of conventional modern Western medicine-based therapy and thus evaluate the role of TCM in promoting the recovery of gastrointestinal function after surgery for esophageal cancer.

Patients and Methods

Patient selection

The inclusion criteria were: patients were pathologically confirmed to be with esophageal cancer and were willing to receive surgical treatment; patients were planning to receive postsurgical enteral nutrition via the enteral feeding tube; patients were naive to drugs that may influence the contraction of smooth muscles; and patients voluntarily agreed to participate by signing an Informed Consent.

The exclusion criteria were: patients with intestinal anastomosis after surgery for esophageal cancer; patients with physical allergy or drug allergy; patients with poor compliance, failing to complete the treatment plan or clinical observation; patients with postoperative mechanical intestinal obstruction; patients required a second surgery due to postoperative complications; patients accompanied with diabetes mellitus, connective tissue disease, or hypothyroidism; patients who refused to accept the TCM-based therapies.

Clinical data

Totally 100 patients (71 men and 29 women, aged 38-75 years (median: 62 years)) who received surgery for esophageal cancer in the Sun Yat-Sen University Cancer Center from October 2009 to July 2011 were enrolled in this study. Pathological examination revealed squamous cell carcinoma in 97 cases and adenocarcinoma in 3 cases. The surgical approaches included right chest approach (n=91) and left chest approach (n=9); intrathoracic anastomosis was performed in 10 cases and cervical anastomosis in 90 cases. Patients were equally randomized into TCM group and control group. All patients received post-surgical enteral nutrition via the enteral feeding tube.

Methods

The control group was managed with conventional Western medicine treatment (gastrointestinal decompression, nutritional support, and maintenance of water -electrolyte and acid-base balances) and received enteral nutrition via a enteral feeding tube one day after surgery. In the TCM group, in addition to the conventional Western medicine-based treatment and enteral nutrition support applied in the control group, TCM preparation was also administered via the enteral feeding tube.

Table 1. Means and standard deviations of four indicators in two groups

	TCM group (h)	Control group (h)	P value
Time to first flatus	58.52±8.986	64.64±10.198	0.002
Time to first stool	90.38±15.379	99.28±15.456	0.005
Time to first audible bowel sounds	34.68±6.912	43.04±8.214	<0.001
Time to bowel sounds recovery	60.56±9.188	68.72±10.180	<0.001

TCM preparation

The TCM preparation was effective in "strengthening the spleen and stomach and nourishing Qi and body fluid". Its main components included codonopsis 20g, Yunnan poria 15g, Atractylodes macrocephala 15 g, Radix astragali preparata 30 g, dried tangerine peel 6 g, Pinellia 10 g, jujube 30 g, bergamot 15 g, Gallus gallus domesticus 15 g, white peony root 15 g, prepared rhizome of rehmannia 15 g, and villous amonmum fruit 10 g (decocted later). The preparation was prepared one dose daily by adding 1000 ml water to decoct into a 200 ml potion for 2 takings.

Administration

The enteral feeding tube was placed into the duodenum or the upper segment of jejunum during the resection of esophageal cancer; meanwhile, a gastrointestinal decompression tube was also inserted. Patients in the TCM group were instilled with the enteral nutrition fluid 24 hour after the surgery, and then with TCM preparation (one dose per day; 200 ml, 80 - 100 drops/min, for two infusions), until the recovery of gastrointestinal function. The infusions of enteral nutrition fluid, TCM preparation, and normal saline were all performed using Infusion thermostat. The gastrointestinal decompression tube was not clamped during infusion. The amount and color of the fluids draining from the gastrointestinal decompression tube were carefully observed to determine if reflux was present. The initial infusion rate was set at 30 - 40 drops/min, and might gradually speed up to 80 to 100 drops/min if no adverse reactions such as abdominal pain/bloating existed. In the control group, only enteral nutrition fluid was infused via the enteral feeding tube. No other prokinetic agent was provided in both two groups.

Main measures

The main indicators are defined as follows: (i) time to first flatus: the interval between surgery completion and flatus, based on the patient's subjective feeling. (ii) time to first stool: the interval between completion and stool, subject to the actual time. (iii) time to the first audible bowel sounds: Auscultation (3 min each) was performed every 4 h after surgery, until relatively clear bowel sounds were heard. and (iv) bowel sound recovery time: The time when the bowel sounds were heard 3 times/min during postoperative auscultation. The abdominal symptoms were scored as follows: "Bloating", 1 point; "nausea", 2 points; "vomiting", 3 points; and, free of the above symptoms, 0 points.

Statistical analysis

All data were managed using SPSS 17.0 software. The differences in the first audible bowel sounds, time to bowel sounds recovery, time to first flatus, and time to first stool between these two groups were compared using t test, while the abdominal symptom scores were compared using chi square test. $P<0.05$ was regarded as statistically significant.

Results

Observational results in TCM group and control group

The time to first flatus, and time to first stool, first audible bowel sounds, time to bowel sounds recovery were 41-90 h (58.52±8.986 h), 60-127 h (90.38±15.379 h), 24-60 h (34.68±6.912 h), and 44-90 h (60.56±9.188 h) in the TCM group and 43-98 h (64.64±10.198 h), 69-140 h (99.28±15.456 h), 28-64 h (43.04±8.214 h), and 48-100 h (68.72±10.180 h) in the control group ($P=0.002$, $P=0.005$, $P<0.001$, $P<0.001$, respectively) (Table 1). The results of adnominal symptom scoring in both two groups are shown in Table 2.

Toxicities

No notable TCM preparation-related toxicities were observed during the application of TCM preparation.

Discussion

Esophageal cancer is one of common malignant tumors in China, and surgery is the most common treatment for this disease. Postoperative delayed gastrointestinal emptying is a common clinical symptoms (6-8), mainly as functional dyspepsia, such as bloating, belching, nausea, and vomiting; in severe cases, it can cause long-term gastrointestinal paralysis, intestinal obstruction,

Table 2. Abdominal symptom scores in TCM group and control group

Group	Abdominal symptoms				*P*
	0	1	2	3	
TCM group	32	14	3	1	0.766
Control group	29	14	6	1	

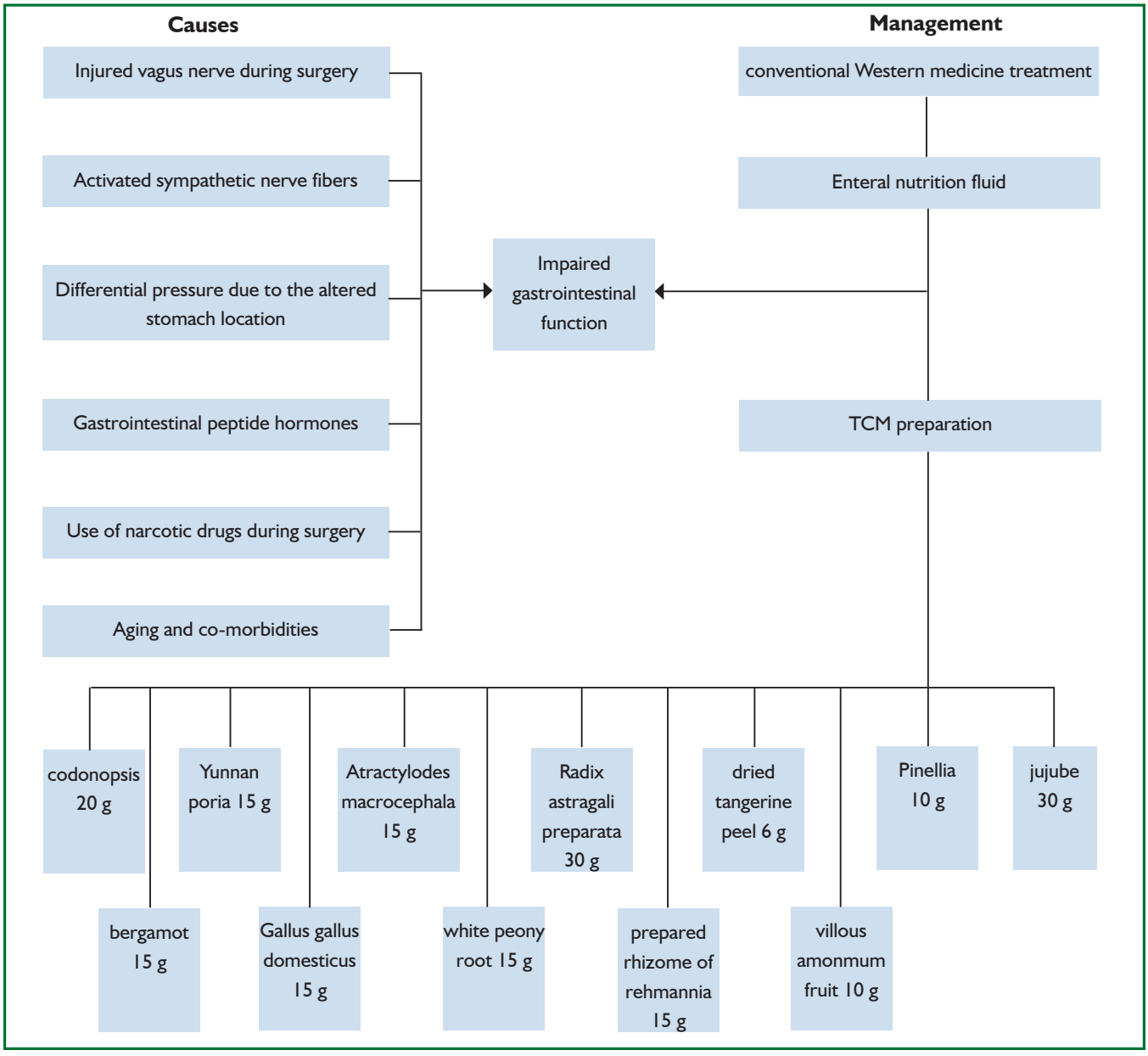

Figure 1. Possible mechanisms of early infusion of TCM preparation in promoting the recovery of gastrointestinal function after esophageal cancer surgery

and even death. The early recovery of gastrointestinal function not only promotes the postoperative rehabilitation, shortens hospital stay, and reduces the financial burden of patients, but also helps to improve the food situation, reduce clinical symptoms, and improve patients' quality of life. Therefore, how to promote recovery of gastrointestinal function after surgery for

esophageal cancer has became a hot research topic.

The current management for the recovery of gastrointestinal function after surgery for esophageal cancer is mainly based on modern Western medicine (6-8). However, even after the above treatment, there is still a high percentage of patients may experience delated gastrointestinal emptying or even gastroparesis, which severely impacted the postoperative rehabilitation, increases pain, and reduces quality of life. Furthermore, the conventional Western medicine-based therapies are often blamed for their high costs, frequent complications, and limited effectiveness. Therefore, the role of TCM in promoting the recovery of gastrointestinal function after surgery for esophageal cancer has increasingly been studied by Chinese researchers.

Most TCM-based preparations have mild side effects and low costs. More importantly, TCM-based therapies (including traditional Chinese medicine, acupuncture, and physiotherapy) have been found to be effective in promoting the recovery of gastrointestinal function in both animal experiments and clinical studies (9-12). Treatment using TCM enema or injection of drug(s) into acupoint Zusanli has shown satisfactory efficacies in adjusting gastrointestinal function and/or promoting the recovery of gastrointestinal function after surgery. According to TCM theories, the esophageal cancer is caused by the deficient and weak "Healthy Qi" and the disordered "Zang" and "Fu" organs. As stated by the Huangdi Neijing ("Yellow Emperor's Inner Canon", circa 2000 BC, an ancient Chinese medical text), "When there is sufficient healthy Qi inside, the pathogenic Qi have no way to invade the healthy body", and, "the pathogenic Qi invades into the body where the healthy Qi must be deficient". The esophageal cancer occurs and develops at the esophagus, which is covered by the gastric Qi.

Patients with esophageal cancer tend to be deficient in both Qi and blood, and therefore the treatment must be focused in "strengthening the spleen and stomach and nourishing the Qi and body fluid". In the TCM preparation, codonopsis, Yunnan poria, Atractylodes macrocephala, and liquorice root, which are also the components of the famous "Decoction of Four Noble Drugs", are used for "strenthening the spleen and nourishing the Qi", which is further enhanced by the usage of a relatively large number of Radix astragali preparata. White peony root is used for "nourishing the blood and harmonizing the nutrients and defense system"; furthermore, it can enhance the prepared rhizome of rehmannia in "benefiting Yin and blood". The dried tangerine peel, pinellia, and villous amonmum fruit are effective in "benefiting Qi and harmonizing the stomach" or, "promoting Qi and warming the spleen and stomach". The bergamot is beneficial for "promoting qi circulation to relieve pain". The jujube can benefit the spleen and stomach and nourish the blood. The Gallus gallus domesticus can invigorating spleen to promote digestion. The whole preparation is effective for "strengthening the spleen and stomach and nourishing Qi and body fluid", particularly for patients who have just received a major surgery.

Also as shown in our current study, the time required for the first audible bowel sounds and bowel sound recovery were significantly shorter in TCM group than in control group. Meanwhile, the time to first flatus and time to first stool were also significantly earlier in TCM group. The abdominal symptoms showed no significant differences between these two groups. These results indicate that the application of the TCD preparation in our study can promote postoperative recovery of gastrointestinal function without causing more abdominal symptoms. Our findings are consistent with domestic and foreign literature (7-14). Meanwhile, this study showed no increase of TCM-related side effects in the TCM group, indicating that this TCM preparation is safe in promoting the postoperative recovery of gastrointestinal function (Figure 1).

Literatures have shown that there are various approaches for the administration of TCM preparations: oral administration, enema, injection into into acupoint Zusanli, infusion via gastric tube, and others (8-12,14). According to our experiences, infusion of TCM preparation via the enteral feeding tube may be superior because it has advantages including mild pain, fast enteral absorption, and rapid onset; meanwhile, it meets the requirement that the patient needs to be fasted after surgery for esophageal cancer.

In summary, early infusion of TCM preparation via the enteral feeding tube after surgery for esophageal cancer can remarkably promote the recovery of gastrointestinal function without causing additional abdominal symptoms and toxicities.

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