Modified Dachengqi Tang improves decreased gastrointestinal motility in postoperative esophageal cancer patients

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Abstract

OBJECTIVE: To investigate the clinical effects of modified Dachengqi Tang (DCQT) on promoting gastrointestinal motility in post-operative esophageal cancer patients.

METHODS: Sixty postoperative esophageal cancer patients were enrolled and randomly assigned to the modified treatment group or the control group (30 patients in each group). Patients in the treatment group were given DCQT made from decocted herbs and administered via nasojejunal tube at a dosage of 150 mL. Gastrointestinal motility was assessed by recording time for recovery of bowel sounds, flatus, defecation, and the total amount of gastric drainage during the first three postoperative days. Plasma motilin (MTL) and vasoactive intestinal peptide (VIP) were measured one hour before and three days after surgery.

RESULTS: Compared with the control group, the times to first bowel sound, flatus, and defecation were significantly shorter and there was less gastric drainage in the treatment group (P < 0.01, P < 0.01, P < 0.01, and P < 0.05, respectively). In the treatment group, postoperative plasma MTL was significantly higher (P < 0.01) and VIP was significantly lower than those in the control group (P < 0.05). There was no difference found in either MTL or VIP from before to after operation in the treatment group (P > 0.05). MTL was significantly lower and VIP was higher postoperatively in the control group, compared to before surgery (P < 0.01).

CONCLUSION: Modified DCQT effectively improved decreased gastrointestinal motility in postoperative esophageal cancer patients by increasing MTL and reducing VIP.

INTRODUCTION

Esophageal cancer is a common malignancy, and the morbidity is increasing yearly. Each year about 200 000
people die from esophageal cancer, which makes it the eighth leading cause of morbidity and sixth leading cause of mortality worldwide. Early surgery is the main treatment for esophageal cancer. However, it tends to induce temporary gastrointestinal dysfunction which is characterized by abdominal distension, belly-ache, nausea, vomiting, weak bowel sounds, and delayed defecation. In some cases, acute gastroparesis and paralytic ileus may occur, which might result in death. Lee et al. reported that 50% of esophagectomy patients showed significantly delayed gastric emptying in the early stage after surgery. These disorders prolong recovery, increase discomfort, and increase hospitalization costs because of additional recovery days. Therefore, promoting gastrointestinal motility after surgery in affected patients is important to decreasing complications and improving prognosis. The etiology of post-operative gastrointestinal dysfunction is unclear and attributed to multiple mechanisms. The mechanisms may include inhibitory sympathetic input, injury or disconnection of the vagus nerve, release of hormones or neurotransmitters, effects of anesthesia or analgesics, negative pressure in the thoracic cavity, psychological stress like anxiety and tension, or inflammatory reactions. Various methods have been used to promote gastrointestinal motility in the clinical setting without much success. The current management for gastrointestinal motility recovery after esophageal cancer surgery uses Western Medicine, includes: routine postoperative indwelling stomach tube; continuous gastrointestinal decompression; fasting; postoperative nutritional support; gastric lavage with a warm saltwater solution; and, use of prokinetic agents. However, the treatments are often expensive and have frequent complications. Therefore, mild and economical Traditional Chinese Medicine (TCM) that can promote the recovery of gastrointestinal function are being increasingly studied. Dachengqi Tang (DCQT), first documented in the classical TCM pharmacopoeia Treatise on Fevers, is an herbal prescription composed of four component herbs or minerals: Dahuang (Radix Et Rhizoma Rhei Palmati) 10 g, Mangxiao (Nalrii Sulfas) 5 g, Houpu (Cortex Magnoliae Officinalis) 15 g, Zhishi (Fructus Aurantii Immaturus) 15 g, Danggui (Radix Angelicae Sinensis) 15 g, Huangqi (Radix Astragali Mongolic) 15 g, Chishao (Radix Paeoniae Rubra) 15 g, and Wuyao (Radix Linderae Agregatae) 10 g. The air-dried herbs were purchased from the Pharmacy Department of the Affiliated Hospital of Shandong University of Traditional Chinese Medicine (Shandong, China). All herbs except Mangxiao (Nalrii Sulfas) were soaked in 500 mL cold water for 1 h. The rhubarb was soaked separately. Herbs were decocted with gentle heat for 15 min. Then, rhubarb and 200 mL cold water were added and filtered to yield the decoction. Finally, the Mangxiao (Nalrii Sulfas) was dissolved in the decoction and the solution was concentrated. The final yield of the prepared decoction was 150 mL, which was stored in a sterile package at 4 °C.

MATERIALS AND METHODS

Patients

Patients were recruited from the Thoracic Surgery Department of Shandong Provincial Tumor Hospital. Patients who met all the following criteria were recruited in this study: age range from 18 to 75 years old; confirmed diagnosis and resection of esophageal cancer according to NCCN guidelines; enteral nutrition being given via a nasal feeding tube after surgery; and compliance to treatment. Those who met one of the following criteria were excluded: an existing intestinal anastomosis after surgery; allergies; poor compliance, indicated by taking less than 80% or more than 120% of the prescribed medication; or receiving medicine or other treatment promoting gastrointestinal function. Sixty patients from March to July 2010 were selected and consecutively numbered according to their admission time. Patients were randomly divided into a treatment and control group with 30 patients in each according to a random number table. In the treatment group, there were 23 males and 7 females with a mean age of (60 ± 3) years (range 49 to 67 years). In the treatment group, 9 patients underwent intrathoracic anastomosis and 21 underwent cervical anastomosis. In the control group, there were 24 males and 6 females with a mean age of (60 ± 7) years (range 42 to 77 years). The control group had 6 patients that underwent intrathoracic anastomosis and 24 that underwent cervical anastomosis. There were no significant differences between the treatment and control groups in sex, age, or surgical approach. This clinical study was approved by the Medical Ethics and Human Clinical Trial Committee, and was conducted in accordance with the guidelines of the Declaration of Helsinki. All participants were clearly informed and consented.

Preparation of modified DCQT

A single dosage of modified DCQT consisted of Dahuang (Radix Et Rhizoma Rhei Palmati) 10 g, Mangxiao (Nalrii Sulfas) 5 g, Houpu (Cortex Magnoliae Officinalis) 15 g, Zhishi (Fructus Aurantii Immaturus) 15 g, Danggui (Radix Angelicae Sinensis) 15 g, Huangqi (Radix Astragali Mongolic) 15 g, Chishao (Radix Paeoniae Rubra) 15 g, and Wuyao (Radix Linderae Agregatae) 10 g. The air-dried herbs were purchased from the Pharmacy Department of the Affiliated Hospital of Shandong University of Traditional Chinese Medicine (Shandong, China). All herbs except Mangxiao (Nalrii Sulfas) were soaked in 500 mL cold water for 1 h. The rhubarb was soaked separately. Herbs were decocted with gentle heat for 15 min. Then, rhubarb and 200 mL cold water were added and filtered to yield the decoction. Finally, the Mangxiao (Nalrii Sulfas) was dissolved in the decoction and the solution was concentrated. The final yield of the prepared decoction was 150 mL, which was stored in a sterile package at 4 °C.

Treatments

All patients received esophageal cancer resection and esophagus-stomach anastomosis (intrathoracic anastomosis or cervical anastomosis). After surgery, all patients were given routine therapies, including fasting, gastrointestinal decompression, antibiotics, and enteral nutrition. Each patient in the treatment group was giv-
en a daily single dose of 150 mL DCQT on the morning of the first, second, and third day after the first enteral nutrition was provided 24 h after surgery. The decoction was infused through a nasojejunal feeding tube at 37 °C with the infusing thermostat at a speed of 80-100 drops per minute. The same regimen was followed in the controls, except that modified DCQT was replaced by 150 mL normal saline. No other medication affecting gastrointestinal motility was given to either group. During the infusion, all patients were closely observed for any adverse effects such as diarrhea, bel-lyache, or abdominal distention.

**Experimental methods**

The time to restoration of flatus, defecation, and intestinal sounds after surgery were recorded. The intestinal sound restoration was defined as at least three clear bowel sounds after surgery were recorded. The intestinal sounds in the 3 days after surgery was measured. The plasma concentrations of motilin (MTL) and vasoactive intestinal peptide (VIP) were measured separately with test tubes containing 40 µL of trasylol and 30 µL Na2-ethylen diamine tetraacetic acid (EDTA). The samples were centrifuged immediately at 3000 rpm (1500 × g) and 4 °C for 10 min and the separated serum was stored at -80 °C for subsequent analysis. Before measurement, the cryopreserved plasma was thawed at room temperature and centrifuged at 3000 rpm and 4 °C for 5 min for radioimmunoassay with an intelligence γ-radioimmunoassay measuring instrument. The radioimmunoassay kit was supplied by the Beijing Puerweiye Biotechnology Company (Beijing, China). The SN-695B intelligence γ-radioimmunoassay apparatus was produced in the First Ring Instrument Factory affiliated to Shanghai Institute of Nuclear Research (Shanghai, China).

**Statistical analysis**

SPSS 13.0 (SPSS Inc., Chicago, IL, USA) was used for data analysis. Data were expressed as mean ± standard deviation (±). T-tests were conducted for differences between groups. P < 0.05 was considered significant.

<table>
<thead>
<tr>
<th>Indicator</th>
<th>Treatment group (n=30)</th>
<th>Control group (n=30)</th>
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<tbody>
<tr>
<td>Time to first flatus (h)</td>
<td>58±8</td>
<td>65±6</td>
</tr>
<tr>
<td>Time to first defecation (h)</td>
<td>97±10</td>
<td>113±12</td>
</tr>
<tr>
<td>Time to bowel sounds restoration (h)</td>
<td>34±6</td>
<td>43±7</td>
</tr>
<tr>
<td>Total gastric drainage (mL)</td>
<td>643±187</td>
<td>777±229</td>
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Notes: control group was treated with routine therapies (fasting, gastrointestinal decompression, antibiotics, and enteral nutrition); treatment group was given a daily single dose of 150 mL modified Dachengqi Tang on the morning of the first, second, and third day after the first enteral nutrition was provided 24 h after surgery.

**RESULTS**

The restoration of flatus, defecation, and intestinal sounds in the treatment group occurred much more quickly than those in the control group (P < 0.01, Table 1). There was significantly less total drainage in the treatment group than that in the control group (P < 0.05, Table 1). Among all the participants, only one woman in the treatment group had diarrhea on the end of the fourth day, which recovered quickly after discontinuing therapy.

There was no significant difference in preoperative plasma MTL or VIP concentrations between the treatment and control groups (both P > 0.05). The postoperative MTL was significantly higher and postoperative VIP was significantly lower in the treatment group compared with the control group (P < 0.01, P < 0.05). No significant differences in MTL or VIP were found from before to after surgery within the treatment group (both P > 0.05). However, the postoperative MTL was significantly lower and VIP was significantly higher than preoperative values in the control group (both P < 0.05) (Table 2).

**DISCUSSION**

According to TCM theory, decreased gastrointestinal motility in postoperative esophageal cancer patients results from Qi and blood stagnation and disordered Zang and Fu organs (i.e. lung, spleen, kidney, heart, stomach, small intestine, and large intestine). Therefore, TCM treatment aims to remove stasis to promote the flow of Qi and activate blood circulation, restore Zang and Fu organs, and purge and dispel toxins and excess heat. DCQT is mainly composed of Da-huang (Radix Et Rhizoma Rhei Palmati), Mangxiao (Nalrii Sulfa), Houpu (Cortex Magnoliae Officinalis), and Zhishi (Fructus Aurantii Immaturi). The decoction aims to unblock interior Qi and purge heat to improve bowel movement. The Dahuang (Radix Et Rhizoma Rhei Palmati)15-17 and Mangxiao (Nalrii Sulfa)18 dispel excess internal heat and toxins, soften hard masses, and purge and cleanse the gastrointestinal tract. However, postoperative esophageal cancer patients tend to be weak and deficient in both Qi and blood, so catharsis should be mild. Therefore, we lowered the ca-
Datharta drugs Dahuang (Radix Et Rhizaoma Rhei Palmati) from 12 to 10 g and Mangxiao (Neluri Sulphas) from 9 to 5 g. DCQT also includes Houpu (Cortex Magnoliae Officinalis) to promote Qi circulation, eliminate dampness, and relieve dyspepsia. Zhishi (Fructus Auranti Immatura) eliminates phlegm and stasis,19 and Danggu (Angelica sinensis) nourishes and activates blood, relieves pain, and lubricates and tonifies the intestine. Huangqi (Radix Astragali Mongolici) is added to DCQT for Qi tonification and Yang lifting.20 Chishao (Radix Paonieae Rubra) is added to clear heat, cool blood, and eliminate stasis to alleviate pain.20 Finally, Wuwaoy (Radix Linderae Aggregatae) is used to promote Qi circulation and relieve pain.21,22 In addition to the pharmacological effect of the herbs, the monosaccharides, polysaccharides, and electrolytes contained in the decoction also provide nutrients for the gastrointestinal mucosa. Overall, DCQT unblocks interior Qi and nourishes the Zang and Fu organs, particularly for those who have just undergone major surgery.

We found that DCQT dramatically improved patient postoperative condition as demonstrated by clinical symptoms and laboratory indexes. Flatus, defecation, and intestinal sounds were restored much more quickly in the treatment group than in the control group. Meanwhile, there was significantly less gastric drainage in the treatment group compared with the control group. Therefore, modified DCQT improved gastrointestinal motility after surgery, which is consistent with other studies.23,25 Among all treatment patients, only one woman had diarrhea on the fourth day, which recovered soon after discontinuing DCQT treatment. This suggests that DCQT treatment is relatively safe, but the specific dosage for individuals should be further investigated.

Gastrointestinal motility is modulated by several hormones. MTL, a polypeptide hormone containing 22 amino acids, is secreted by endocrine M cells and acts at motilin receptors to promote gastrointestinal motility by stimulating migrating myoelectric complex phase III and pepsin production.26-30 Studies have shown that motilin receptor agonists ameliorated functional dyspepsia by increasing the level of plasma motilin.31,32 Lu et al.33 found that plasma MTL levels in preoperative esophageal cancer patients were higher compared with normal people, and MTL levels increased gradually with the development of cancer. In this study, no differences in MTL levels were found between esophageal cancer patients and healthy patients. This may be because patients had earlier stage esophageal cancer, or the small sample size was too small. Experimental results indicate that the postoperative level of plasma MTL was significantly higher in the treatment group than that in the control group, but there was no significant difference between the two groups preoperatively. The postoperative level of MTL was significantly lower than the preoperative level in the control group but not the treatment group. These MTL results indicate that gastrointestinal motility recovered earlier in the treatment group.

VIP, a 28-amino acid polypeptide acting at G-protein-coupled receptors in the gastrointestinal tract,36 induces intestinal smooth muscle relaxation, stimulates water and bicarbonate secretion, and inhibits secretion of gastric acid and pepsin.37 One animal study found that VIP has an inhibitory effect on gastrointestinal motility and gastric emptying.37 In this study, VIP was significantly lower in the treatment group compared with the control group postoperatively while there was no significant difference between the two groups preoperatively. The level of plasma VIP was significantly higher after surgery in the control group but not the treatment group. Therefore, postoperative gastrointestinal motility was suppressed in the control group, but not the treatment group. DCQT promoted gastrointestinal motility after esophageal cancer resection by improving MTL and reducing VIP, which is in accordance with previous study.36 Studies have shown that there are various approaches for DCQT administration, including oral administration, enema, or nasal feeding.27-31 We found that nasal feeding via nasojejunal tube may be superior because of higher tolerance, lower risk of reflux, and faster absorption.

DCQT significantly promoted gastrointestinal motility in postoperative esophageal cancer patients by improv...
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REFERENCES


