



Retrospective Study

Therapeutic effect of Wendan Decoction combined with mosapride on gastroesophageal reflux disease after esophageal cancer surgery

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Abstract

BACKGROUND

Gastroesophageal reflux disease (GERD) is a common complication of esophageal cancer surgery that can affect quality of life and increase the risk of esophageal stricture and anastomotic leakage. Wendan Decoction (WDD) is a traditional Chinese herbal formula used to treat various gastrointestinal disorders, such as gastritis, functional dyspepsia, and irritable bowel syndrome. Mosapride, a prokinetic agent, functions as a selective 5-hydroxytryptamine 4 agonist, enhancing gastrointestinal motility.

AIM

To evaluate the therapeutic effects of WDD combined with mosapride on GERD after esophageal cancer surgery.

METHODS

Eighty patients with GERD were randomly divided into treatment (receiving WDD combined with mosapride) and control (receiving mosapride alone) groups. The treatment was conducted from January 2021 to January 2023. The primary outcome was improved GERD symptoms as measured using the reflux disease questionnaire (RDQ). The secondary outcomes were improved esophageal motility (measured using esophageal manometry), gastric emptying (measured using gastric scintigraphy), and quality of life [measured *via* the Short Form-36 (SF-36) Health Survey].

RESULTS

The treatment group showed a notably reduced RDQ score and improved esophageal motility parameters, such as lower esophageal sphincter pressure, peristaltic amplitude, and peristaltic velocity compared to the control group. The treatment group showed significantly higher gastric emptying rates and SF-36 scores (in both physical and mental domains) compared to the control group. No serious adverse effects were observed in either group.

CONCLUSION

WDD combined with mosapride is an effective and safe therapy for GERD after esophageal cancer surgery. It can improve GERD symptoms, esophageal motility, gastric emptying, and the quality of life of patients. Further studies with larger sample sizes and longer follow-up periods are required to confirm these findings.

Key Words: Gastroesophageal reflux disease; Esophageal cancer surgery; Wendan Decoction; Mosapride; Treatment effects; Gastroesophageal reflux disease symptoms

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Core Tip: This study suggests that combining Wendan Decoction with mosapride is an effective and safe therapy for managing gastroesophageal reflux disease (GERD) after esophageal cancer surgery. It improves GERD symptoms, esophageal motility, gastric emptying, and the quality of life of patients. Larger studies with longer follow-up periods are needed to further validate these findings.

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INTRODUCTION

Esophageal cancer is a common malignant tumor of the digestive tract with high incidence and mortality rates worldwide, seriously affecting the quality of life and prognosis of patients[1]. The treatment of esophageal cancer includes surgery, radiotherapy, and chemotherapy, among which surgery is one of the most effective radical methods[2]. However, the postoperative complication rate of esophageal cancer is high, with gastroesophageal reflux disease (GERD) being the most common. GERD refers to a series of symptoms and complications, such as heartburn, acid regurgitation, retrosternal pain, dysphagia, esophagitis, esophageal ulcer, esophageal stricture, hiatal hernia, caused by the reflux of gastric contents into the esophagus[3,4]. GERD not only affects the quality of life of patients but also increases the risk of anastomotic leakage and stricture and may even lead to the recurrence and metastasis of esophageal cancer.

Currently, drugs for treating GERD mainly include proton pump inhibitors (PPI), H₂ receptor antagonists (H₂RA), and prokinetic agents[5]. Prokinetic agents can enhance the motility of the gastrointestinal tract, accelerate gastric emptying, and reduce the stimulation of gastric contents in the esophagus. Mosapride is a selective 5-hydroxytryptamine 4 (5-HT₄) receptor agonist that can increase the intracellular calcium ion concentration in gastrointestinal smooth muscle cells by stimulating 5-HT₄ receptors, thereby enhancing peristalsis and tension in the gastrointestinal tract. Mosapride has been widely used in the treatment of various digestive system diseases, such as functional dyspepsia and constipation, and some clinical studies have shown that mosapride has a therapeutic effect on GERD after esophageal cancer surgery[6].

Wendan Decoction (WDD) is a traditional Chinese herbal formula composed of five herbs: *Poria cocos*, *Citrus reticulata*, *Pinellia ternata*, *Zingiber officinale*, and *Aurantium fructus*[7]. It warms the middle, regulates qi, resolves phlegm, and opens the orifices. WDD is mainly used to treat neurological and psychiatric diseases caused by cold spleen-stomach deficiency, qi stagnation, and phlegm obstruction, such as coma, epilepsy, convulsion[8]. In recent years, WDD has been used to treat various digestive system diseases, such as chronic gastritis, functional dyspepsia, and irritable bowel syndrome[7]. WDD can improve the digestive and absorptive function of the gastrointestinal tract by warming the spleen and stomach, regulating qi flow, dissolving sticky food retention, thereby relieving indigestion and reflux symptoms. This study aimed to evaluate the therapeutic effect of WDD combined with mosapride on GERD after esophageal cancer surgery.

MATERIALS AND METHODS

Study design and approval

This experiment was conducted at the Beijing Integrated Traditional Chinese and Western Medicine Hospital in China. The research protocol was approved by the hospital ethics committee, and all patients provided written informed consent before participating in the study.

Inclusion and exclusion criteria

This study included patients: (1) Who underwent esophagectomy for esophageal cancer with anastomosis of the stomach and cervical esophagus; (2) who developed GERD symptoms, such as heartburn, acid regurgitation, retrosternal pain, or dysphagia, within 6 months after surgery; (3) with a reflux disease questionnaire (RDQ) score of > 12 points; (4) aged between 18 and 75 years; and (5) with no contraindications to WDD or mosapride. The exclusion criteria were as follows:

(1) patients with severe complications after surgery, such as anastomotic leakage, bleeding, infection, or fistula; (2) patients with other gastrointestinal diseases, such as peptic ulcer, gastric cancer, or inflammatory bowel disease; (3) patients with severe diseases, such as liver cirrhosis, renal failure, or cardiovascular disease; (4) pregnant or lactating females; (5) individuals allergic to WDD or mosapride; and (6) patients taking drugs that could affect the gastrointestinal motility or acid secretion, such as PPI, H2RA, anticholinergics, opioids.

Randomization and intervention

Eligible patients were randomly assigned to either the treatment or control group using a computer-generated random number table. The allocation ratio was set at 1:1. The treatment group received WDD in combination with mosapride, whereas the control group received mosapride alone. The treatment was conducted from January 2021 to January 2023. The dosage and administration of WDD and mosapride were as follows: WDD was prepared by decocting 15 g *Poria cocos*, 10 g *Citrus reticulata*, 9 g *Pinellia ternata*, 6 g *Zingiber officinale*, and 6 g *Aurantium fructus* in 300 mL water for 30 min. The decoction was divided into two doses and administered orally twice daily before breakfast and dinner. Mosapride was administered orally at a dose of 5 mg three times daily before each meal. Patient compliance was monitored by counting the remaining pills and decoction bags at each follow-up visit.

Outcome measures

The primary outcome was improvement in GERD symptoms, as measured with the RDQ. The RDQ is a self-administered questionnaire consisting of 12 items covering four domains: Heartburn, regurgitation, chest pain, and dysphagia. Each item is rated on a six-point Likert scale ranging from 0 (no symptoms) to 5 (very severe symptoms). The total score ranges from 0 to 60 points, with higher scores indicating more severe symptoms. The RDQ was administered at baseline and every 6 months during the follow-up period.

The secondary outcomes were improvement in esophageal motility function, measured using esophageal manometry; gastric emptying function, measured using gastric scintigraphy; and quality of life, as measured with the Short Form-36 (SF-36) Health Survey. Esophageal manometry measures the pressure and coordination of the esophageal muscles during swallowing. It can provide information on lower esophageal sphincter pressure (LESP), peristaltic amplitude (PA), and peristaltic velocity (PV). It can provide information on the gastric emptying half-life (GEHT), the time required for half of a test meal to leave the stomach. The SF-36 is a self-administered questionnaire that assesses eight domains of health-related quality of life: Physical functioning, role-physical, bodily pain, general health, vitality, social functioning, role-emotional, and mental health. Each domain was scored from 0 to 100 points, with higher scores indicating a better quality of life. Esophageal manometry, gastric scintigraphy, and the SF-36 Health Survey were performed at baseline and at the end of the follow-up period.

Sample size calculation

The sample size was calculated based on the primary outcomes. According to previous studies^[9], the mean RDQ score of patients with GERD after esophageal cancer surgery is approximately 25 points, with a standard deviation of approximately 10 points. Assuming a significance level of 0.05, power of 0.80, and mean difference of 5 points between the two groups, the required sample size was 34 patients per group. Considering a dropout rate of 20%, the final sample size was 40 patients per group.

Data analysis

Data were analyzed using SPSS 22.0. The baseline characteristics of the patients were compared using *t*- or chi-square test, as appropriate. Changes in the RDQ and SF-36 scores over time were analyzed using repeated-measures analysis of variance (ANOVA), with group, time, and group-by-time interactions as factors. Changes in esophageal manometry and gastric scintigraphy parameters from baseline to the end of the follow-up period were compared using the *t*- or Mann-Whitney *U* test, as appropriate. The significance level was set at $P < 0.05$.

RESULTS

Patient enrollment and characteristics

Eighty patients were enrolled in the study and were randomly and equally assigned to each group. The baseline patient characteristics are shown in Table 1. No significant differences were observed between the two groups in terms of age, sex, tumor stage, surgical approach, or RDQ score.

RDQ score over time

The changes in the RDQ scores over time are shown in Table 2. Repeated-measures ANOVA revealed a significant group-by-time interaction effect on the RDQ score ($F = 5.32$, $P < 0.01$), indicating that the treatment group had a greater improvement in GERD symptoms than the control group over time. *Post hoc* tests showed that the treatment group had a significantly lower RDQ score than the control group at each time point after baseline ($P < 0.05$).

Esophageal manometry and gastric emptying

The changes in esophageal manometry parameters from baseline to the end of the follow-up period are shown in Table 3. The *t*- or Mann-Whitney *U* test showed that the treatment group had significantly higher LESP, PA, and PV than the

Table 1 Baseline characteristics of patients

Variable	Treatment group (n = 40)	Control group (n = 40)	P value
Age (yr)	58.3 ± 9.2	57.6 ± 8.7	0.68
Sex (male/female)	28/12	26/14	0.67
Tumor stage (I/II/III)	10/18/12	12/16/12	0.81
Surgical approach (open/thoracoscopic)	22/18	24/16	0.69
RDQ score	25.4 ± 9.8	24.8 ± 10.2	0.76

RDQ: Reflux disease questionnaire.

Table 2 Changes in the reflux disease questionnaire score over time

Time	Treatment group (n = 40)	Control group (n = 40)	P value
Baseline	25.4 ± 9.8	24.8 ± 10.2	0.76
6 months	18.2 ± 8.6 ^a	21.6 ± 9.4 ^a	< 0.05
12 months	14.6 ± 7.8 ^a	18.4 ± 8.2 ^a	< 0.05
18 months	12.4 ± 7.2 ^a	16.2 ± 7.6 ^a	< 0.05
24 months	10.2 ± 6.4 ^a	14.8 ± 7.4 ^a	< 0.05

^aP < 0.05, compared with baseline within each group.

Table 3 Changes in the esophageal manometry parameters from baseline to the end of the follow-up period

Variable	Treatment group (n = 40)	Control group (n = 40)	P value
LESP (mmHg)	Baseline: 11.2 ± 3.4	Baseline: 10.8 ± 3.6	< 0.01
	End: 15.6 ± 4.2 ^a	End: 12.4 ± 3.8 ^a	
PA (mmHg)	Baseline: 38.6 ± 11.2	Baseline: 37.4 ± 10.8	< 0.01
	End: 52.4 ± 12.6 ^a	End: 41.2 ± 11.4 ^a	
PV (cm/s)	Baseline: 2.8 ± 0.9	Baseline: 2.7 ± 0.8	< 0.01
	End: 3.6 ± 1.1 ^a	End: 2.9 ± 0.9 ^a	

^aP < 0.05, compared with baseline within each group.

LESP: Lower esophageal sphincter pressure; PA: Peristaltic amplitude; PV: Peristaltic velocity.

control group at the end of the follow-up period ($P < 0.05$).

Changes in gastric emptying function

Changes in gastric emptying function from baseline to the end of the follow-up period are shown in Table 4. The *t*-test showed that the treatment group had a significantly lower GEHT than the control group at the end of the follow-up period ($P < 0.05$).

SF-36 score over time

Changes in SF-36 scores over time are shown in Table 5. The repeated measures ANOVA indicated a significant group-by-time interaction effect on both the physical and mental domains of the SF-36 score ($F = 6.24$, $P < 0.01$ for the physical domain; $F = 4.56$, $P < 0.01$ for the mental domain). This implies that, over time, the treatment group experienced a more substantial improvement in quality of life than the control group. *Post hoc* tests corroborated that at each subsequent time point, the treatment group registered a significantly higher SF-36 score than the control group in both the physical and mental domains.

Table 4 Changes in the gastric emptying function from baseline to the end of the follow-up period			
Variable	Treatment group (n = 40)	Control group (n = 40)	P value
GEHT (min)	Baseline: 76.4 ± 18.6	Baseline: 75.6 ± 19.2	< 0.05
	End: 58.2 ± 15.4 ^a	End: 68.4 ± 16.8 ^a	

^aP < 0.05, compared with baseline within each group.
GEHT: Gastric emptying half-life.

Table 5 Changes in the Short Form-36 score over time			
Time	Treatment group (n = 40)	Control group (n = 40)	P value (physical/mental)
Physical domain	Baseline: 72.4 ± 15.6	Baseline: 71.6 ± 16.2	< 0.05
	End: 82.6 ± 14.2 ^a	End: 76.4 ± 15.8 ^a	
Mental domain	Baseline: 68.2 ± 13.4	Baseline: 67.4 ± 14.2	< 0.05
	End: 78.4 ± 12.6 ^a	End: 72.2 ± 13.8 ^a	

^aP < 0.05, compared with baseline within each group.

DISCUSSION

This study assessed the therapeutic effect of WDD combined with mosapride on GERD post-esophageal cancer surgery, finding that the combination significantly improves GERD symptoms, esophageal motility function, gastric emptying function, and quality of life and is safe. These results are consistent with those of previous studies and provide innovative ideas and evidence for the integrated treatment of GERD after esophageal cancer surgery[10-14].

WDD is a traditional Chinese herbal formula, and its main mechanism of action may be related to the various aspects. First, WDD can warm the spleen and stomach, regulate qi flow, dissolve sticky food retention, and improve the digestive and absorptive functions of the gastrointestinal tract, thereby relieving indigestion and reflux symptoms. Second, WDD can reduce gastric acid secretion and increase mucus secretion by lowering stomach pH and increasing bicarbonate concentration, thus protecting the esophageal mucosa from stimulation and damage by gastric contents. Third, WDD inhibited inflammatory cytokines and oxidative stress, thereby reducing the inflammatory response and oxidative damage to the esophageal mucosa. Fourth, WDD can regulate the nervous and endocrine systems, improve the tension and coordination of the lower esophageal sphincter, and prevent the reflux of gastric contents[15-17].

Mosapride is a selective 5-HT₄ receptor agonist, and its main mechanism of action may be related to the following. First, mosapride can increase the intracellular calcium ion concentration of gastrointestinal smooth muscle cells by stimulating 5-HT₄ receptors, thereby enhancing the peristalsis and tension of the gastrointestinal tract. Second, mosapride can promote gastric emptying, thereby reducing the stimulation time and the degree of gastric content in the esophagus. Third, mosapride can increase lower esophageal sphincter pressure by stimulating 5-HT₄ receptors on cholinergic neurons in the myenteric plexus, preventing the reflux of gastric contents. Fourth, mosapride can inhibit 5-HT₃ receptors, reducing adverse reactions such as nausea and vomiting[18-20].

The therapeutic effect of WDD combined with mosapride on GERD after esophageal cancer surgery may be due to their synergistic effect, which can adjust the spleen-stomach function from the perspective of traditional Chinese medicine theory and improve gastrointestinal motility function from the perspective of Western medicine theory, thus comprehensively intervening in the occurrence and development of GERD[21,22]. The novelty of this study is that it is the first to apply WDD combined with mosapride to treat GERD after esophageal cancer surgery and to use multiple evaluation indicators for a comprehensive assessment, providing innovative data and insights for this field.

This study has some limitations, such as a small sample size, short follow-up duration, and lack of a placebo control group. Therefore, further large-scale, long-term follow-up, multicenter, double-blind, placebo-controlled clinical trials are needed to verify the results of this study and explore the mechanism and optimization scheme of WDD combined with mosapride for the treatment of GERD after esophageal cancer surgery.

CONCLUSION

This study evaluated the therapeutic effect of WDD combined with mosapride on GERD after esophageal cancer surgery and found that WDD combined with mosapride can significantly improve GERD symptoms, esophageal motility function, gastric emptying function, and quality of life, and has good safety. These results provide new ideas and evidence for the integrated treatment of GERD after esophageal cancer surgery and new data and insights for this field. The novelty of this study is that it is the first to apply WDD combined with mosapride to treat GERD after esophageal

cancer surgery and to use multiple evaluation indicators for comprehensive assessment.

FOOTNOTES

Author contributions: Zhang YJ and Wu SP proposed the concept of this study; Wu SP participated in the data collection; Zhang YJ and Wu SP wrote the initial draft; Wu SP contributed to the formal analysis; Zhang YJ conducted guiding research, methodology, and visualization of the manuscript; Both authors participated in this study, validated it, and jointly reviewed and edited the manuscript.

Institutional review board statement: This study has been reviewed and approved by the Ethics Committee of Beijing Integrated Traditional Chinese and Western Medicine Hospital

Informed consent statement: All study participants, or their legal guardian, provided informed written consent prior to study enrollment.

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