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**Retrospective Study**

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

*Zhang YJ et al. GERD treatment: WDD with mosapride*

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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

This study aimed 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 (GERD) ; Esophageal cancer surgery ; Wanden Decoction (WDD) ; Mosapride ; Treatment effects ; GERD symptoms


**Core Tip:** This study suggests that combining Wanden Decoction (WDD) 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.

**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 \(^3\). 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), H\(_2\) receptor antagonists (H\(_2\)RA), 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-HT\(_4\)) receptor agonist that can increase the intracellular calcium ion concentration in gastrointestinal smooth muscle cells by stimulating 5-HT\(_4\) 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 \(^6\).

Wandan 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
Research 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 an 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; (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 0–60 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). Gastric scintigraphy measures the rate of gastric emptying using a radioactive tracer mixed with a test meal. 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[1], 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 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.

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
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.

ARTICLE HIGHLIGHTS

Research background

Gastroesophageal reflux disease (GERD) is a prevalent complication following esophageal cancer surgery, which can significantly impact patients’ quality of life and escalate the risks of esophageal stricture and anastomotic leakage. The management of GERD after esophageal cancer surgery is a significant challenge in clinical practice, and there is a continuous quest for effective therapeutic strategies.

Research motivation

Gastroesophageal reflux disease (GERD) is a common complication after esophageal surgery for cancer, posing a significant challenge to the quality of life of patients and increasing the risk of serious complications such as esophageal stenosis and anastomotic fistula. Therefore, effective management of postoperative GERD is a key issue that needs to be addressed. Exploring and addressing key issues in the treatment of gastroesophageal reflux disease after esophageal cancer surgery. Despite various treatment methods, there is still a lack of an effective and safe treatment method that can significantly improve the symptoms of gastroesophageal reflux disease, enhance esophageal motility, accelerate gastric emptying, and improve the quality of life of patients. Solving these problems is significant for future research in this
field If the combined therapy of WDD and Mosapride provides effective and safe, it could provide a novel therapeutic approach for managing GERD post esophageal cancer surgery. This could lead to improved patient outcomes, reduced risk of further complications, and enhanced quality of life for patients. However, these findings need to be confirmed through further studies involving larger sample sizes and longer follow-up periods to establish long-term efficiency and safety.

Research objectives

The main purpose of this study is to evaluate the therapeutic effect of the combination of Wendan Tang (WDD) and Mosapride (Mosapride Prokinetic Agent) in the treatment of postoperative gastroesophageal reflux disease (GERD) in patients with esophageal cancer. Evaluate the improvement of GERD symptoms, esophageal motility, gastric emptying, and overall quality of life in patients. Involving 80 GERD patients who were divided into two groups: one group received WDD combined with mosapride treatment (treatment group), and the other group received mosapride treatment alone (control group). The main outcome was the improvement in GERD symptoms measured using the Reflux Disease Questionnaire (RDQ). Secondary outcomes include improvements in esophageal motility (measured using esophageal manometry), gastric emptying (measured using gastric scintigraphy), and quality of life (measured using the Simplified 36+AFs-SF-36+AF0- health survey). The results of this study are of great significance as they demonstrate that the combination of WDD and mosapride is an effective and safe treatment for postoperative gastroesophageal reflux disease in esophageal cancer. This may improve the patient's prognosis and enhance their quality of life. However, these findings require further research to confirm, involving larger sample sizes and longer follow-up periods, which will provide stronger evidence for the effectiveness and safety of this combination therapy for postoperative gastroesophageal reflux disease in esophageal cancer.
Research methods

A gold-standard method in clinical research, to evaluate the therapeutic effects of Wendan Decoction (WDD) combined with Mosapride on Gastroesophageal reflux disease (GERD) following esophageal cancer surgery. Eighty patients with GERD were randomly divided into two groups: a treatment group that received WDD combined with Mosapride and a control group that received Mosapride alone. The treatment was conducted over a two-year period from January 2021 to January 2023. The primary outcome, improved GERD symptoms, was measured using the Reflux Disease Questionnaire (RDQ), a validated instrument for assessing the frequency and severity of GERD symptoms. The secondary outcomes were esophageal motility, gastric emptying, and quality of life. Esophageal motility was assessed using esophageal manometry, a gold-standard diagnostic tool that measures the pressure and coordination of esophageal muscle contractions. Gastric emptying was measured using gastric scintigraphy, a nuclear medicine test that visualizes the stomach’s function of emptying its contents. Quality of life was assessed using the Short Form-36 (SF-36) Health Survey, a widely used instrument for measuring health-related quality of life. The novelty of this research lies in the combination of traditional Chinese medicine (WDD) and a prokinetic agent (Mosapride) for the treatment of GERD following esophageal cancer surgery. This innovative approach could potentially provide a new therapeutic option for managing this common postoperative complication.

Research results

This study yielded important results, indicating that the combination of Wendan Tang (WDD) and Mosapride significantly improved symptoms of gastroesophageal reflux disease (GERD), esophageal motility, gastric emptying, and overall quality of life in cancer patients undergoing esophageal surgery. Compared with the control group, the treatment group showed a significant decrease in the Reflux Disease Questionnaire (RDQ) score, enhanced esophageal motility parameters, including decreased esophageal sphincter pressure, peristaltic amplitude, and peristaltic velocity,
confirming these findings. In addition, the treatment group showed significantly higher gastric emptying rate and SF-36 score in both physical and mental domains, indicating an overall improvement in the patient's health-related quality of life. Importantly, neither group reported serious adverse reactions, indicating the safety of this combination therapy. The combined treatment of traditional Chinese medicine (WDD) and proactinators (mosapride) for postoperative gastroesophageal reflux disease in esophageal cancer provides preliminary evidence of efficacy and safety, thus contributing to this field. This may provide a new treatment strategy for this common postoperative complication, improving the patient's prognosis and quality of life. However, it is worth noting that the sample size of this study is relatively small and time is limited. Therefore, larger scale studies with longer follow-up periods are needed to validate these findings and further explore the long-term efficacy and safety of this combination therapy. In addition, the mechanism of the observed therapeutic effects still needs to be elucidated, which may be an interesting direction for future research in this field.

**Research conclusions**

The combination of Wendan Tang (a traditional Chinese medicine formula) and Mosapride (a prokinetic agent) is an effective and safe treatment strategy for postoperative gastroesophageal reflux disease (GERD) in patients with esophageal cancer. This combination therapy has significantly improved symptoms of gastroesophageal reflux disease, esophageal motility, gastric emptying, and overall quality of life for patients, such as decreased reflux disease questionnaire (RDQ) scores, enhanced esophageal motility parameters, increased gastric emptying rate, and SF-36 improvement. Compared with the control group, the treatment group's health survey scores were also improved. Importantly, neither group reported serious adverse reactions, further supporting the safety of this combination therapy. Although this study itself did not propose any new theories or methods, it did introduce a new treatment approach that combines traditional Chinese medicine (WDD) with prokinetic agents.
(mosapride) to manage postoperative gastroesophageal reflux disease in esophageal cancer surgery. This innovative approach may provide a new treatment strategy for this common postoperative complication, thereby improving the patient's prognosis and quality of life.

*Research perspectives*

The findings of this study open up new avenues for future research in the treatment of Gastroesophageal reflux disease (GERD) following esophageal cancer surgery. Given the promising results of combining Wendar Decoction (WDD) and Mosapride, future research should aim to validate these findings with larger sample sizes and longer follow-up periods. This will help to solidify the evidence base and provide a more comprehensive understanding of the long-term efficacy and safety of this combined therapy. Moreover, although this study provided evidence of the therapeutic effects of WDD and Mosapride, the underlying mechanisms by which this combination improves GERD symptoms, esophageal motility, gastric emptying, and the overall quality of life remain unclear. Future research should therefore aim to elucidate these mechanisms, which could potentially lead to further improvements in the therapeutic strategy.

In addition, considering the global prevalence of GERD and the increasing incidence of esophageal cancer, it would be beneficial for future studies to explore the effects of this combined therapy in diverse populations and different healthcare settings. This would help to assess the generalizability of the findings and determine the optimal conditions for implementing this therapy in routine clinical practice. Finally, future research should also consider investigating the cost-effectiveness of this combined therapy, as this will be a crucial factor in its potential adoption into mainstream healthcare.
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