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Analysis on Therapeutic Effect of Biling Weitong Granules Combined with Pantoprazole on Patients with Gastroesophageal Reflux Disease of Qi Stagnation and Phlegm Retention Type

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Keywords

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Abstract

Aim: This study is designed to unravel the therapeutic effect of Biling Weitong granules (BWG) combined with pantoprazole on patients with gastroesophageal reflux disease (GERD) of qi stagnation and phlegm retention type. **Methods:** 60 patients with GERD of qi stagnation and phlegm retention type, who were treated in our hospital from January 2022 to June 2023 and received BWG combined with pantoprazole, were perceived as combination group. Meanwhile, 45 patients treated with BWG were set as BWG group and 75 patients administrated with pantoprazole were constructed as pantoprazole group. The treatment in the three groups lasted for 2 months. The clinical therapeutic efficacy, symptom score, gastroesophageal reflux disease questionnaire (GERDQ) score and adverse reactions were recorded and compared among the three groups. **Results:** After treatment, the symptom score and GERDQ score were reduced in the three groups, and the two scores were the lowest in combination group by comparison ($p < 0.05$). Among the three groups, the clinical total effective rate was the highest in combination group ($p < 0.05$), and the incidence of adverse reactions had no obvious differences ($p > 0.05$). **Conclusion:** BWG combined with pantoprazole can effectively improve GERD of qi stagnation and phlegm retention type, which relieves patients' clinical symptoms without severe adverse reactions.

1 Introduction

Gastroesophageal reflux disease (GERD) refers to symptoms and/or complications resulting from gastric contents that aberrantly flow back into esophagus [1]. Eating habits, older age, excessive body mass index (BMI), smoking, anxiety/depression, and less physical activity at work are all risk factors for GERD [2,3]. The general manifestation of GERD includes sour regurgitation, heartburn, substernal causalgia, etc., and in the absence of timely intervention, the patient' s stomach and esophageal mucosa are susceptible to ulcers, bleeding, and even canceration due to reflux, which seriously affect their life and health [4]. Therefore, it is important to find better treatments to intervene.

Current clinical treatment of GERD mainly depends on inhibiting gastric acid and protecting the gastric mucosa. Pantoprazole, belonging to proton pump inhibitors, is a commonly used drug to treat GERD and can effectively repress gastric acid secretion. However, drug discontinuance may result in recurrence, which negatively impacts clinical efficacy [5]. In addition, there has been a rise concerns of proton pump inhibitors contributing to the development of bone fractures, electrolyte deficiencies, and renal insufficiency [6]. Therefore, other combined drugs are necessary for treatment.

As the traditional Chinese medicine (TCM) research is booming, the clinical efficacy of TCM on treating GERD has been widely recognized [7]. According to TCM theory and GERD clinical manifestations, GERD belongs to "acid regurgitation" and "stomachache", featuring qi stagnation and phlegm retention, with the etiology of emotional dysregulation, qi stagnation and phlegm retention. Accordingly, treatment should be based on transforming phlegm, down-regulating and activating qi, and dissipating nodules [8]. It has been reported that Modified Xiaochaihu Decoction (MXD) has a similar therapeutic effect to omeprazole in mild-to-moderate GERD, and MXD increased the resting pressure of the lower esophageal sphincter, improved ineffective swallowing and the mechanism of reflux is partially corrected [9]. Biling Weitong granules (BWG) are mainly composed of Litseae Fructus, Corydalis Rhizoma and Coptidis Rhizoma, etc., which together can function in clearing heat, dissipating cold, inhibiting acid secretion, relieving pain, promoting qi, activating blood and soothing the liver and stomach [10]. It has been confirmed that BWG have many medicinal effects, such as inhibiting gastric acid secretion, anti-inflammation, reducing mucosal inflammation, and promoting mucosal repair, which exert good therapeutic effects in the treatment of various spleen and stomach system diseases [11]. Accordingly, this study applied pantoprazole combined with BWG to treat patients with GERD of qi stagnation and phlegm retention type, and expected to achieve better efficacy.

2 Materials and methods

2.1 General information

60 patients with GERD of qi stagnation and phlegm retention type, who were treated in our hospital from January 2022 to June 2023 and received BWG combined with pantoprazole, were perceived as combination group. Meanwhile, 45 patients treated with BWG were set as BWG group and 75 patients administrated with pantoprazole were constructed as pantoprazole group. The general information of the three groups had no evident difference ($p > 0.05$) and was comparable (Table 1). This study obtained the approval from the Ethics Committee of our hospital, and written informed consent from all patients.

2.2 Diagnostic criteria

(1) Western medicine criteria: GERD meeting the diagnostic criteria of Chinese expert consensus on gastroesophageal reflux disease in 2020 [12]; (2) TCM criteria: GERD belonging to qi stagnation and phlegm

retention pattern according to Research progress on the identification and management of swallowing disorders in stroke with evidence-based nursing practice, with the main symptoms of discomfort in the throat, such as phlegm obstruction, and chest discomfort, as well as secondary symptoms of belching or reflux, dysphagia, hoarse voice, coughing in the midnight, and tongue pulse: a. white and greasy tongue coating; b. wiry and slippery pulse [13].

2.3 Inclusion criteria

(1) Normal esophageal mucosa confirmed by gastroscopy; (2) Meeting the diagnostic criteria of TCM and Western medicine for GERD; (3) First onset of illness.

Table 1 Comparison of general information among the three groups.

Group		BWG group (n = 45)	Pantoprazole group (n = 75)	Combination group (n = 60)	χ^2/F	p
Sex (case)	Male	28	43	36	0.290	0.865
	Female	17	32	24		
Age (year old)		63.98 ± 4.86	64.89 ± 2.53	64.48 ± 3.77	0.318	0.728
BMI (kg/m^2)		25.20 ± 2.86	24.79 ± 1.82	25.59 ± 2.10	2.188	0.115
Waist-hip rate		0.85 ± 0.08	0.87 ± 0.10	0.86 ± 0.08	0.726	0.485
Smoking (cases)	Yes	13	25	21	0.454	0.797
	No	32	50	39		
Drinking (cases)	Yes	24	38	27	0.791	0.673
	No	21	37	33		
Intake of vegetables in each meal (cases)	Yes	35	51	38	2.551	0.279
	No	10	24	22		
Diachoresis per week (times)		6.60 ± 1.89	6.51 ± 1.83	7.07 ± 2.04	1.536	0.218
Course of disease (year)		1.08 ± 0.37	1.13 ± 0.22	1.04 ± 0.20	2.099	0.126
Types of disease	Reflux esophagitis	26	34	35	2.862	0.239
	Non-erosive reflux disease	19	41	25		

2.4 Exclusion criteria

(1) Fungal, corrosive, and drug-induced esophagitis; (2) Immunity-related or esophageal cancer-caused esophageal lesions; (3) A history of gastric, esophageal, or duodenal surgery; (4) Upper

respiratory tract and lung infections; (5) Allergies to BWG and Pantoprazole; (6) Severe liver and kidney diseases, hypertension and diabetes; (7) Other digestive system diseases; (8) Pregnant or lactating women.

2.5 Treatment methods

In BWG group, patients orally took BWG (5 g*9 bags; granules; National medicine permission number (NMPN): Z19990069; Yangtze River Pharmaceutical Group, Jiangsu Pharmaceutical Co., LTD.) 5 g/time and 3 times/day. In pantoprazole group, patients orally took pantoprazole (40 mg*14 tablets, tablets, NMPN: H20084498, Hubei Ji'antang Pharmaceutical Co., LTD.) 40 mg/time and 1 time/day. In combination group, patients received both BWG and pantoprazole. The treatment in the three groups lasted for 2 months.

2.6 Study indicators

This study collected clinical data, including symptom scores and gastroesophageal reflux disease questionnaire (GERDQ) scores, from three groups of patients with GERD of qi stagnation and phlegm retention type during treatment. Symptom changes and incidence of adverse events during treatment were organized based on medical records.

(1) Clinical efficacy: The clinical efficacy of three groups after 2 months of treatment was compared. Recovery: clinical symptoms (such as heartburn, nausea, reflux, etc.) disappeared; Significant effectiveness: clinical symptoms have been significantly improved; Effectiveness: some clinical symptoms have been improved; Ineffectiveness: clinical symptoms have not been evidently improved or even worsened. Total effective rate = (recovery + significant effectiveness + effectiveness)/total number of cases × 100% [14].

(2) Symptom scores: The questionnaire scores of sour regurgitation, heartburn, abdominal pain, belching, and foreign body sensation in throat were contrasted before treatment and 2 months after treatment in three groups. 1 point: having symptoms but no significant impact on daily activities; 2 points: having symptoms that affect daily activities; 3 points: unbearable symptoms and inability to engage in daily activities. The higher total score indicates more severe clinical symptoms of the patient [15].

(3) GERDQ scores: The GERDQ scores of three groups were compared after 2 months of treatment, and patients were asked to review their symptoms in the past week: a. Frequency of reflux attacks (0 point for 0 days, 1 point for 1 day, 2 points for 2-3 days, 3 points for 4-7 days); b. Frequency of heartburn attacks (0 point for 0 day, 1 point for 1 day, 2 points for 2-3 days, 3 points for 4-7 days); c. Frequency of nausea (3 points for 0 day, 2 points for 1 day, 1 point for 2-3 days and 0 point for 4-7 days, with 6 points as the highest score); d. Frequency of epigastric pain (3 points for 0 day, 2 points for 1 day, 1 point for 2-3 days and 0 point for 4-7 days); e. Frequency of self-medication for sleep disorders (0 point for 0 day, 1 point for 1 day, 2 points for 2-3 days, 3 points for 4-7 days); f. Frequency of taking OTC drug (0 point for 0 day, 1 point for 1 day, 2 points for 2-3 days, and 3 points for 4-7 days, with 6 points as the highest score). In this study, a total score of 6 items $\geqslant$ 8 points was used as a diagnostic indicator for GERD [16].

(4) Adverse reactions: Possible adverse reactions occurring in the patients among the three groups during treatment were recorded.

2.7 Statistical methods

Statistical analyses were conducted using SPSS 26.0. Count data were represented by case (%) and were compared by χ^2. The measurement data were described by mean ± standard deviation, the normality analysis of which was achieved using the Kruskal-Wallis method. The measurement data that conformed to the normal distribution was expressed in the form of mean ± standard deviation. Independent

samples *t*-tests were applied for two-group comparison, and paired samples *t*-tests were exploited for contrast before and after treatment in the same group. The difference of $p < 0.05$ on both sides was considered as statistically significant.

3 Results

3.1 Comparison of clinical efficacy among the three groups

The clinical total effective rate was higher in combination group than Pantoprazole and BWG groups ($p < 0.05$, Table 2).

Table 2 Comparison of clinical efficacy among the three groups [case (%)].

Group	Case	Significant effectiveness	Effectiveness	Ineffectiveness	Total effective rate
BWG group	45	16 (35.56)	5 (11.11)	24 (53.33)	21 (46.67)
Pantoprazole group	75	19 (25.33)	17 (22.67)	39 (52.00)	36 (48.00)
Combination group	60	13 (31.67)	26 (40.00)	11 (18.33)	49 (81.67)
χ^2					24.218
p					0.000

3.2 Comparison of symptom scores before and after treatment among the three groups

Before treatment, there was no significant difference in symptom scores among the three groups ($p > 0.05$). After treatment, the symptom scores of patients were decreased ($p < 0.05$), which were the lowest in combination group among the three groups ($p < 0.05$) and the highest in BWG group ($p < 0.05$, Table 3).

3.3 Comparison of GERDQ scores before and after treatment among the three groups

Before treatment, GERDQ scores were barely different among the three groups of patients ($p > 0.05$). Of note, the GERDQ scores of the three groups were diminished due to treatment ($p < 0.05$), and the decreasing trend was more obvious in the combination group ($p < 0.05$). In addition, the GERDQ scores of in Pantoprazole group was lower than that in BWG group ($p < 0.05$, Table 4).

3.4 Comparison of adverse reactions among the three groups

No remarkable difference was detected in terms of the incidence of adverse reactions among the three groups ($p > 0.05$, Table 5).

Table 3 Comparison of symptom scores before and after treatment among the three groups (mean ± standard deviation, score).

Observation indicators		BWG group (n = 45)	Pantoprazole group (n = 75)	Combination group (n = 60)	F	p
Foreign body sensation in the throat or dysphagia	Before treatment	2.66 ± 0.47	2.70 ± 0.40	2.56 ± 0.34	2.022	0.135
	After treatment	1.69 ± 0.24 *	1.38 ± 0.12 *[a]	1.17 ± 0.15 *[ab]	123.000	0.000
Forebreast discomfort	Before treatment	2.30 ± 0.20	2.35 ± 0.20	2.29 ± 0.14	1.939	0.147
	After treatment	1.42 ± 0.19 *	1.20 ± 0.17 *[a]	1.00 ± 0.18 *[ab]	89.110	0.000
Belching	Before treatment	2.37 ± 0.34	2.44 ± 0.38	2.39 ± 0.30	0.745	0.476
	After treatment	1.27 ± 0.17 *	1.06 ± 0.15 *[a]	0.86±0.13 *[ab]	100.900	0.000
Sour regurgitation	Before treatment	2.32 ± 0.18	2.25 ± 0.26	2.26 ± 0.15	1.994	0.139
	After treatment	1.32 ± 0.21 *	1.13±0.21 *[a]	0.95±0.19 *[ab]	42.710	0.000

Note: *p < 0.05 vs before treatment; [a]p < 0.05 vs BWG group; [b]p < 0.05 vs Pantoprazole group.

Table 4 Comparison of GERDQ scores before and after treatment among the three groups (mean ± standard deviation).

Group	Case	GERDQ score (scores)	
		Before treatment	After treatment
BWG group	45	17.38 ± 2.02	12.09 ± 1.21 *
Pantoprazole group	75	18.01 ± 2.80	10.46 ± 1.43 *[a]
Combination group	60	17.28 ± 1.38	8.57 ± 1.31 *[ab]
F		2.122	90.130
p		0.123	0.000

Note: *p<0.05 vs before treatment; [a]p<0.05 vs BWG group; [b]p<0.05 vs Pantoprazole group.

Table 5 Comparison of adverse reactions among the three groups [cases (%)].

Group	Case	Abdominal pain and diarrhea	Constipation	Headache	Nausea	Adverse reaction rate
BWG group	45	4 (8.89)	2 (4.44)	0 (0.00)	0 (0.00)	6 (13.33)
Pantoprazole group	75	6 (8.00)	0 (0.00)	1 (1.33)	0 (0.00)	7 (9.33)
Combination group	60	3 (5.00)	0 (0.00)	0 (0.00)	2 (3.33)	5 (8.33)
χ^2						11.077
p						0.086

4 Discussion

To improve the clinical efficacy, this study explored the effect of BWG combined with pantoprazole on the treatment of GERD patients. The results showed that the combined therapy may have a good therapeutic effect on GERD patients.

This study confirmed that BWG and pantoprazole in combination were more effective than them alone in treating GERD. Pantoprazole can be activated as cyclosulfonamide in the acidic environment of gastric parietal cells and bind to sulfydryl on the proton pump, thus reducing gastric acid secretion, increasing esophageal sphincter pressure, and ultimately suppressing reflux [17]. BWG consists of Litseae Fructus (to warm spleen and stomach and remove cold), Toosendan Fructus (to promote qi circulation and alleviate pain), Corydalis Rhizoma (to activate blood and circulate qi), Coptidis Rhizoma (to clear heat and dry dampness), Euodiae Fructus (to dissipate cold and alleviate pain), Citri Fructus (to sooth the diaphragm and arrest vomiting), Citri Sarcodactylis Fructus (to harmonize the stomach and relieve pain), Cyperi Rhizoma (to disperse stagnated liver and relieve depression), yellow rice wine-processed Rhubarb (to clear heat and purge fire), Sepiae Endoconcha (to disperse dampness and heal sores), Arcae Concha (to eliminating phlegm and transform blood stasis), etc. These components in combination can regulate qi, circulate blood, clear heat, dissipate cold, suppress sour regurgitation and alleviate pain [18]. Accordingly, BWG combined with pantoprazole was superior to them alone in treating GERD.

GERD is a clinically common disease, with the typical symptoms (heartburn and reflux), atypical symptoms (chest pain, epigastric pain, stomach burning sensation, epigastric distension, belching, etc.), and extraesophageal symptoms (throat discomfort, foreign body sensation in throat, hoarseness, cough, asthma, etc.) [19]. This study evaluated the clinical symptom recovery of three groups by observing TCM symptom score and GERDQ score. The results proved that compared with BWG or pantoprazole alone in treating GERD, their combination was more effective in improving clinical symptoms such as heartburn, reflux, and epigastric pain of GERD patients. Pantoprazole is a third-generation proton pump inhibitor that can specifically act on gastric mucosal parietal cells, where hydrogen/potassium adenosine triphosphate (H/K-ATPase) activity is reduced, thereby inhibiting gastric fluid metabolism, regulating gastrointestinal hormone levels, and improving clinical

symptoms such as heartburn and reflux in GERD patients [20]. Tetrahydropalmatine from BWG blocks gastric dopamine receptors, increases gastric mucosal blood flow, promotes gastric mucosal recovery, and improves symptoms such as epigastric distension and belching in GERD patients [21]. Euodiae Fructus relieves epigastric pain via dampening expressions of transient receptor potential ankyrin 1 protein (TRPA1) and transient receptor potential vanilloid 1 (TRPV1) in thermosensitive channels [22]. Hence, the combination of BWG and pantoprazole in the treatment of GERD patients can better recover the clinical symptoms of heartburn, reflux, epigastric pain, etc., which was a more scientific treatment plan than BWG or pantoprazole alone.

This study revealed no severe adverse reaction among the three groups during treatment, indicating that combined treatment of GERD would not increase adverse reactions and had good safety.

5 Conclusion

BWG combined with pantoprazole exerts a specific therapeutic effect on patients with GERD of qi stagnation and phlegm retention type, which alleviates clinical symptoms without severe adverse reactions. Nonetheless, this study has a relatively short observation time and has not investigated the role of the combined therapy in the recurrence rate of GERD patients. Long term follow-up is needed in the future to confirm the long-term efficacy of this treatment plan.

Acknowledgements

Not applicable.

Conflicts of Interest

The authors declare no conflicts of interest.

Author Contributions

Conceptualization: M.L.; Data curation: J.C.; Formal analysis: Z.Z.; Methodology: C.Z.; Writing – original draft: M.L. and J.C.; Writing – review and editing: Z.Z. and C. Z.; All authors have read and agreed to the published version of manuscript.

Ethics Approval and Consent to Participate

This study was approved by Medical Ethics Committee, and patients were informed and agreed.

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Availability of Data and Materials

The analyzed data sets generated during the study are available from the corresponding author on reasonable request.

Supplementary Materials

Not applicable.

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