# ORIGINAL RESEARCH

# Clinical Effects of Biling Weitong Granules in Combination with Quadruple Therapy on Refractory *Helicobacter pylori* Infection

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## ABSTRACT

**Objective** • The prevalence of antimicrobial resistance in *Helicobacter pylori* (HP) infection has increased globally. This study aimed to compare the efficacy of Biling Weitong granules (BLWTG) combined with quadruple therapy in patients with refractory HP infection who had previously failed eradication therapy.

**Methods** • This single-center prospective study enrolled patients with two or more consecutive failed HP treatments. A total of 122 patients with previously failed HP treatment from our hospital were recruited as participants and randomly (1:1) allocated to two eradication groups: patients treated with bismuthcontaining quadruple therapy (esomeprazole 40 mg, amoxicillin 1.0 g, bismuth potassium citrate 220 mg, and clarithromycin 500 mg, twice daily [EACB group]) for 14 days. And those treated with BLWTG (5 g three times daily) combined with the EACB group for 14 days (BLWTG+EACB group). The therapeutic effects of the two treatment programs were comprehensively evaluated.

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### INTRODUCTION

*Helicobacter pylori (HP)* is a human pathogen with high global prevalence, responsible for multiple gastrointestinal diseases, particularly chronic gastritis, peptic ulcers, gastric mucosa-associated lymphoid tissue lymphoma, and gastric malignancies.<sup>1,2</sup> Antibiotic therapies are the mainstay for HP eradication. However, the eradication rates of HP are

**Results** • The study group had a significantly higher improvement rate in symptoms (dull stomach pain, nausea, gastric distension, loss of appetite, and belching) compared to the control group (P < .05). Eight weeks after drug withdrawal, the eradication rates in the control and study groups were 49.18% and 73.77%, respectively. The levels of interleukin-6, C-reactive protein, and tumor necrosis factor- $\alpha$  were significantly lower in both groups after treatment but were significantly lower in the study group than in the control group (P < .05).

**Conclusions** • The combination of BLWTG and standard four-drug therapy had a high eradication rate and low recurrence rate in patients with refractory HP infection. Additionally, this combined therapy could regulate inflammatory reactions and reduce drug-related adverse reactions. (*Altern Ther Health Med.* 2023;29(5):274-277).

decreasing with a significant concomitant increase in the prevalence of antibiotic resistance worldwide,<sup>2</sup> including in China. Refractory HP infection has been increasingly identified worldwide,<sup>3</sup> and it is essential to address factors that might contribute to eradication failure.<sup>4</sup>

The treatment of HP infection is a crucial area of research. Traditional Chinese medicine has various methods for treating gastric diseases, and traditional Chinese medicine is widely recommended for treating HP infections in China.<sup>5</sup> Therefore, the present single-center, prospective, randomized, controlled trial was conducted to evaluate the eradication efficacy and safety of BLWTG in the rescue treatment of HP in patients who had undergone at least two previously failed treatment regimens.

## MATERIALS AND METHODS

### **Study Design and Patient Selection**

This study utilized a single-center prospective design, enrolling patients who had previously experienced two or **Table 1.** Comparison of General Data between theBLWTG+EACB Group and EACB Group

	BLWTG+EACB	EACB				
	Group	Group				
Characteristics	(n = 61)	(n = 61)	t	P value		
Male: Female	31/30	32/29	0.033	.856		
Age (years), mean ± SD	$48.05 \pm 8.3$	$47.52 \pm 8.26$	0.683	.496		
Course of Disease	$2.025 \pm 0.41$	$2.04\pm0.35$	0.738	.462		
Smoking	22	19	0.331	.565		
Alcohol intake	9	12	0.518	.472		
Symptom						
Dull stomach pain	48	42	1.525	.217		
Nausea	12	14	0.196	.658		
Gastric distension	32	39	1.651	.199		
Loss of appetite	7	7	< 0.001	1.000		
Number of previous eradication attempts						
2	23	26	0.307	.580		
≥3	38	35	0.307	.580		

Note: BLWTG+EACB denotes the combination of Buqi Lishui decoction (BLWTG) with esomeprazole, amoxicillin, clarithromycin, and bismuth potassium (EACB) therapy. *P* value less than .05 indicates statistical significance.

more consecutive failed HP treatments. From January 2021 to May 2022, adult inpatients and outpatients with refractory HP infection were recruited for this study (Table 1). The study protocol was approved by the Science and Technology Project of Baoding City (No. 2241ZF110) and the Affiliated Hospital of Hebei University, and written informed consent was obtained from all patients. The study followed the principles of the CONSORT statement for randomized controlled trials in parallel.

# **Inclusion Criteria**

The inclusion criteria were as follows: (1) age 18-65 years; (2) absence of clinically significant associated conditions, such as neoplastic diseases, coagulation disorders, and hepatic, cardiorespiratory, pregnancy, or renal diseases; (3) no evidence of allergy to any of the drugs used in the study; (4) no prescription of antacid drugs, antibiotics, or other probiotic preparations within one month prior to enrollment; (5) failure of at least two consecutive treatments (HP quadruple therapy) to eradicate HP infection; (6) willingness to participate in the study. Patients who did not complete the specified treatment cycle or the above evaluations, regardless of the reason, were excluded.

# **Treatment Protocol**

Eligible patients were randomly assigned to two treatment groups, each with a 14-day treatment regimen. Randomization was conducted using the random number table method to ensure the unbiased allocation of patients to the control and study groups. Patients were then divided into the control group, which received the standard treatment, and the study group, which received the intervention treatment.

# Therapy: Control Group and Study Group Interventions

**Control Group**. The control group was treated with standard quadruple therapy (EACB), which included esomeprazole (AstraZeneca Pharmaceuticals, Ltd., H2004637) 40 mg twice daily (before breakfast/dinner), bismuth potassium citrate (Lizhu Group, Lizhu Pharmaceutical Factory, H10920098) 220 mg twice daily (before breakfast/dinner), amoxicillin (Guangzhou Baiyunshan Pharmaceutical Group Co., Ltd., Baiyunshan Pharmaceutical General Factory, H44021518) 1.0 g twice daily (after breakfast/lunch/dinner), and clarithromycin (Hainan Puli Pharmaceutical Co., Ltd., H20051296) 500 mg twice daily (after breakfast/dinner).

**Study Group**. The study group was treated with EACB and BLWTG (production batch number: 090118, Jiangsu Pharmaceutical Co., Ltd., specification: 5 g per bag), 5 g three times per day.

During the entire course of this study, any drugs or substances related to treating gastrointestinal diseases were prohibited except for the above drug therapy. All patients were advised to eat regularly to avoid overeating, fatigue, emotional stress, and other difficulties.

## **Observational Indicators**

The study used observational indicators to evaluate various parameters, including HP eradication rate, symptom scores, serum inflammatory factors, and adverse reactions.

**HP Eradication Rate Evaluation.** HP eradication rate was evaluated using the 14C urea breath test 8 weeks after completion of therapy. The HUBT-01 HP tester was used, and a 14C-YBT of  $\geq$ 100dpm/mmol was considered positive for HP infection. The primary outcome measure was the overall eradication rate.

**Symptom Scores and Points Calculation.** Symptom scores were evaluated at three stages before treatment, one week after treatment, and two weeks after treatment to calculate symptom points. Symptoms such as upper abdominal burning, postprandial abdominal distension, and abdominal pain were primarily observed. The following points system was used: 0, no symptoms; 1, occasional but nonobvious symptoms; 2 points, common symptoms with slight interference in daily life; 3 points, frequent symptoms significantly affecting daily life; and 4 points, severe symptoms requiring emergency treatment.

Serum Inflammatory Factors Measurement. Changes in serum inflammatory factors were observed before treatment and two weeks after treatment, and the levels of C-reactive protein (CRP), tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ), and interleukin-6 (IL-6) in the serum were measured using enzyme-linked immunosorbent assay (ELISA). 8-OHdG was measured using an ELISA kit (Shanghai Enzyme-Linked Biotechnology Co., LTD.) per the manufacturer's instructions.

Adverse Reactions Recording and Analysis. Adverse reactions were recorded, and their type, time, frequency, severity, treatment required, measures taken, and relationship with treatment was noted for further analysis.

### **Statistical Analysis**

Data were collected in Excel and analyzed using SPSS 20.0 statistical software. Continuous variables are presented as mean  $\pm$  standard deviations and were analyzed using Student's *t* test. Categorical variables are presented as percentages and are compared using the chisquared test. A significance level of *P* < .05 was considered statistically significant.

## RESULTS

### **Baseline Characteristics of the Participants**

Both groups included 61 patients each, and no patient was lost to follow-up or withdrew due to adverse reactions. Table 1 presents the information of the two groups before treatment, and no significant differences were observed in the baseline characteristics, including demographics, medical history, smoking and alcohol intake, symptoms, and antibiotic therapy, between the two groups (all P > .05).

# Rates of Symptom Improvement and Adverse Events

The onset of epigastric pain symptoms was compared between the two groups before treatment. The research group showed a lower symptom score under different treatment schemes than the control group, and the symptom relief rate after the first and second week of treatment significantly differed between the two groups (P<.05; Table 2).

During treatment, adverse events were observed in 10 (16.4%) and 3 (4.9%) participants in the EACB and BLWTG+EACB groups, respectively (Table 2). The common adverse events were nausea, vomiting, diarrhea, and anorexia. The total incidence rate of adverse events in the BLWTG+EACB group was significantly lower than in the EACB group (P<.01).

### Efficacy of HP Eradication Therapy

In analysis, the eradication rates were 49.18% (30/61) in the EACB group and 73.77% (45/61) in the BLWTG+EACB group, and the difference was statistically significant ( $\chi^2$  = 8.239; *P* = .004; Table3).

## **Inflammatory Factors**

The levels of CRP, IL-6, and TNF- $\alpha$  between the groups prior to treatment were not significantly different (P > .05). However, after treatment, both groups showed a reduction in CRP, IL-6, and TNF- $\alpha$  levels, with the levels being significantly lower in the BLWTG+EACB group compared to the control group (P < .05; Table 3).

**Table 2.** Comparison of Symptoms between the EACB Group andBLWTG+EACB Group before and after Treatment

	EACB Group	BLWTG+EACB Group		
Characteristics	(n = 61)	(n = 61)	Statistics	P value
Symptoms Integral				
Before Treatment (points)	$13.05 \pm 1.04$	$13.18 \pm 1.20$	0.636ª	.526
One Week After Treatment	$8.36 \pm 0.57$	$6.15 \pm 0.52$	22.287ª	<.001
Two Weeks After Treatment	$5.24 \pm 0.35$	$3.05 \pm 0.21$	41.815 <sup>a</sup>	<.001
Comparison of Adverse Effects			4.354 <sup>b</sup>	.037
Nausea	3 (4.9%)	1 (1.64%)		
Vomiting	1 (1.64%)	0 (0.00%)		
Diarrhea	3 (4.9%)	1 (1.64%)		
Anorexia	3 (4.9%)	1 (1.64%)		

<sup>a</sup>t test;

<sup>b</sup>Chi-square values

Note: EACB denotes esome prazole, amoxicillin, clarithromycin, and bismuth potassium therapy. BLWTG+EACB denotes the combination of Buqi Lishui decoction (BLWTG) with EACB therapy. Data are presented as mean  $\pm$  standard deviation. *P* value less than .05 indicates statistical significance.

**Table 3.** Comparison of Indexes Before and After Treatment between Two

 Groups

	EACB Group	BLWTG+EACB		
Characteristics	(n = 61)	Group (n = 61)	Statistics	P value
HP Eradication Rate (n, %)	30/61 (49.18%)	45/61 (73.77%)	8.239ª	.004
CRP (ng/ml)				
Prior to Treatment	$5.74 \pm 0.68$	$5.80 \pm 0.64$	0.500 <sup>b</sup>	.618
Two Weeks After Treatment	$4.78 \pm 0.39$	$3.69 \pm 0.47$	13.871 <sup>b</sup>	<.001
TNF-α (μg/ml)				
Prior to Treatment	$2.71 \pm 0.36$	$2.74 \pm 0.41$	0.427 <sup>b</sup>	.670
Two Weeks After Treatment	$1.95 \pm 0.24$	$1.12 \pm 0.34$	15.490 <sup>b</sup>	<.001
IL-6 (ng/ml)				
Prior to Treatment	$65.26 \pm 5.41$	$66.05 \pm 5.18$	0.821 <sup>b</sup>	.414
Two Weeks After Treatment	36.56 ± 3.69	$22.15 \pm 3.02$	23.525 <sup>b</sup>	<.001

<sup>a</sup>Chi-square values

<sup>b</sup>t test

Note: EACB denotes esomeprazole, amoxicillin capsule, bismuth potassium citrate, and clarithromycin therapy. BLWTG+EACB denotes the combination of Biling Weitong Granules (BLWTG) with EACB therapy. Data are presented as mean  $\pm$  standard deviation. *P* value less than 0.05 indicates statistical significance.

### DISCUSSION

HP, a highly prevalent worldwide infection, is estimated to affect 50% of the world's population, and 70%-90% of people in developing countries are colonized with HP.<sup>6,7</sup> It is a major cause of gastritis, peptic ulcers, and gastric cancer,<sup>8</sup> necessitating treatment for all patients with HP.<sup>9</sup> However, despite being discovered less than half a century ago, antibiotic resistance, non-adherence to medication, and inefficacy of proton-pump inhibitors have contributed to the substantial growth of refractory HP infection,<sup>10,11</sup> explaining the rising incidence of refractory HP infection.

After the first treatment failure of HP infection, secondary resistance to antibiotics can occur in approximately 50% of HP bacterial strains,<sup>12</sup> making eradication increasingly difficult with each additional course of therapy that fails.<sup>13</sup> HP occurs in a coccoid form with antibiotic resistance at pH 3-6. Protonpump inhibitors (PPIs) increase the intragastric pH to 6.0-7.0, enhancing the susceptibility of HP to antibiotics during its replicative phase.<sup>14</sup> Regimens for eradicating HP infection are typically chosen empirically based on regional bacterial resistance patterns, local recommendations, and drug availability.<sup>15</sup> If HP infection persists after treatment with second-line therapy, bacterial cultures along with antibiotic susceptibility testing are recommended.<sup>16</sup> Amoxicillin and clarithromycin were selected as the base antibiotics in this study, as they are still sensitive to bacteria in Baoding City. Additionally, esomeprazole, a potent acid-suppressant, was chosen in combination with bismuth potassium.

The present prospective trial study assessed individuals with  $\geq 2$  failed HP eradication treatments, and the results revealed that the HP eradication rate was higher in patients treated with combined BLWTG (73.77%) and quadruple therapy compared to those treated with quadruple therapy alone (49.18%). Moreover, the levels of CRP, TNF- $\alpha$ , and IL-6 (P < .001) were reduced to a greater extent in the BLWTG group. The BLWTG group was also more effective in improving symptoms and reducing adverse reactions (4.9%: 16.4%) (P < .05). These results suggest that the combination of traditional Chinese medicine and Western medicine is a good treatment choice for HP eradication.

Many traditional Chinese medicinal herbs have been found to regulate the body's overall health and offer unique advantages in treating HP.<sup>16-17</sup> BLWTG comprises 11 proprietary Chinese patent medicines, including Fructus Litseae, Fructus Meliae Toosendan, Rhizoma Corydalis, Radix et Rhizoma Rhei, Rhizoma Coptidis, Fructus Evodiae, Rhizoma Cyperi, Fructus Citri, Fructus Citri Sarcodactylis, Endoconcha Sepia, and Concha Arcae. These herbs are known to promote qi and blood circulation and provide relief from stomach pain. BLWTG results from research conducted by academician Dong Jianhua, a renowned master of traditional Chinese medicine. Pharmacodynamic studies have shown that BLWTG can inhibit gastric acid secretion, increase the pH level of gastric juice, suppress pepsin activity, prevent and repair gastric mucosal damage, and exhibit analgesic and antispasmodic effects on gastric pain spasm.<sup>17</sup>

The results of this study indicate that the combination of BLWTG with quadruple antibiotic therapy may be effective in the rescue treatment of HP infection, with a higher eradication rate and improved reduction in inflammatory markers compared to quadruple therapy alone.

### Limitations

Limitations of the study include the small sample size and single-center setting, which may limit the generalizability of the findings. Future studies with larger sample sizes and multicenter settings are needed to confirm further the efficacy of the combination of BLWTG with quadruple therapy for HP rescue treatment.

### CONCLUSION

The results of this study suggest that the concomitant use of BLWTG with the quadruple antibiotic regimen may be beneficial for individuals with HP infection. However, further research is warranted to fully understand the nature and extent of the benefits of this combination treatment. The findings of this study could be utilized to explore new rational approaches for addressing antibiotic resistance in HP and developing strategies to prevent the emergence of novel anti-HP medications.

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#### AUTHOR CONTRIBUTIONS

Ya-Lan Chen and Da-Lei Chen designed the study and drafted the manuscript; Zeng-Sheng Li contributed to statistical analysis; Hui-Qing Zhang contributed to data collection. All authors read and approved the final manuscript.

#### CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

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