

Effect Analysis of Zuojin Pill Combined with Quadruple Therapy on *Helicobacter pylori* Infection

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Keywords

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Abstract

Background: Our study aims to investigate the curative effect of Xiangsha Liujunzi Decoction combined with Weifuchun Tablet in functional dyspepsia. **Methods:** 45 patients with functional dyspepsia treated with Xiangsha Liujunzi Decoction combined with Weifuchun Tablet for 8 weeks from February 2022 to February 2023 in our hospital were selected into the observation group, and 45 patients with functional dyspepsia treated with Weifuchun tablet for 8 weeks were selected into control group during the same period. The clinical efficacy and adverse reactions of the two groups were compared, and the changes of TCM symptom score, gastric dynamics parameters, and inflammatory factor (CRP, TNF- α , and IL-6) levels in serum before and after treatment were observed. **Results:** The total effective rate of clinical efficacy in observation group was significantly higher than that in control group ($p < 0.05$). After treatment, the levels of TCM symptom score, half-empty time, 2 h retention rate, C-reactive protein, tumor necrosis factor- α , and Interleukin-6 in both groups were obviously reduced, and those in the observation group was visibly lower than those in the control group ($p < 0.05$). The emptying rate in the two groups was strikingly increased, and that in the observation group was remarkably higher than that in the control group ($p < 0.05$). There was no significant difference in the occurrence of diarrhea, vomiting, and nausea between the two groups ($p > 0.05$). **Conclusion:** Xiangsha Liujunzi Decoction combined with Weifuchun Tablet has a good clinical effect in the treatment of patients with functional dyspepsia, which can alleviate clinical symptoms, improve gastric motility, reduce inflammation, and has good safety.



1 Introduction

Helicobacter pylori (HP) is a gram-negative bacterium mainly found in the stomach and duodenum, which can penetrate the mucus layer of gastric mucosal epithelial cells, causing gastric mucosal damage and gastric mucosal ulceration [1]. HP infection is closely related to chronic gastritis, peptic ulcer, and gastric cancer, and it is the main factor influencing the development of many digestive diseases [2-4]. Hence, HP eradication treatment is important for the prevention and treatment of HP infection-related diseases [5,6].

Currently, the empirical treatment options for HP eradication include western triple therapy and quadruple therapy, among which quadruple therapy (bismuth quadruple and concomitant) is the recommended regimens for the first-line treatment [7]. Commonly used drugs include bismuth, proton pump inhibitor (PPI), and antibiotics. However, clinical antibiotic abuse and poor compliance of patients will lead to HP resistance to some antibiotics and the decline in the eradication rate of HP, which often makes the efficacy of the above treatment options poor [8,9]. Therefore, the treatment of HP infection needs to be combined with other drugs in addition to antibiotics. Traditional Chinese medicine (TCM) shows a unique advantage in the treatment of HP infection, which has an obvious bactericidal effect on HP and can regulate the intestinal flora. For instance, Sanhuang Xiexin Decoction or Jiedu Wuyou Decoction combined with the quadruple therapy has achieved significant therapeutic effects, and fewer patients experience adverse effect during the treatment [10,11]. Zuojin pill is a Chinese patent medicine composed of *Coptidis Rhizoma* and *Euodia rutaecarpa*, which has the efficacy of clearing the liver and fire, detoxifying the liver and relieving depression, and relieving stomach pain. Zuojin pill has been shown to have a better effect of HP eradication in in-vitro bacteriostatic experiments

and in-vivo animal experiments [12].

Based on this, this study compares the efficacy of Zuojin pill alone or combined with quadruple therapy on HP infection, and explores the application value of Zuojin pill combined with quadruple therapy on this disease, so as to provide references and guidance for the clinical treatment of HP infection.

2 Materials and methods

2.1 General data

49 patients with HP infection treated with Zuojin pill combined with quadruple therapy in our hospital from July 2020 to July 2022 were allocated into combination group, 46 patients suffering from the same type of disease treated with Zuojin pill alone during the same period were assigned into Zuojin pill group, and 48 patients with the same type of disease receiving quadruple therapy were divided into quadruple group. There were no significant differences in gender, age, body mass index (BMI), smoking, alcohol consumption, family members' infections, eating out, total clinical symptom scores, total mucosal pathology scores, prostaglandin E₂ (PGE₂), heat shock proteins (HSP-70), and interleukin-8 (IL-8) among the three groups ($p > 0.05$), but these data were comparable, as shown in Table 1.

2.2 Inclusion and exclusion criteria

2.2.1 Inclusion criteria

(1) Patients met the diagnostic criteria for HP infection in the Fifth Chinese National Consensus Report on Management of *Helicobacter pylori* Infection [5]. (2) Patients had a positive ¹⁴C breath test examination. (3) Patients had not taken non-steroidal anti-inflammatory drugs in the last two weeks before enrollment.

Table 1 Comparison of general data in the three groups.

Group	Case	Gender (case)		Age (years old)	BMI (kg/m ²)	Smoking (cases)	Alcohol consumption	
		Male	Female					
Zuojin pill group	46	25	21	43.87 ± 7.23	18.97 ± 2.64	6	11	
Quadruple group	48	24	24	44.11 ± 8.97	19.34 ± 2.82	7	11	
Combination group	49	25	24	43.76 ± 9.56	19.13 ± 2.73	7	6	
		X ² /F		0.194	0.021	0.217	0.052	2.562
		ρ		0.908	0.980	0.805	0.974	0.278

Group	Case	Family members' infections (cases)			Eating out (cases)		
		Yes	No	Unclear	< 3 times/week	≥3 times/week	
Zuojin pill group	46	21	17	8	30	16	
Quadruple group	48	9	22	7	25	23	
Combination group	49	18	18	13	29	20	
		X ² /F			3.063		1.678
		ρ			0.547		0.432

Group	Case	Total clinical symptom scores (points)	Total mucosal pathology scores (points)	PGE ₂ (pg/mg)	HSP-70 (pg/mg)	IL-8 (pg/mg)		
		Zuojin pill group	46				7.94 ± 1.56	7.94 ± 1.60
Quadruple group	48	7.92 ± 1.55	7.92 ± 1.57	248.62 ± 32.41	175.67 ± 38.47	829.61 ± 58.66		
Combination group	49	7.95 ± 1.58	7.96 ± 1.62	247.17 ± 30.18	176.18 ± 39.51	830.66 ± 58.78		
		X ² /F		0.005	0.008	0.027	0.025	0.004
		ρ		0.995	0.992	0.974	0.975	0.996

2.2.2 Exclusion criteria

(1) Patients who were allergic to the drugs in this study. (2) Patients with previous history of gastrointestinal surgery. (3) Patients with complications such as pyloric obstruction, haemorrhage, and perforation. (4) Patients with acute gastric mucosal lesions. (5) Patients with malignant tumors. (6) Patients with cardiac, hepatic, and renal insufficiencies. (7) Patients with administration of other vaccines in the last two weeks, e.g., the cervical cancer vaccine. (8) Patients with psychiatric disorders and poor adherence to treatment. (9) Patients with incomplete clinical data. (10) Women during pregnancy and lactation.

2.3 Methods

Patients in Zuojin pill group were given Zuojin pill. Zuojin pill consisted of Coptidis Rhizoma and Euodia

rutaecarpa in the ratio of 6:1. In regular dosage, there was 6 g of Coptidis Rhizoma and 1 g of Euodia rutaecarpa, and the proportion of drugs was adjusted according to the degree of heat and cold. 200 mL of the medicinal juice was obtained after Zuojin pill was decocted in 400 mL of water for 30 min and taken by the patients in the morning and the evening, 100 mL/times. Patients in quadruple group were given quadruple therapy. Quadruple therapy: patients were given with rabeprazole enteric-coated tablets twice a day, with a total of 10 mg per time (Shanghai Shangyao Xinyi Pharmaceutical Co., Ltd., National Medical Products Administration (NMPA) approval no.: H20031292, specification: 10 mg). Amoxicillin capsules (Shanghai Fuda Pharmaceutical Co., Ltd., NMPA approval no.: H43022230, specification: 0.25 g) were given twice a day, with a total of 1.0 g per time. Clarithromycin capsules (Zhejiang Yongning

Pharmaceutical Co., Ltd., NMPA approval no.: H19991034, specification: 0.25 g) were given twice a day, with a total of 0.5 g per time. Bismuth potassium citrate granules (Livzon (GROUP) Pharmaceutical FACTORY, NMPA approval no.: H10900086, specification: 110 mg) were given twice a day, with a total of 220 mg per day. Patients in combination group were given Zuojin pill combined with quadruple therapy. Patients in the three groups were treated continuously for 14 days.

2.4 Observational indicators

2.4.1 Curative effect

The clinical efficacy in the three groups of patients after 14 days of treatment was evaluated and compared. Criteria for assessment of efficacy [13] are detailed below. Cured: the disappearance of clinical symptoms such as peptic ulcer and the complete disappearance of the lesion according to the results of gastroscopy, and complete eradication of HP. Effective: the obvious alleviation of clinical symptoms and the reduction of lesion area by more than 50%, and complete eradication of HP. Ineffective: the absence of changes in clinical symptoms and the reduction of lesion area by no more than 50%, HP non-eradication. Total effective rate = (number of cured cases + number of effective cases)/total number of cases × 100%.

2.4.2 HP eradication rate

HP eradication rate in the three groups of patients was assessed and compared. 4 weeks after treatment, all patients were examined by ¹⁴C breath test, with negative result as HP eradication and positive results as HP non-eradication. HP eradication rate was calculated. HP eradication rate = number of negative cases/total number of cases × 100%.

2.4.3 Adverse reactions

Adverse reactions such as diarrhoea, abdominal distension and rash occurred during the treatment were recorded and compared among these three groups of patients.

2.4.4 HP recurrence rate after 1 year

HP recurrence rate after 1 year in the three groups of patients was evaluated and compared. Patients were followed up one year after stopping the drug, the number of recurrence cases was recorded, and the HP recurrence rate was calculated. HP recurrence rate = the number of recurrence cases/total number of cases × 100%.

2.5 Statistical analysis

Statistical analysis was performed using SPSS 20.0. Count data were expressed as cases (%), comparisons between the three groups were carried out using χ^2 test, and measurement data were expressed as mean ± standard deviation. One-way analysis of variance (ANOVA) was used for comparisons between groups, and LSD test was applied for two-way comparisons between groups. The difference of $p < 0.05$ was statistically significant.

3 Results

3.1 Comparison of curative effect among the three groups

The total effective rate in combination group was significantly higher than that in Zuojin pill group and quadruple group ($p < 0.05$), as displayed in [Table 2](#).

3.2 Comparison of HP eradication in the three groups

The eradication rate of HP in combination group was obviously higher than that in Zuojin pill group and quadruple group ($p < 0.05$), as seen in [Table 3](#).

3.3 Comparison of adverse reactions in the three groups

There was no significant difference in the occurrence of adverse reactions among the three groups ($p > 0.05$), as shown in Table 4.

3.4 Comparison of HP recurrence rate after 1 year in the three groups

The recurrence rate of HP in combination group after 1 year was visibly lower than that in Zuojin pill group and quadruple group ($p < 0.05$), as exhibited in Table 5.

Table 2 Comparison of curative effect among the three groups [cases (%)].

Group	Case	Cured	Effective	Ineffective	Total effective rate
Quadruple group	46	28 (60.87)	5 (10.87)	13 (28.26)	33 (71.74) *
Zuojin pill group	48	29 (60.42)	7 (14.58)	12 (25.00)	36 (75.00) *
Combination group	49	40 (81.63)	5 (10.21)	4 (8.16)	45 (91.84)
χ^2					6.623
p					0.031

Note: Comparison with the combination group: * $p < 0.05$.

Table 3 Comparison of HP eradication in the three groups.

Group	Case	Negative (cases)	Positive (cases)	Eradication rate (%)
Quadruple group	46	35	11	76.09 *
Zuojin pill group	48	38	10	79.17 *
Combination group	49	46	3	93.88
χ^2				6.225
p				0.045

Note: Comparison with the combination group: * $p < 0.05$.

Table 4 Comparison of adverse reactions in the three groups [cases (%)].

Group	Case	Diarrhoea	Abdominal distension	Rash	Dry and bitter taste	Decreased appetite	Dizziness and fatigue	Nausea	Total occurrence rate
Quadruple group	46	2 (4.34)	2 (4.34)	1 (2.17)	1 (2.17)	1 (2.17)	0 (0.00)	1 (2.17)	8 (17.36)
Zuojin pill group	48	1 (2.08)	2 (4.16)	1 (2.08)	0 (0.00)	0 (0.00)	1 (2.08)	0 (0.00)	5 (10.40)
Combination group	49	1 (2.04)	1 (2.04)	0 (0.00)	0 (0.00)	0 (0.00)	1 (2.04)	0 (0.00)	3 (6.12)
χ^2		0.600	0.470	1.059	2.124	2.124	0.962	2.124	3.183
p		0.741	0.790	0.589	0.346	0.346	0.618	0.346	0.204

Table 5 Comparison of HP recurrence rate after 1 year in the three groups.

Group	Case	Negative (cases)	Positive (cases)	Recurrence rate (%)
Quadruple group	46	36	10	21.74 *
Zuojin pill group	48	39	9	18.75 *
Combination group	49	47	2	4.08
χ^2				6.857
p				0.032

Note: Comparison with the combination group: * $p < 0.05$.

4 Discussion

In order to improve the effect of clinical HP eradication, this study explored the efficacy of Zuojin pill combined with quadruple therapy for the treatment of patients with HP infection. Our results demonstrated that Zuojin pill combined with quadruple therapy for the patients with HP infection may have better curative effect.

HP infection is closely related to the occurrence and development of many digestive diseases, and if not treated in time, it will increase the risk of gastric cancer and seriously affect the quality of patients' life [14]. This study revealed that Zuojin pill combined with quadruple therapy was more effective in treating patients with HP infection and had a higher HP eradication rate compared with Zuojin pill alone. The commonly used drugs in quadruple therapy are PPI, amoxicillin, clarithromycin, and bismuth, among which PPI can inhibit the secretion of gastric acid, amoxicillin binds to transpeptidases in HP bacteria, and clindamycin can block the linkage of 50S subunit of the cytosolic protein. The three abovementioned drugs have a strong effect on clearing HP [15]. The bismuth in the action of the gastric acid can form a protective layer of gastric mucous membrane, and plays a protective effect on mucous membrane [16]. Also, bismuth is most effective in improving the eradication rate of dual-resistant HP strains [17]. Piyakorn et al. have highlighted that the 14-day high dose PPI-bismuth-containing quadruple therapy with probiotic can provide an excellent cure rate for HP infection as first line treatment irrespective of CYP2C19 and antibiotic resistance pattern [18]. Additionally, it has been acknowledged that tetracycline-containing bismuth quadruple regimens such as tetracycline combined with metronidazole or furazolidone or amoxicillin or levofloxacin can achieve better HP eradication rate [19]. Zuojin pill is a commonly used formula for the treatment of digestive

system diseases, such as chronic atrophic gastritis [20] and gastric injury [21]. In its composition, Coptidis Rhizoma plays a role in the meridians of heart, spleen, stomach, liver, gallbladder, and large intestine, which has the efficacy of clearing the fire of the liver and gallbladder and purging the heat of the stomach and intestines. Euodia rutaecarpa acts on the meridians of liver, spleen, stomach, and kidney, which has the efficacy of dispersing cold, relieving pain, calming the adverse-rising energy, stopping vomiting, and supporting the yang. The two medicines share cold and heat properties, disperse pungent, and descend bitter, exerting the effects of purging liver-fire, soothing liver, and relieving depression [22]. Much evidence has manifested that Zuojin pill exerts therapeutic effects on HP-induced chronic atrophic gastritis by inhibiting the JMJD2B/COX-2/VEGF axis and HMGB1/NF- κ B signaling pathway [8]. Shi et al. have investigated that Zuojin pill is effective in the treatment of chronic gastritis, which can improve the clinical efficiency, HP infection eradication rate, 1-year recurrent rate, symptom scores, efficacy under endoscopy, and patients' quality of life [23]. Researches have uncovered that Zuojin pill has good therapeutic effects on chronic non-atrophic gastritis and ulcerative colitis, which is consistent with the results of this study [24,25]. Zuojin pill combined with quadruple therapy has better efficacy, and the reason may be that both of them can improve the gastrointestinal microenvironment, protect the gastric mucosa, enhance HP eradication, so as to alleviate the clinical symptoms. Most up-to-date research has elucidated that patients' adherence to the treatment is one of the most important factors affecting the effect of anti-HP treatment. In other words, during the treatment of HP infection, inappropriate administration of the drugs used in quadruple therapy may increase the toxic side effects, reduce patients' quality of life, and affect their tolerance and adherence to the treatment [26]. In our study, through the

combination of Zuojin pill, it can reduce the frequency of quadruple therapy, the clinical antibiotic resistance, and the risk of adverse reactions occurring during the treatment, and effectively improve patients' adherence to the treatment and HP eradication. Peng et al. unveiled that modified Zuojin pill combined with quadruple therapy had better efficacy in treating patients with HP-positive functional dyspepsia, which was in lined with the results of the current study [27]. Therefore, Zuojin pill combined with quadruple therapy for the patients with HP infection may have better curative effect, with better HP eradication.

In addition, we observed the occurrence of adverse reactions in patients with HP infection treated with ZuoJin pill alone or combined with quadruple therapy and compared the safety of the two treatments. In our study, no adverse reactions such as asthma, oral malodor, and memory loss were found, indicating that Zuojin pill combined with quadruple therapy for HP infection patients did not increase the risk of adverse reactions such as diarrhoea, abdominal distension, and decreased appetite, with good safety and a low HP recurrence rate after 1 year.

Considering that patients with HP infection must be treated, there is no blank control in this study. However, due to the limited number of sample cases in this study, the sample source has limitations, so the results of this study are not sufficient to represent the situation of all patients. The efficacy of Zuojin pill combined with quadruple therapy needs further experimentation and verification.

5 Conclusion

Our study has put forward that Zuojin pill combined with quadruple therapy for the patients with HP infection may have better curative effect, with a better effect of HP eradication, good safety, and a low HP recurrence rate after 1 year.

Acknowledgements

Not applicable.

Conflicts of Interest

The authors declare no conflicts of interest.

Author Contributions

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

Ethics Approval and Consent to Participate

This study was approved by the Ethics Committee, and patients were informed and consented.

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Availability of Data and Materials

The data presented in this study are available on request from the corresponding author.

Supplementary Materials

Not applicable.

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