

Effect of Monotherapy Weifuchun Tablets on Chronic Atrophic Gastritis: A Randomized Controlled Trial

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Research Article

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Abstract

Background and Aim:

Chronic atrophic gastritis is a common gastric disease which shows a positive correlation with the occurrence of gastric cancer. Traditional chinese medicines have been used in the treatment of chronic atrophic gastritis. There is no solid evidence for the curative effects of traditional chinese medicines. This study aimed to investigate the clinical efficacy of Weifuchun tablets on patients with chronic atrophic gastritis.

Methods

97 patients of chronic atrophic gastritis without current *H. pylori* infection were divided into two groups: an experiment group treated with Weifuchun and a control group treated with teprenone and folic acid for six months. Pathological examination of gastric biopsies and clinical symptoms assessment were performed for all patients before and after treatments. Primary outcome was the pathological response rate in each group evaluated by changes of histological scores. Secondary outcome was the clinical symptom scores.

Results

Twenty four patients in the Weifuchun group and twenty eight patients in the control group completed the study. The pathological response rates for atrophy and intestinal metaplasia were 66.7% and 45.8% in the Weifuchun group and 66.7% and 42.9% in the folic acid group, respectively, without statistical significance between groups. Clinical symptoms failed to improve after treatments in either group.

Conclusions

Weifuchun is effective to improve pathological changes of chronic atrophic gastritis in patients without current *H. pylori* infection. Monotherapy of Weifuchun had a similar efficacy to the combined therapy by teprenone and folic acid in the treatment of chronic atrophic gastritis.

Trial registration:

Evaluation of Weifuchun Pills on chronic atrophic gastritis, ChiCTR-IPR-17013939, Registered 15 December 2017, <http://www.chictr.org.cn/showproj.aspx?proj=23910>.

Background

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Chronic atrophic gastritis (CAG) is a common troublesome gastric disease induced by various factors, such as *H.pylori* infection, autoimmune attack and other uncertain environmental factors[1]. It is characterized by a chronic inflammatory condition of the gastric mucosa, with loss of normal glandular structures, and replacement by intestinal-type epithelium, pyloric-type glands and fibrous tissue [1, 2]. As most patients with chronic atrophic gastritis are asymptomatic, it is difficult to ascertain the exact prevalence rate. The Chinese Society of Digestive Endoscopy reported that 17.7% of the Chinese patients with gastrointestinal symptoms presented CAG at diagnostic upper endoscopy [3]. CAG shows a significant positive correlation with the occurrence of gastric cancer (GC), especially intestinal type GC [4]. Previous studies demonstrated that 0.1% and 1.44% of CAG developed into GC within 5 years of follow-up in Netherland[5] and in China [6], respectively. It is of great importance to intervene and block the development of CAG to prevent the occurrence of gastric cancer.

At present, there are two main thoughts to treat CAG. One is to reduce the harmful stimulations to the gastric mucosa, and the other one is to enhance the defense of the gastric mucosa [7]. Therefore, investigators are keeping seeking effective treatments to block inflammation, promote tissue repair and reverse CAG, such as the regiments for *Helicobacter pylori* eradication [8] and using various gastric mucosal protectors to reduce tissue damage and protect gastric integrity [3]. Previous study reported that withdrawal of a drug which induced specific loss of parietal cells could lead to complete restitution of the normal oxyntic mucosa[9]. This proposed that even the gastric mucosa with sever atrophy still had the capacity to self-renewal. That indicated that a small number of stem cells with the ability to proliferate and differentiate might still present in the gastric mucosa from patients with CAG.

In China, teprenone is frequently prescribed as an effective mucoprotective agent for gastric mucosal injuries and dyspepsia symptoms in chronic gastritis patients without *H. pylori* infection or history of gastroduodenal ulcer[10, 11]. Folic acid, a one-carbon derivative of tetrahydrofolate, plays a critical role in the prevention of chromosome breakage and hypomethylation of DNA[12]. It was reported that folic acid might treat atrophic gastritis by preventing or reversing precancerous lesions[13]. We previously reported that combined application of teprenone and folic acid could significantly promote the reversal of gastric precancerous lesions, with an efficacy rate of pathological mucosa improvement reaching 49.8% [14].

The same as these western medicines, various Traditional Chinese Medicines (TCM) have been used in the treatment of CAG for decades [15–17]. However, there is no solid evidence for the curative effects of TCM because of the lack of high quality studies conducted with multi-center, large-sample size and long-term follow-up. Previous experimental study demonstrated that Weifuchun could reduce *H. pylori*-induced IL-8 and IL-4 production by blocking the NF-kappaB pathway[18]. This hinted that Weifuchun could be an effective drug to treat *H. pylori*-associated chronic gastritis. Although Weifuchun has been widely used in treatment of CAG in China, there is no high quality clinical study to report its efficacy on CAG among patients without *H. pylori* infection [19]. Thus, we carried out a randomized controlled clinical trial with long-term follow-up to determine the therapeutic effect of Weifuchun on CAG among *H. pylori*-negative or *H. pylori* eradicated successfully patients. Combined application of teprenone and folic acid was used as

Methods

Subjects

This is a single-center, randomized, controlled study. In total, 97 subjects diagnosed with CAG were recruited from the outpatient clinic from December 2017 to June 2018. All patients were required to provide a medical history and undergo gastroscopies with mucosa biopsies before and after interventions.

Inclusion criteria

Patients with CAG were diagnosed according to the criteria from Consensus on Chronic Gastritis in China (2017, Shanghai) [7] and the updated Sydney system [20]. Patients with *H. pylori* infection were required to eradicate *H. pylori* before the randomization. Only those whose *H. pylori* status was negative, determined by C^{13}/C^{14} urea breath test, were considered as eligible subjects to include.

Exclusion criteria

Patients were excluded if they were: 1) aged < 20 or > 70; 2) diagnosed or unable to exclude, malignant tumors, especially esophageal cancer and gastric cancer; diagnosed of peptic ulcer or Barrett's esophagus and other upper gastrointestinal diseases; 3) taking concomitant medication (such as proton pump inhibitors (PPI), prokinetic agents or other gastric mucosal protective agents) over 4 weeks during the trial; 4) pregnant or planning to be pregnant, currently breastfeeding mothers; 5) serious primary diseases involving critical organs such as the heart, brain, lungs, liver, kidneys or the hematopoietic system; 6) unwilling to undergo repeated endoscopy after treatment or to cooperate with researchers;

Patients who met the inclusion and exclusion criteria described above were finally enrolled for randomization. Written informed consents and detailed records of concomitant medication were obtained from all subjects.

Dosage and administration

Eligible patients were randomly assigned into two intervention groups. Patients in the experiment group received four Weifuchun tablets (360mg) three times per day for six months. Weifuchun tablets were mainly prepared by medicinal herbs such as Hong Shen (Red Ginseng), Xiang Cha Cai (Isodon) and Zhi Ke (Citrus Aurantium), which was established by a high-performance liquid chromatography method (HuqingYuTang Pharmaceutical Co., Ltd., Hangzhou, Zhejiang, China; lot number: 20090120)[21]. Patients in the control group received one teprenone tablet (50mg, Eisai China Pharmaceutical Co., Ltd. Suzhou, Jiangsu, China) and one folic acid tablet (10mg, Tianjing Lisheng Pharmaceutical Co., Ltd. Tianjing, China), three times per day for six months. Standard quadruple eradication regimen was given to the *H. pylori*-positive patients and a two-week washout period was required to exclude the effects of *H. pylori* eradication before the randomization. During treatment, patients in both groups were required to discontinue any medications that could interfere with the results of the study.

Gastroscopy and mucosa biopsy

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Endoscopy procedures were performed in all participants twice by senior endoscopists before and after interventions, respectively. Biopsy specimens were obtained from the lesser curvature of the antrum, 2–3 cm from the pylorus, gastric angle and middle of the corpus according to the updated Sydney system[20]. The size and depth of the biopsy specimens were large enough to reach the muscularis mucosa[7]. *H. pylori* infection status was further determined by pathological examination.

Gastrointestinal symptom and adverse reaction assessment

Gastrointestinal symptoms of each participant including epigastric pain, poor appetite, acid regurgitation, abdominal distention, belching, nausea and vomiting were evaluated by Gastrointestinal Symptom Rating Scale (GSRS) questionnaire before and after treatment as previously described[22]. Any adverse reactions occurred during the trials were recorded in details.

Outcome measurements

The primary outcome was the improvement of pathological findings from the gastric mucosa after the treatments. The secondary outcome was the symptomatic benefits from the treatments.

Pathological findings including gastric mucosal inflammation, atrophy, intestinal metaplasia and allotypic hyperplasia were evaluated by a 4-point scale in severity to get a histological score (0: absent; 1: mild intestinal metaplasia and allotypic hyperplasia, and less than one third of the mucosa present inflammation and atrophy; 2: moderate intestinal metaplasia and allotypic hyperplasia, and one third to two third of the mucosa present inflammation and atrophy; 3: severe intestinal metaplasia and allotypic hyperplasia, and more than two third of the mucosa present inflammation and atrophy)[23].

The most advanced area in the stomach was selected as the object for diagnosis.

Individual gastrointestinal symptoms including (epigastric pain, poor appetite, acid regurgitation, abdominal distention, belching, nausea and vomiting) were assessed by a 4-point scale in severity as previously described: (0: absent, 1: mild symptoms easily to be tolerated; 2: moderate symptoms interfering with normal activities; 3: severe symptoms leading to inability to perform normal activities [22].

Response to treatment was determined by assessing changes of the scores from pathological evaluation and individual symptoms. Pathological effective was defined by a > 1 point reduction in histological scores from baseline, and a ≥ 2 points reduction from baseline was further defined as remarkably effective.

Statistical analysis

Continuous variables are expressed as mean \pm standard deviation and categorical variables are expressed as frequencies (percentages). For comparisons of continuous variation from baseline to endpoint, Student's t-tests or Wilcoxon signed-ranks were performed for normal or abnormal distributed variables, respectively. Response rates for the outcomes were analyzed by the Chi-squared tests or

Fisher's exact tests. All statistical analyses were performed using GraphPad Prism 8.0 software (GraphPad, Inc., San Diego, CA, USA) and were considered statistically significant at a level of two side $P < 0.05$.

Results

Subjects

By the time of project termination, a total of 52 patients had completed the study, as shown in Fig. 1. 24 patients (13 men, 11 women; mean age 55.29 ± 12.05 years) were from Weifuchun group and 28 patients (16 men, 12 women; mean age 54.21 ± 11.86 years) were from teprenone and folic acid group. Baseline demographic data including age and gender were similar between groups. Eleven patients in the Weifuchun group and nine patients in the control group occasionally took PPI or prokinetic drugs during intervention period less than four weeks.

Primary Outcome Assessment

The pathological response rates for inflammation, atrophy and intestinal metaplasia were 37.5%, 66.7% and 45.8% respectively in the Weifuchun treatment group and 21.4%, 66.7% and 42.9% in the control group, without statistically significant difference between groups. The remarkable response rates for atrophy and intestinal metaplasia were 33.3% and 20.8% respectively in the Weifuchun group and 33.3% and 21.4% in the folic acid group, with no significance between groups (Table 1 and Fig. 2).

Table 1
Response Rate of Pathological Lesions [Case (%)]

Variables	Pathological response	Weifuchun (n/N (%))	Teprenone and folic acid (n/N (%))	P value
Inflammation	Effective	9/24(37.5)	6/28(21.4)	0.2022
	Remarkably effective	0/24(0)	5/28(17.9)	0.0542
Atrophy	Effective	8/12(66.7)	12/18(66.7)	> 0.9999
	Remarkably effective	4/12(33.3)	6/18(33.3)	> 0.9999
Intestinal metaplasia	Effective	11/24(45.8)	12/28(42.9)	0.8294
	Remarkably effective	5/24(20.8)	6/28(21.4)	0.9528

Secondary Outcome Assessment

The reductions observed in scores for clinical symptoms were not statistically significant compared with baseline in the two groups, and there was no significant difference between groups in all parameters after

treatments(Table 2).

Table 2
Comparison of Clinical Symptom (Score, $\bar{x} \pm s$)

Variables	Weifuchun (n = 24)		Teprenone and folic acid (n = 28)		P value
	Baseline 6-months		Baseline 6-months		
Symptoms score					
epigastric pain	0.375 ± 0.647	0.125 ± 0.338	0.321 ± 0.612	0.107 ± 0.315	0.8455
poor appetite	0.167 ± 0.381	0.167 ± 0.381	0.143 ± 0.448	0.036 ± 0.189	0.1354
acid regurgitation	0.250 ± 0.532	0.083 ± 0.282	0.357 ± 0.559	0.179 ± 0.390	0.3254
abdominal distention	0.708 ± 0.806	0.250 ± 0.532	0.464 ± 0.693	0.214 ± 0.418	0.7874
belching	0.333 ± 0.702	0.083 ± 0.282	0.393 ± 0.832	0.214 ± 0.499	0.2422
nausea	0.208 ± 0.658	0.042 ± 0.204	0.250 ± 0.645	0.071 ± 0.262	0.6540
vomit	0	0	0.071 ± 0.262	0	-

Adverse reactions

During the trial, one patient in the control group reported abnormal liver function. No adverse reactions were reported in the Weifuchun group.

Discussion

This randomized controlled clinical trial confirms the similar efficacy of Weifuchun to the traditional mucosal-protective regimen (teprenone combined with folic acid) in the treatment of patients with chronic atrophic gastritis in Chinese population. To avoid the effects of *H. pylori* infection and eradication on the results, we focused on the *H. pylori*-negative or *H. pylori* successfully eradicated chronic atrophic gastritis patients in this study. Both treatments provided adequate pathological improvement on the gastric mucosa in 40–60% of patients, especially for the atrophy and intestinal metaplasia. No adverse reactions were reported during the treatment of Weifuchun.

Mucosal-protective agents and PPI are known to be the most commonly prescribed medications for chronic atrophic gastritis in China [2]. Teprenone (geranylgeranylacetone) is one kind of safe and

effective mucosal-protective agent, which has been widely used for gastric mucosal injuries and dyspepsia symptoms in patients [10, 24, 25]. Folic acid plays a key role in DNA synthesis and cell replication [26]. It was reported that folic acid supplementation can improve gastric mucosal atrophy and intestinal metaplasia by involving DNA methylation and inhibition of cell proliferation [27, 28]. Studies demonstrated that some patients with chronic atrophic gastritis had a low level of foliate and adequate folic acid supplementation could improve the histopathological status of the gastric mucosa and reduce the incidence of gastric cancer[29–31]. Therefore, we chose combined application of teprenone and folic acid as a positive control treatment for CAG in this study.

In China, TCMs have shown great advantages in the treatment of CAG, due to their multiple components and characteristics. There have been growing literatures demonstrating the notion that TCM herbal prescriptions can treat CAG effectively by relieving symptoms, inhibiting mucosal inflammation and reversing atrophy[32–35]. Our previous study reported a kind of TCM, Weierkang tablets [36], could significantly improve atrophy and intestinal metaplasia, and promote the reversal of gastric precancerous lesions. In a multicenter randomized controlled trial from Beijing, Moluodan, could improve dysplasia scores in histopathology, and was superior to folic acid in improving epigastric pain, epigastric suffocation, belching and decreased appetite[15].

In our study, the pathological response rate for gastric atrophy and intestinal metaplasia in the Weifuchun group reached 66.6% and 45.80%, respectively, which represented the similar curative efficacy to the control group. Previous study reported that Weifuchun could dramatically improve clinical outcomes in patients with gastric precancerous lesions by targeting multiple pathways, such as involving NF- κ B, RUNX3/TGF-beta/Smad, Hedgehog (Hh) and Wnt signaling pathways[37]. Red ginseng, a major component of Weifuchun, has been shown to induction of cell cycle arrest and apoptosis and inhibition of angiogenesis[38]. Amethystoides, another important ingredient of Weifuchun could promoting gastrointestinal motility[39]. Besides, the possible mechanism of Weifuchun in treating CAG and preventing malignant transformation might be regulating tumor suppressor genes and inflammatory factors by bio-network analysis[40]. Our results provided new evidences for regarding Weifuchun as an ideal treatment for reversal of chronic gastritis. Weifuchun has a good therapeutic effect on CAG and is worthy of further study.

S. Redéen *et al.* found that the severity of symptoms in patients with chronic gastritis did not correlate with endoscopic or histopathologic findings[41]. Though Weifuchun showed similar improvement in pathological lesions as the western medicine regimen, both treatments failed to improve individual clinical symptoms in our study. Our clinical experience indicated that, patients often focus more on their physical symptoms, which could affect their quality of life and work. It was inevitable to take additional PPI or prokinetic drugs occasionally to relieve physical symptoms. This might account for the high rate of concomitant medications during this trial. We suppose that Weifuchun combined with prokinetic drugs or digestive enzyme agents may improve individual symptoms of CAG. Besides this, making individual adjustments to lifestyle and diet may also be a reasonable advice for relief of symptoms in CAG patients.

There are some limitations in our study. First of all, the accuracy and consistency of biopsies between pre- and post-treatment might affect the quality of study data and comparability of the results. Technique of the mucosa marking targeting biopsy (MTB)[42] by providing a safe and reliable long-term marker could be used in our future studies to improve the accuracy and consistency of biopsies. Secondly, the final sample size was not large in this study. Multi-center and large-sample clinical studies are needed to further confirm the effect of Weifuchun in CAG. In addition, the drop-out rate in this study is high. Fifteen cases were lost to follow-up and 15 cases showed poor compliance. Long term (6 months) medication and required repeated invasive procedures (endoscopy) might be the main reasons for drop-out. In order to reduce the high drop-out rate, relevant measures should be taken in future studies, including expense deduction, periodic inspection, expert participation, facilitating consultation and prescription.

Conclusions

In summary, *H. pylori*-negative or *H. pylori* eradicated successfully chronic atrophic gastritis patients, Weifuchun treatment is effective for reducing pathological scores in chronic atrophic gastritis. Monotherapy of the Weifuchun treatments has the similar efficacy to the combination of teprenone and folic acid in the treatment of chronic atrophic gastritis.

Abbreviations

CAG Chronic atrophic gastritis

GC Gastric cancer

TCM Traditional Chinese Medicines

PPI Proton pump inhibitors

GSRS Gastrointestinal Symptom Rating Scale

MTB Marking targeting biopsy

Declarations

Ethics approval and consent to participate: This study was performed in line with the principles of the Declaration of Helsinki. Approval was granted by Sir Run Run Shaw Hospital Clinical Trials and Biomedical Ethics Committee (Date: December 15, 2017/No.20171107-10) and has been registered in the Chinese Clinical Trial Registry (ChiCTR-IPR-17013939, <http://www.chictr.org.cn/showproj.aspx?proj=23910>). Informed consent was obtained from all individual participants included in the study.

Availability of data and materials: The datasets generated during the current study are available from the corresponding author on reasonable request.

Competing interests: The authors declare that they have no competing interests.

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Figures

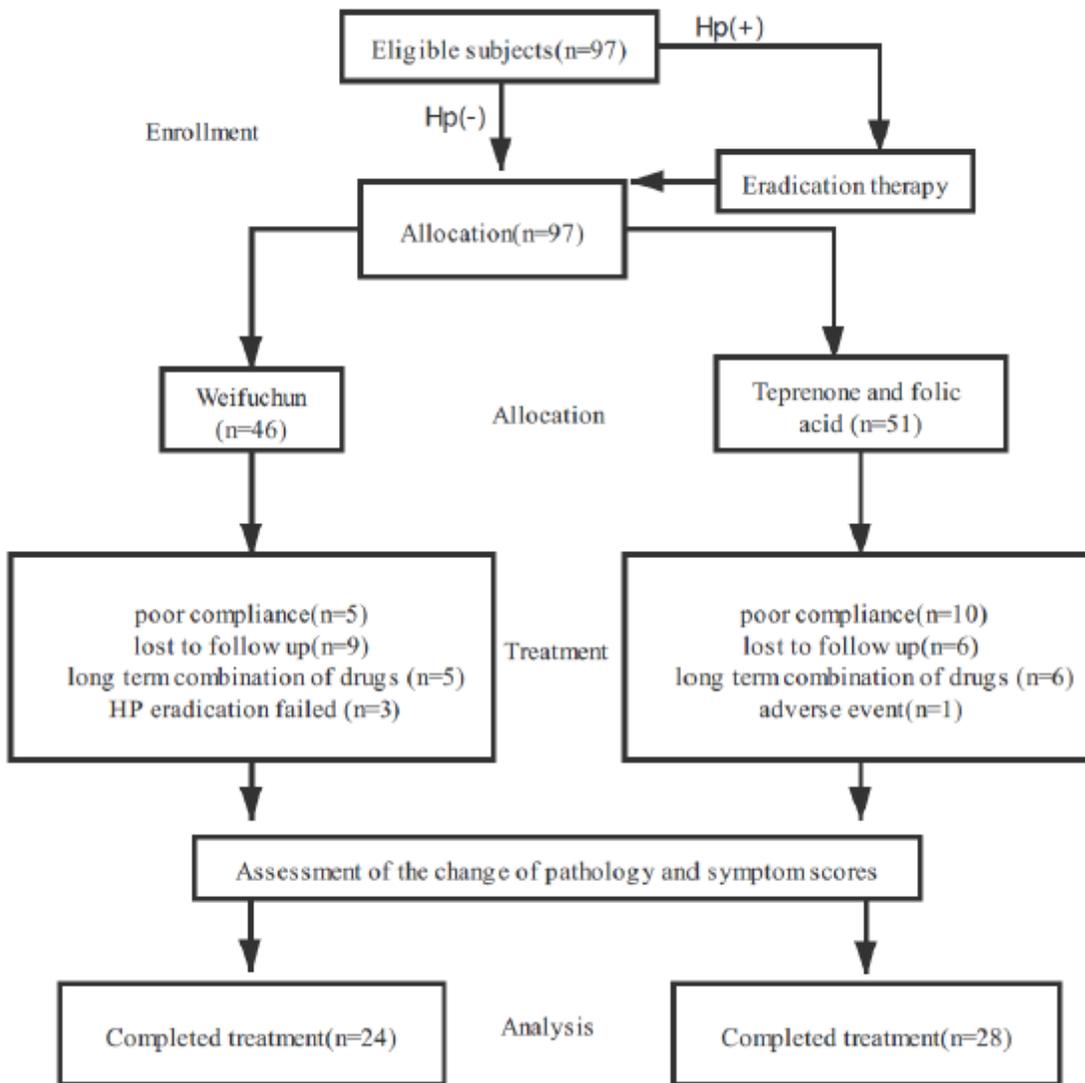


Figure 1

Flow chart of the patients with chronic atrophic gastritis in the clinical trial. Hp indicates *Helicobacter pylori*.

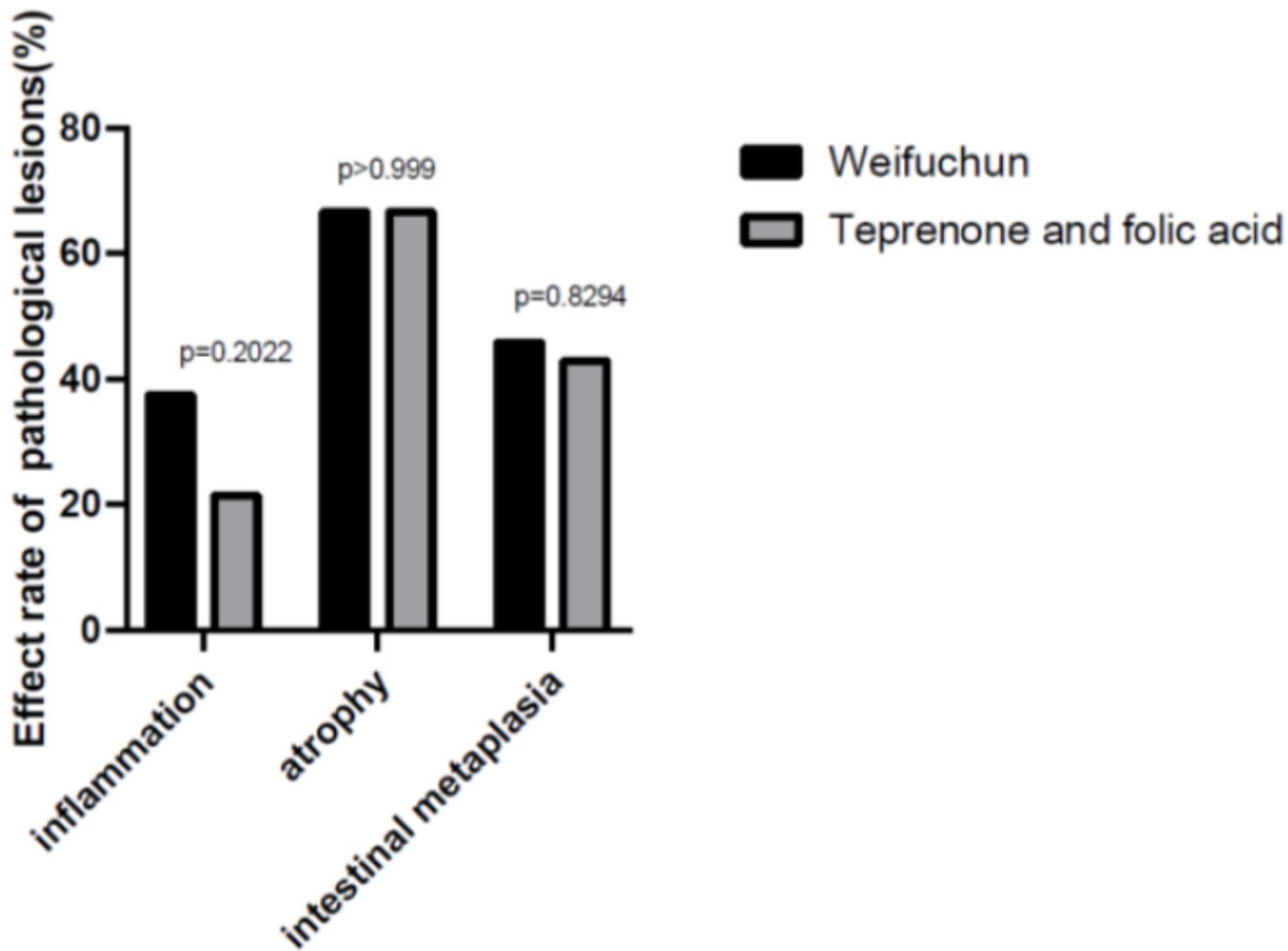


Figure 2

Effect rates of pathological lesions between the two groups.