The effect of the fortifying the spleen, clearing heat, activating blood method on chronic atrophic gastritis: a real-world study

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Abstract

Introduction: Chronic atrophic gastritis (CAG) is a precancerous disease that is difficult to treat. Even after eradication of the *Helicobacter pylori* (HP) infection, complete resolution of the symptoms is difficult to achieve. The fortifying the spleen, clearing heat, activating blood method (FSCHABM) has an excellent curative effect in the treatment of CAG. A real-world study is particularly suitable for researching the treatment of CAG, but there are currently no reports on CAG trials. Our aim is to design a high-quality trial to investigate the efficacy and safety of FSCHABM in treating CAG patients.

Methods and analysis: This protocol is designed as a real-world study for 10 years. A total of 5000 participants will be assigned to a FSCHABM treatment group or a non-FSCHABM treatment group at a 1:1 ratio at the first Affiliated Hospital of Guangzhou University of Chinese Medicine. Patients are given 1-2 courses of a 24-week-long treatment. The participants will be followed up for observation and measurement of the following indicators: the primary outcome is the histopathological indicator; the secondary outcome includes evaluation of gastric lesions, syndrome curative effect, evaluation of symptoms, evaluation of quality of life, evaluation of anxiety and depression, economic evaluation and other indicators. This is the first real-world study evaluating the therapeutic effect of FSCHABM in the treatment of CAG in clinical practice. This protocol can provide a reference for future multi-center, randomized, controlled trials.

Strengths and limitations of this study: it is the first time to carry out TCM study related to CAG by using the real-world study. A large number of patients and a long-term study can effectively reflect the effect of TCM treatment and reduce the bias. The precise research protocol makes the whole research more accurate and reliable. The limitations of implementing this protocol are expending a lot of time, manpower and economic resources inevitably.

Ethics and dissemination: this study was approved by Ethical committee of the first Affiliated Hospital of Guangzhou University of Chinese Medicine. Study findings will be shared with participants, healthcare providers, and policymakers through research reports, conference presentations, and the Internet. The results will also be disseminated through publication in peer reviewed journals.

Trial registration: The registration number, ChiCTR1900027177, was assigned by the Chinese Clinical Trial Registry on 3 November 2019.

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Keywords: fortifying the spleen, clearing heat, activating blood method (FSCHABM); real-world study; histopathological indicator; Chronic atrophic gastritis (CAG).
**Introduction**

Chronic atrophic gastritis (CAG) is a common type of precancerous lesion, in which the repeated damage to the gastric mucosa epithelium causes a reduction of the intrinsic glands. Helicobacter pylori (HP) infection is the most important cause of CAG\(^1\), 2\(^\)\), which is epidemiologically associated with the occurrence of gastric cancer (GC)\(^3\), 4\(^\)\) and an unhealthy lifestyle, including alcohol abuse, tobacco abuse, high intake of sodium, preserved and spicy food\(^5\)-\(^7\). A national multicenter cross-sectional study\(^8\) showed that 17.7\% of the examined patients (1,573/ 8,892) was diagnosed with CAG at endoscopy. The annual incidence of GC for patients with CAG within 5 years of diagnosis was 0.1\% \(^9\). A global cancer investigation\(^10\) reported approximately 18.1 million new cancer cases and 9.6 million cancer deaths globally in 2018, with GC being the fifth most common cancer and the third cause of cancer death.

There are various treatments for CAG, including the eradication of HP, antacids, acupuncture, prokinetics and mucosal-protective agents\(^8\), \(^11\). For HP positive patients, eradication therapy is still the most basic and effective treatment for CAG\(^12\) that strongly improves the quality of life\(^13\), and promotes the revitalization of the gastric mucosa\(^14\). A follow-up study of 7.5 years indicated that eradication of HP in patients without precancerous lesions could significantly reduce the risk of gastric cancer\(^15\). Compared to chemical drugs, traditional Chinese medicine (TCM) has a unique advantage in the treatment of CAG and produces no serious side effects\(^16\). For example, Weiqi Decoction attenuated CAG with precancerous lesions by regulating the disturbed gastric mucosal blood flow and the HIF-1 signaling pathway\(^17\). Tian G et al\(^18\) adopted immune repertoire sequencing techniques to evaluate the effect of Modified Sijunzi Decoction for treating CAG. Results indicated that MSD could availably relieve CAG symptoms and improve pathological changes in CAG. According to the Consensus on TCM Diagnosis and Treatment of Chronic Gastritis (2017)\(^19\), the main pathogenesis of CAG is the spleen-stomach vacuity, qi stagnation and blood stasis, therefore, the fortifying the spleen, clearing heat, activating blood method (FSCHABM) is recommended for the entire treatment process of CAG.

TCM attaches importance to the concept of holism, and the TCM practitioner uses different treatment methods according to the constitution of the patient, the season and the area, providing a personalized treatment. Due to the limitations of randomized controlled trials (RCTs), this study design is unable to show the situation of each individual patient during the study of TCM treatments. A real-world study pays attention to the clinical application, especially the patient’s symptoms after treatment\(^20\). He Wei\(^21\) thinks the advantages and characteristics of TCM’s comprehensive therapy can be fully implemented under real world conditions. In addition, the evidence-based level of TCM treatment of CAG is low, and RCTs fails to represent the reality of TCM treatment. Thus, there is a need for a new clinical research method to provide high-level results-based evidence. Compared to RCTs, a real-world study is more suitable for clinical research of TCM.

**Methods and analysis**

This current study is designed as a real-world study for 10 years which complies with the Declaration of Helsinki, Good Clinical Practice (GCP) Guidelines\(^22\) and the requirements of clinical trials by the Drug Administration Law of the People’s Republic of China, and will strictly...
abide by all laws governing TCM drugs. It is a real-world study that requires mass of data. Therefore, we determined 5000 sample as our research objects. A total of 5000 patients will be recruited voluntarily at the out- and in-patient department of the first Affiliated Hospital of Guangzhou University of Chinese Medicine. Depending on the type of medication the patients want to take without doctor’s intervention, the patients will be divided into FSCHABM group whose patients will receive FSCHABM treatment, and non-FSCHABM group whose patients receive western medicine, traditional Chinese medicine decoction (non-FSCHABM), acupuncture and other treatment methods. All patients will be requested to sign a written informed consent. The researchers participating in this experimental study will be trained strictly and individually to ensure the authenticity and accuracy of the research. This study is blind to outcome evaluators and data analysts. They are concealed the treatment plan of each subject and rejected to participate in the drug intervention process, in order to independently evaluated and analyzed the outcome of the subjects and their clinical data. Figure 1 shows the flow chart of this trial.

**Diagnosis in Western medicine**

Referred to Chinese consensus on chronic gastritis (2017, Shanghai)[11], CAG will be diagnosed by digestive endoscopy and pathological biopsy of gastric mucosa.

**Clinical manifestations**

Most patients with CAG have silent clinical symptoms. These include non-specific gastrointestinal symptoms, such as upper abdominal discomfort, loss of appetite, belching, which can be accompanied by systemic or mental symptoms such as fatigue, wasting, forgetfulness, anxiety, etc. It has been reported that heartburn, regurgitation and early satiety are present in approximately 24%, 12%, and 10.1% of patients respectively [23].

**Endoscopic characteristics**

Under the endoscope, the gastric mucosa can be seen between the mucous membrane as a red and white phase, white-based, wrinkled flattening or even nonexistent. Part of the mucous membrane blood vessels are observed, and can be accompanied by mucosa particles, nodules, and other manifestations.

Changes in mucosal inflammation seen by the gastroscopic doctor or special imaging methods under the endoscope should be combined with the results of pathological biopsy for the final judgment. Special imaging methods, such as magnifying endoscopy combined with staining and confocal laser microendoscopy, provide certain value in the diagnosis of CAG.

**Histopathological diagnosis**

If the pathological biopsy of chronic gastritis shows inherent atrophy of the glandular body, CAG can be diagnosed, regardless of the number and degree of atrophy of the biopsy specimens. Clinicians can judge the scope and extent of gastric mucosa atrophy according to the pathological results combined with the gastroscopy.

**TCM syndrome diagnostic criteria of CAG**
In acknowledgement of the consensus on diagnosis and treatment of CAG with TCM[24], the TCM syndrome diagnostic criteria of CAG patients are listed as follows:

1. Pattern of liver and stomach qi stagnation: Main symptoms: distention or pain in the stomach; rib-side distention and pain. Secondary symptoms: symptoms induced or aggravated by emotional factors; frequent belching; choking sensation in the chest; thin white tongue coating; string pulse.

2. Pattern of intense liver-stomach fire: Main symptoms: clamoring stomach or burning pain in the stomach; string or rapid pulse. Secondary symptoms: heart vexation and irritable; clamoring and acid reflux in the stomach; bitter mouth and dry throat; dry stool; red tongue with yellow moss.

3. Pattern of weak spleen and stomach (pattern of cold spleen and stomach deficiency): Main symptoms: distention or dull pain in the stomach; the stomach likes to be pressed or warmed. Secondary symptoms: decreased food intake; dilute stool; fatigue and lack of strength; shortness of breath and laziness of speech; distended stomach after eating; pale tongue and weak pulse.

4. Pattern of spleen-stomach damp-heat: Main symptoms: stomach distension or pain; red tongue with yellow thick or greasy coating. Secondary symptoms: bitter mouth and halitosis; nausea or vomiting; heartburn; Sticky or dilute stool; slip and rapid pulse.

5. Pattern of insufficiency of stomach yin: Main symptoms: stomach oppression or burning pain; red tongue with less fluid and less coating. Secondary symptoms: loss of appetite and clamoring stomach; dry mouth; dry stool; thin body and decreased food intake; fine pulse.

6. Pattern of blood stasis in stomach collaterals: Main symptoms: fullness and compression in the stomach or pain in a specific location; the tongue is dark red or has petechiae or ecchymosis. Secondary symptoms: persistent stomachache; black stool; dark complexion; string and rough pulse.

Syndrome determination: the main symptoms must be present, and more than 2 secondary diseases be added to the diagnosis. In addition, the above syndromes may appear individually or simultaneously. In case of non-listed syndromes or simultaneous syndromes, syndrome differentiation can be standardized on the basis of the National Standard of the People's Republic of China "Terminology of Clinical Diagnosis and Treatment of Traditional Chinese Medicine-Syndrome Part." With the passage of time, the syndrome may change dynamically, requiring careful follow-up.

HP diagnosis and detection:
1. Invasive detection: rapid urea test; silver staining of biopsy pathological tissues.
2. Non-invasive detection: 13C urea breath test; 14C urea breath test.

Note: PPI, H2RA, bismuth, antibiotics and other drugs that may affect the results of the examination were discontinued for two weeks before the examination.

Inclusion criteria
1. Age of 18-65 years old, regardless of gender.
2. CAG diagnostic by gastroscopy and histopathological examination.
3. Clear TCM syndrome types according to standard syndrome differentiation.
4. A one-minute rapid urease test, a 13C breath test or a 14C breath test were performed within the past month.
5. Voluntary provision of written informed consent.

Exclusion criteria
1. Participated in other drug treatment studies within the past month.
2. Patients with autoimmune gastritis, peptic ulcer (A1-H2 phase), reflux esophagitis, gastric polyp, Gastric mucosa high-level intraepithelial neoplasia, gastrointestinal tumors, a history of gastrointestinal cancer and other digestive system disease.
3. Patients with serious organic diseases, such as: heart (NYHIII-IV grade of cardiac function, etc.), liver (decompensation stage of liver cirrhosis, etc.), kidney (uremia stage of chronic renal failure, etc.), lung (tuberculosis, acute attack of asthma, pulmonary infection, etc.), autoimmune system (active stage of systemic lupus erythematosus), etc.
4. Allergic constitution or allergy to multiple drugs.
5. Patients with severe mental diseases who cannot cooperate with researchers, such as schizophrenia, depression, dementia, etc.
6. Pregnant and nursing women.
7. Patients who do not cooperate.

Withdrawal criteria
1. Loss of follow-up: ≥ 2 methods of contact (such as telephone, text message, mail) were followed up continuously for ≥ 3 times without reply.
2. Subjects voluntarily withdrew their informed consent and withdrew from the study.

Rejection criteria
1. Misdiagnosis of the disease.
2. The proportion of missing items in the case report questionnaire exceeds 20%.
3. During the study period, intervention measures other than the scheme were combined.
4. Patients who fail to take the medicine according to instructions, for example, adjust the type, dosage, and usage of the medicine.

Termination criteria
1. During the study period, the subjects developed new diseases that belong to the exclusion criteria.
2. Researchers found serious safety problems.
3. Research funds were insufficient to complete the study.
4. The administrative departments canceled the test.

Therapeutic regimen
The therapeutic scheme of FSCHABM was formulated according to the Report Specification for Clinical Randomized Controlled Trials of Traditional Chinese Medicine Compound 2017. Patients with CAG were divided into sub-groups according to the main symptoms: asymptomatic patients; patients with stomachache; patients with stomach distension.
Core prescription: *Atractylodes Rhizome* 10 g, *Radix Pseudostellariae* 15 g, *Poria* 20 g, *Fructus Aurantii* 10 g, *Perilla Stem* 15 g, *Pericarpium Arecae* 15 g, *Herba Scutellariae Barbatae* 20 g, and *Curcumae Rhizoma* 10 g.
1. Asymptomatic (spleen and stomach weakness syndrome): core prescription.
2. Stomachache: core prescription + *Radix Aucklandiae* 10 g; Chicken bone broth 10 g.
3. Stomach distension: core prescription + Haematitum 15-30 g; *Lignum Aquilariae Resinatum* 3
The dosage form of the above treatment scheme is a TCM decoction, which is prepared with 250 ml-300 ml of water twice a day for oral administration.

**Pattern identification and treatment administration**

Pattern of liver and stomach qi stagnation: core prescription + Haematitum 15 g-30 g; *Lignum Aquilariae Resinatum* 3 g; *Dalbergia odorifera* 10 g.

Pattern of intense liver-stomach fire: core prescription + *Coptis chinensis* 5 g; *Evodia rutaecarpa* 3 g.

Pattern of spleen and stomach deficiency cold: core prescription + prepared aconite root 5 g-10 g; galangal root 10 g; pickled ginger 10 g.

Pattern of spleen-stomach damp-heat:

1. Pattern of equal severity of dampness and heat: the core prescription + *Poria cocos* is changed to *Smilax glabra* 30 g; talc 10 g to 20 g; calamus 20 g; *Agastache rugosa* 10 g; *Scutellaria baicalensis* 10 g.

2. Pattern of dampness predominating over heat: core prescription + *Herba Artemisiae Scopariae* 30 g; *Agastache rugosa* 10 g; slag leaf 15 g.

Pattern of insufficiency of stomach yin: core prescription + *Ophiopogon japonicus* 15 g; *Dendrobium* 20 g; lily 30 g.

Pattern of blood stasis in stomach collaterals: core prescription + *Pollen Typhae* 5 g; *Oletum Trogopterori* 5 g; ground beetle 10 g.

**Differentiation of Symptoms**

Intestinal metaplasia: core prescription + *Rhaponticum uniflorum* 20 g; *Sarcandra glabra* 20 g-30 g.

Intraepithelial neoplasia: core prescription + ground beetle 10 g; *Aspongopus* 10 g.

Accompanied by acid regurgitation: core prescription + *Coptis chinensis* 5 g; *Evodia rutaecarpa* 3 g.

Accompanied by belching: core prescription + haematite 15 g-30 g; *Lignum Aquilariae Resinatum* 3 g; *Dalbergia odorifera* 10 g.

Accompanied by poor appetite: core prescription + burnt hawthorn 10-20 g; medicated leaven 15 g-20 g.

Accompanied by throat blockage or sputum in the pharynx: core prescription + *Rhizoma Pinelliae Preparata* 10 g; snakegourd peel 20 g; *Allium macrostemon* 20 g.

Accompanied by chest tightness and discomfort: core prescription + sandalwood 10 g; snakegourd peel 20 g; *Allium macrostemon* 20 g.

Accompanied by loose stool: core prescription + white *Atractylodes* rhizome changed to fried *Atractylodes* 15 g; fried white lentils 30 g; *Agastache rugosa* 15 g.

**Therapeutic regimen for Control Group**

Western medicine and other TCM are used as control drugs, and the treatment plan is implemented according to Chinese Consensus on Chronic Gastritis (2017, Shanghai)\(^\text{[25]}\).

**Course of treatment**

24 weeks of treatment is considered a course of treatment, and patients are given 1-2 courses of
Treatment.

Drug administration
All drugs are clinical routine drugs provided and managed by the first Affiliated Hospital of Guangzhou University of Chinese Medicine. The western medicines are quasi-Chinese medicines. The pharmacy department of the center will implement standardized management of the drugs involved in the research to ensure the effectiveness and safety of each drug.

Concomitant medication
Subjects should stop taking drugs for the treatment of CAG 1 month before entering this study. Subjects should take drugs according to the doctor's treatment plan during the study period, and are forbidden to adjust the treatment plan by themselves. During the study period, the subjects can take drugs (e.g. antihypertensive drugs, hypoglycemic drugs, lipid-lowering drugs, etc.) to treat complicated diseases, which is recorded in detail in the medication records.

Observation indicators
Epidemiological Indicators
1. Demographic data: subject's name, age, sex, date of birth, occupation, place of birth, address, and contact information.
2. Disease-related factors: 1. drinking history, smoking history, working environment, intensity and time; 2. dietary preferences; 3. dietary habits; 4. use of NSAID drugs; 5. HP infection; 6. duration of digestive system symptoms; 7. inducing or aggravating factors (such as emotion, diet, climate, drug, etc.); 8. previous history of digestive system diseases; 9. family history and allergy history; 10. combined diseases and current medication, etc.
3. Physical examination: height, weight, blood pressure, heart rate, respiratory rate, pregnancy test.
4. Disease diagnosis indicators: gastroscopy, histopathological examination, HP examination.
5. Observation time: all the above items were completed during the screening period.

Outcome measurements
Primary outcome
1. Histopathological indicator
Histopathological observation of chronic gastritis includes 5 histological changes and 4 grades. The grading method takes the consensus for diagnostic pathology in biopsies of chronic gastritis and epithelial neoplasms\(^{[26]}\) as a standard and is used in combination with the intuitive simulation scoring method of the New Sydney System.
The 5 histological changes are: 1. HP infection; 2. chronic inflammatory reaction (infiltration of mononuclear cells); 3. activity (neutrophil infiltration); 4. atrophy (reduction of intrinsic glands); 5. intestinal metaplasia. The four grades are: 0 (none); + (mild); ++ (moderate); +++ (severe).
The gastric epithelial tumor and its precursor lesions are classified into 5 grades: 1. no intraepithelial tumor; 2. uncertain intraepithelial tumors; 3. low-grade intraepithelial tumor; 4. high-grade intraepithelial tumor; 5. Cancer.
2. Evaluation method of histopathological efficacy: according to the consensus on diagnosis and treatment of CAG with TCM\(^{[24]}\), and referring to the histopathological characteristics of CAG,
different variables are divided into main and secondary variables. The main variables include atrophy, intestinal metaplasia, and intraepithelial tumor, while the secondary variables include chronic inflammatory reaction, activity, and HP infection. According to the consensus for diagnostic pathology of biopsies of chronic gastritis and epithelial neoplasms\textsuperscript{[26]} (focusing on text description) and the intuitive simulation scoring method (focusing on picture images) of the new Sydney system, all variables are classified into "none," "mild," "moderate," and "severe" 4 grades (note: grade 5, cancer in intraepithelial tumors, does not belong to the scope of this study). The 4 grades of main variables are scored as 0, 3, 6, and 9, and the 4 grades of secondary variables are scored as 0, 1, 2, and 3 respectively. Lesions often occurs in 5 parts: greater curvature of gastric antrum; lesser curvature of gastric antrum; the gastric angle; greater curvature of stomach; lesser curvature of stomach. The scores will be recorded based on the lesion in each part. The score of each variable is compared before and after treatment as the histopathological curative effect. Pathological diagnosis will report the histological changes of biopsy specimens in each site. When the multiple pathological sections in the same site is different, scores shall be given according to the most severe lesion. Table 1 show the histopathological scores.

3. Detection time: before treatment, after treatment, and during follow-up, each examination shall be conducted once for a total of 3 times.

**Secondary Outcome**

1. Gastroscope evaluation indicator
   Gastroscopy observation: Grading standards are formulated according to the endoscopic classification and grading standard for chronic gastritis and trial opinions on treatment\textsuperscript{[27]}. Main pathological changes: mucosal white phase, vascular exposure, plica flattening, mucosal granules, intestinal nodules. Secondary pathological changes include erosion, hemorrhage, and bile reflux. According to the endoscopic mucosal manifestations, the main and secondary pathological changes are divided into 4 grades, and the 4 grades were marked with 0, 3, 6 and 9 respectively, and the 4 grades of secondary pathological changes were scored as 0, 1, 2, and 3 respectively. Lesions often occur in the five parts (same as mentioned above), and the scores will be recorded in each part. The score of each variable is compared before and after treatment as gastroscope evaluation indicator. Table 2 show the gastroscope scores.

2. Syndrome curative effect evaluation indicator
   Nimodipine was used to evaluate the curative effect, with symptoms as the main factor, and tongue coating and pulse condition as part of the evaluation. Nimodipine calculation method: efficacy index (%) = (score before treatment-score after treatment)/score before treatment x 100%. Clinical recovery: main symptoms and signs disappear or almost disappear, with an efficacy index \( \geq 95\% \); Obvious effect: the main symptoms and signs were significantly improved; with 70\% \leq efficacy index < 95\%; Effective: main symptoms and signs improved significantly, with 30\% \leq efficacy index < 70\%; Invalid: main symptoms, signs and symptoms are not significantly improved, or aggravated, with efficacy index < 30\%.

3. Symptom evaluation indicator
   The clinical symptoms of CAG and the clinical outcomes were evaluated by using the physician report outcome scale (Clinician reported outcome, CRO) recommended by expert consensus opinion on standard quantification of spleen and stomach diseases\textsuperscript{[28]}. 
4. Quality of life evaluation
In terms of quality of life, the chronic gastritis PRO (patient reported outcomes) scale, the clinical
outcome evaluation scale for patients with chronic gastrointestinal diseases, the Chinese Health
Status Scale and the SF-36 Health Survey Scale were used for evaluation.
5. Evaluation of anxiety and depression
Hospital Anxiety and Depression Scale (HAD) was adopted to evaluate subjects who may suffer
from anxiety and depression states.
6. Economic evaluation: collect the medical expense data of the subjects during the study period
and make cost-effectiveness analysis and cost-benefit analysis.
7. Other indicators: 1. Serum indicators: serum pepsinogen I, II and gastrin 17. 2. Gastric Mucosa
Index: key RNA and related pathway proteins in "Inflammation-Cancer" evolution of CAG. 3.
Saliva index.
8. Observation time of all the above-mentioned indicators: before treatment, after treatment, and
during follow-up, each examination was conducted once for a total of 3 times.

Research evaluation Indicators
1. Compliance indicators:
Observation items: whether medication is taken on time and in quantity; whether other drugs are
taken; whether regular follow-up visits are required; whether the observation project is completed
according to the research requirements.
Evaluation method: The medication compliance of the subjects was calculated by the formula
actual dosage/required dosage * 100%, and other observation contents were recorded in detail and
their effects on the research results were analyzed.
Observation time: The patients were followed up once after treatment and twice during treatment.
2. Combined medication index
During the study period, subjects can take drugs for the treatment of concomitant diseases.
Researchers will make detailed medication records, analyze the combined medication, and explain
its impact on the research results.
3. Rejection and termination
Researchers will record in detail the number of cases rejected and terminated in each group and
describe and record in detail the reasons for suspension, withdrawal, missed visit and rejection.

Safety Evaluation
1. Safety indicators
The subject voluntarily accepts the examination or the doctor requires the examination according
to the patient's condition.
Test items: blood analysis, urine analysis, stool routine and occult blood, electrocardiogram, liver
function (ALT, AST), renal function (Cr, BUN), electrocardiogram, liver, gallbladder, spleen,
pancreas and double kidney color Doppler ultrasound (the results are valid in the past month).
Researchers will record in detail the safety indicators in the research process. Abnormal safety
indicators in the research process require doctors to judge its clinical significance and explain the
results. If safety indicators are defined as adverse reactions or adverse events, adverse reactions
and adverse events shall be recorded and reported, and corresponding countermeasures shall be
taken in a timely manner.
2. Safety evaluation indicators
The main indicators are both occurrence rate and detailed situation of adverse events and adverse reactions.
Detection time of all the above-mentioned indicators: before treatment, after treatment, and during follow-up, each examination was conducted once for a total of 3 times.

Follow-up
The subjects were followed up for 24 weeks. The incidence rate of gastric mucosa high-level intraepithelial neoplasia was the endpoint outcome index. The relapse and progress of the disease were tracked for a long time to evaluate the long-term efficacy of treatment.

Quality management of research
This study will establish standard operating procedures (SOP) for each stage in the study, such as: the recruitment process of subjects; the process of filling in eCRF; subject management; selection of treatment plan; gastroscope standard operation and sampling; gastric mucosa specimen processing and transportation; handling and transporting serum samples; handling and transporting saliva samples. All SOPs will be entered into the electronic database. In addition, this study will carry out regular maintenance and testing of the equipment needed in the study to avoid laboratory errors.

Data management
Researchers need to ensure the authenticity and integrity of the data in the case report form and treat the inevitable missing data according to the missing values in statistics.
Statistical analysis
1. Descriptive statistics: SPSS 17.0 software was used for calculations. Counting data are expressed by frequency and composition ratio. Measurement data conform to the mean and standard deviation of normal distribution, while measurement data that do not conform to normal distribution are expressed by median or mode.
2. Difference test: SPSS 17.0 software was used for calculations, and chi-square was used for comparison between counting data groups. Covariance analysis/repeated measurement analysis of variance is used when the normal distribution is compared between measurement data groups and the variance is uniform. Paired rank sum test is used for non-normal distribution or uneven variance.

Discussion
To date, the treatment of CAG still revolves around the eradication of HP, antacids, prokinetics and mucosal-protective agents[29]. However, HP has developed resistance to several antibiotics[30], which means that HP eradication may be ineffective in some HP positive patients. TCM treatment can provide a powerful and safe therapeutic approach for the treatment of CAG.
According to the Consensus on TCM Diagnosis and Treatment of Chronic Gastritis (2017)[19], FSCHABM is appropriate for the entire treatment process of CAG. In clinical practice, TCM practitioners will flexibly change Chinese herbs and prescriptions according to the patient's symptoms and signs, but the method of treatment always revolves around FSCHABM.
Regarding CAG's existing RCT report, however, CAG has a short treatment course and is at high risk of selection and performance bias due to a lack of reporting of information regarding
allocation concealment and blindness, especially for TCM research. RCT strictly requires random grouping and to give medicines uniformly, which contradicts the concept of holism and treatment based on syndrome differentiation, and fails to give full play to the curative effect of TCM. To pander to the basic theory of TCM, and pursue high-quality clinical trials, a new model of research is required for truly reflecting the efficacy of TCM. Undoubtedly, the real-world study is consistent with the clinical practice of TCM, and is also suitable for chronic disease research. As a chronically developed disease, CAG urgently needs this research model to explore the development and efficacy of the disease treatment. However, the real-world study of CAG has not been reported up to now. The treatment of FSCHABM after repeated clinical practices shows that it is always effective in improving the symptoms of CAG patients. However, the occurrence and development of CAG, the curative effect and therapeutic mechanism of FSCHABM are unclear. Therefore, the purpose of this protocol is to evaluate the clinical efficacy and safety of FSCHABM in the treatment of CAG. We conducted a clinical research and comprehensive evaluation of TCM’s intervention for CAG and explored the molecular mechanism of FSCHABM in the treatment of CAG. Moreover, this protocol is designed to provide an excellent clinical study protocol for clinical researches of CAG or other chronic diseases, which is a more realistic display of the development and curative effect of TCM, and provides a reference for the multi-center, randomized, controlled trials.

**Trial status**
The protocol version number is 2.0. Trial recruitment was started on March 30, 2018, and the trial has enrolled 458 patients at the time of manuscript submission. Recruitment is expected to be completed in March 2028.

**Ethics and dissemination**
Study findings will be shared with participants, healthcare providers, and policymakers through research reports, conference presentations, and the Internet. The results will also be disseminated through publication in peer reviewed journals.

**Abbreviations**
CAG: Chronic atrophic gastritis; HP: *Helicobacter pylori*; FSCHABM: the fortifying the spleen, clearing heat, activating blood method; TCM: traditional Chinese medicine; RCT: randomized controlled trial; PRO: patient reported outcomes; HAD: Hospital Anxiety and Depression Scale; SOP: standard operating procedures.

**Authors’ contributions**
Zhihua Zheng and YI Wen designed the study and drafted the manuscript; Peiwu Li and Jinglin Pan provided methodological advice and critically revised the manuscript; Yanhua Yan, Zhiheng Xu, Kecao Nie, Xu Chen, Fengbin Liu were involved with recruitment and follow-up; All authors have read and approved the final version of the manuscript.
Competing interests
The authors declare that they have no competing interests.

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Fernández Salazar L, Valle Muñoz J. Treating Helicobacter pylori infection in the face of growing antibiotic resistance. *Rev Esp Enferm Dig* 2019;111:653–4.
Subjects participating voluntarily in the trial

Screening eligibility

Meet inclusion criteria

Meet exclusion criteria

Enrolling failure

Written informed consent obtained and baseline collection

Elution period of clinical trial

Grouping (n = 5000)

MFHSABRT treatment (n = 2500)  Non-MFHSABRT treatment (n = 2500)

Follow-up

Indicators for observation and measurement

Outcomes assessment
| Table 1. Histopathological scores |
|----------------------------------|
|                                   |
|                                   |
| Grade                        | Score |
|--------------------------------|-------|
| None  | Mild | Moderate | Severe |
|-------|------|----------|--------|
| Atrophy | 0  | 3        | 6      | 9      |
| Intestinal metaplasia | 0  | 3        | 6      | 9      |
| Intraepithelial tumor | 0  | 3        | 6      | 9      |
| Chronic inflammatory reaction Activity | 0  | 1        | 2      | 3      |
| HP infection           | 0  | 1        | 2      | 3      |

Note: The score of each variable in each part is compared before and after treatment as the histopathological curative effect.
### Table 2. Gastroscope scores

| Grade | Score |
|-------|-------|
| None  | Mild  | Moderate | Severe |

**Main variables**

| Mucosal white phase | 0 | 3 | 6 | 9 |
|---------------------|---|---|---|---|
| Vascular exposure    | 0 | 3 | 6 | 9 |
| Plica flattening     | 0 | 3 | 6 | 9 |
| Mucosal granules     | 0 | 3 | 6 | 9 |
| Intestinal nodules   | 0 | 3 | 6 | 9 |

**Secondary variables**

| Erosion            | 0 | 1 | 2 | 3 |
|--------------------|---|---|---|---|
| Hemorrhage         | 0 | 1 | 2 | 3 |
| Bile reflux        | 0 | 1 | 2 | 3 |

**Total score**

*Note: The score of each variable in each part is compared before and after treatment as the gastroscope evaluation indicator.*
# Approval Letter

**项目名称**

基于真实世界的健脾和胃活血解毒法治疗慢性萎缩性胃炎的临床观察研究

**试验目的**

□ Ⅰ期临床试验： □ Ⅱ期临床试验： □ Ⅲ期临床试验： □ Ⅳ期临床试验：

□ 生物等效性试验： □ 进口药注册临床试验： □ 上市药再评价： □ 中药保护品种试验：

■ 科研课题： □ 医疗器械临床试验： □ 医疗器械临床验证： □ 研究生教育： □ 其他

**科室/专业名称**

脾胃病科

**主要研究者**

刘凤斌 主任医师

**批准材料 documents**

1. 伦理审查申请；
2. 临床研究方案（版本号 2.0, 20180326）；
3. 知情同意书（版本号 2.0, 20180326）；
4. 主要研究者履历与 GCP 培训证书；
5. 病例报告表（第 1 版，20180106）；
6. 课题立项通知/课题计划书；
7. 研究者手册（第 1 版，20180106）；
8. 招募受试者材料（第 1 版，20180106）。

**审查情况 Review modes**

初始审查方式 Initial Review:

■ 快速审查 Expedited

□ 会议审查 Full Board

会议时间 Date:

（另附会议签到副本）

**结论 Decision**

复审结论：同意 approve

**年度/定期跟踪审查频率 Annual Follow-Up Review Frequency**

12 个月，

请于 2019 年 3 月 30 日 前 1 个月提交年度/定期跟踪审查（研究进展报告）

**批件有效期 Expiry of Approval Letter**

2018 年 3 月 30 日 ~ 2019 年 3 月 30 日

若在批件有效期内研究项目没有启动，请重新提交伦理初始审查。

在研项目：若超出批件有效期，没有递交《研究进展报告》及获得伦理审查批准继续研究，研究者必须立即停止所有研究活动，包括干预措施和数据收集。假若停止研究干预可能会对受试者造成伤害，研究者应当要求伦理委员会批准在研的受试者继续参与研究。

共 2 页 1
| 注意事项 | Attention |
|--------------------|-----------|
| 联系方式（委员会秘书） | Contact/EC Secretary |
| 黎老师，外线：020-36588667（周一、周三，14:30-17:30）/020-36591965；医院内线：1530（周一、周三，14:30-17:30）/1965；传真：020-36591346；邮箱：gztcmlyptail@163.com |
| 主任委员/被授权者签名 | Signature of the Chair/Authorized Person |

声明：本伦理委员会严格按照中国GCP及相关法规组成和工作。
知情同意书

敬爱的患者朋友：

您的医生已经确诊您为慢性萎缩性胃炎患者。

我们想邀请您参加一项广东省教育厅高水平大学团队资助项目（基于疑难病的调理脾胃方药作用机制研究）的子课题--基于真实世界的健脾和胃活血解毒法治疗慢性萎缩性胃炎的临床观察研究。在您决定是否参加这项研究之前，请尽可能仔细阅读以下内容，它可以帮助您了解本项研究的目的、内容以及参加研究后可能给您带来的益处、风险和不适。如果您愿意，可以与您的亲属、朋友一起讨论，或者请您们的医生给予适当解释及参考意见，帮助您决定是否参加本项研究。

1. 研究背景和研究目的

慢性萎缩性胃炎是消化系统常见病、疑难病之一，在其基础上伴发的肠上皮化生、异型增生（上皮内瘤变）是胃癌前病变。权威文献报道：慢性萎缩性胃炎患者10～20年后胃癌发生率约8%；慢性萎缩性胃炎伴肠上皮化生胃癌年发生率为0.25%，异型增生（上皮内瘤变）胃癌年发生率为0.6-6%。

慢性萎缩性胃炎病因及发病机制尚不明确，治疗上以缓解症状为主，目前尚无一种药物被证实治疗慢性萎缩性胃炎有效。中医药治疗本病从整体观念出发，病证结合，独具优势。

为了评价中医药治疗慢性萎缩性胃炎的有效性及安全性。为了寻找治疗慢性萎缩性胃炎更有效的中药，在前期文献研究基础上，本项目研究团队优化本院院内制剂--加味胃炎消片的组方，提出健脾和胃活血解毒法为治疗慢性萎缩性胃炎的核心治法。

2. 研究内容

本项目为广东省教育厅高水平大学团队资助项目，采用真实世界的研究方法评价健脾和胃活血解毒法治疗慢性萎缩性胃炎的有效性及安全性。

本项目是在真实的医疗环境下，观察中医药治疗慢性萎缩性胃炎的疗效及安全性。预计有5000例像您一样诊断为慢性萎缩性胃炎的患者参加，每个受试者的筛选时间为7天（1周）。如果您符合入选标准，同意参加研究，我们将为您建立个体化详细病历档案，采集疾病相关的信息，详细记录您的治疗过程及病情变化。

根据您的主诊医师为您制定的诊疗方案，我们将您归类为健脾和胃活血解毒法观察组或非健脾和胃活血解毒法观察组，每组约2500人次。健脾和胃活血解毒法
知情同意书

基于真实世界的健脾和胃活血解毒法治疗慢性萎缩性胃炎的临床观察研究

观察组以核心组方（白术、太子参、茯苓、半枝莲等）进行辨证及辨症加减治疗。非健脾和胃活血解毒法观察组的治疗措施为西药、非健脾和胃活血法的中成药、中药汤剂、针灸、穴位贴敷等治疗手段。

特别说明，本研究只进行疗效观察，额外采集临床标本进行检测，不干预主诊医师为您制定的诊疗方案。在临床研究开始前既往合并疾病或症状必须接受某种药物或非药物治疗手段者，可以继续使用。医生将在病例报告表中详细记录药物通用名或其它疗法名、用量、使用原因、次数和时间等信息。

本研究遵从赫尔辛基宣言原则，研究方案已获得广州中医药大学第一附属医院伦理委员会批准。研究人员将向您详细介绍研究流程，参加与否完全遵循自愿的原则。

3. 如果您志愿受试将需要配合完成以下工作：

（1）您经研究人员筛查合格后，如果您参加本研究前4周仍在服用与本病相关的药物，请您告知医生。

（2）在观察期间，请您遵照主诊医生医嘱，规律服药，避免擅自调整用药。

（3）在观察期间，您每周需填写症状及服药周记。您必须按医生指导用药，并请您在每次服药后及时、客观地在“服药记录卡”中记录。包括您有其它合并疾病须继续服用的药物。请您不要将药物给其他人服用，并将其存放在远离儿童的地方。

（4）治疗疗程：24周为1疗程，根据具体病情，您可能需要接受1-2个疗程的治疗。研究人员将详细记录您每次就诊的信息（包括病程记录、处方信息、四诊信息）并且每8周对您进行1次访视。每次访视研究人员会检查您的症状及服药周记情况，同时会询问您的情况并对其进行必要的体格检查，填写疗效相关的量表，评估药效及不良反应。

（5）如果您治疗期间中出现身体不适，请您及时反馈给医生。医生将会给您合适的指导，必要时适度调整您的治疗方案。请您不要随意服用其他药物，尤其是治疗慢性胃炎相关的药物。如因为其他疾病服用药物，请您务必在周记中详细记录您的服药情况并反馈给医生。如果出现不良事件或严重不良事件医生将从您的利益出发，考虑您是否继续参与临床试验。

（6）治疗结束我们建议您行胃镜及病理组织活检评估疗效。为巩固疗效，监
知情同意书

基于真实世界的健脾和胃活血解毒法治疗慢性萎缩性胃炎的临床观察研究

测病情变化，治疗结束后 8 周内我们将对您进行 1 次访视，治疗结束后 24 周我们建议您行胃镜及病理组织活检。

（7）在您配合上述检查的同时，我们需要在治疗前/后额外采集您的唾液、2 支 5ml 血液以及 2 块胃黏膜标本以备后期检测慢性萎缩性胃炎“炎-癌”相关的指标，评估药效。

（8）为方便医生与您沟通和交流，请您留下至少 3 种联系方式。

4. 两点说明

（1）费用说明：整个研究中涉及的检查费用、诊疗费用、药品费用均需您自行承担。

（2）我们额外采集的唾液、血液以及 1-2 块胃黏膜标本将由本中心检测慢性萎缩性胃炎“炎-癌”相关的指标，所检测的指标不产生任何费用。

5. 参加研究可能的受益

（1）本中心为国家临床重点建设脾胃病专科，从事中医药防治慢性萎缩性胃炎研究已有 30 年，多位脾胃病专家临床经验丰富。

（2）整个研究周期您将免费享受本研究团队提供的热情周到的医疗服务。包括：生活调理指导、宣教疾病相关的科普小知识、24 小时全天咨询、预约胃镜检查等。

（3）慢性萎缩性胃炎为胃癌前疾病，在此基础上伴发的低级别上皮内瘤变为胃癌前病变。因此，需要您定期进行胃镜检查以监测病情变化，尽早采取积极治疗措施。在您参加研究期间，本研究团队将为您建立病历档案，详细记录您的病情变化，必要时给予合理的建议，帮助您监测疾病的进展情况。

（4）如果您在研究期间出现不良事件或严重不良事件，本研究已制定相关备案，尽可能保证您的生命安全。

特别指出：本研究对您可能会有直接好处，但也可能没有。您的慢性萎缩性胃炎病情可能会治愈或减轻，也可能会加重。但是，通过研究所得到的信息可能会有助于进一步改进针对此病的治疗方法，这可能会给病情和您类似的其他患者带来好处。

6. 您的义务

（1）坚持自愿参加的原则，在研究开始之前签署知情同意书。
知情同意书

基于真实世界的健脾和胃活血解毒法治疗慢性萎缩性胃炎的临床观察研究

7. 参加研究的风险

（1）药物过敏：您对本研究所使用的中药、西药产生过敏反应。本研究中心所使用的中药到目前为止还未发现过敏反应。所使用的西药过敏反应详见药品说明书。所有治疗药物都可能产生一些过敏反应。如果您对我们的研究药物过敏，请您务必提前说明。

（2）药物不良反应：本研究所使用的中药可能出现腹泻、腹胀等不良反应。所使用的西药可能出现的不良反应详见药品说明书。如发生不良反应时，主诊医师会建议您进行一系列的安全性检查，请您务必配合，最大限度地监测您的病情变化，减少不良反应。一旦发生不良反应，本项目组将启动应急预案对您的病情进行及时处理。

（3）采血风险：采血存在血肿、针孔感染、晕血、反复穿刺、神经损伤等风险。本研究将规范采血操作，最大限度规避该风险。

（4）胃镜检查及病理组织活检风险：胃镜检查为侵入性检查，现将可能发生的风险告知您。该操作技术有一定的创伤性和危险性，在病理取材过程中/后可能出现下列并发症和风险：消化道出血；消化道穿孔；疼痛；吸入性肺炎；肺部感染；呼吸衰竭；心绞痛；心律失常；心脏骤停；损伤临近器官和血管；一些并发症需外科手术补救治疗，外科手术也具有相应的风险；如发生意外、并发症和不良反应时可能会相应增加医疗费用；其他无法预知的意外和风险；如不实施胃镜的风险等。此外，每次胃镜下胃黏膜病理活检块数约3-5块，为预防消化道出血本研究建议您活检后口服云南白药胶囊及磷酸铝凝胶预防消化道出血。胃镜检查将严格按照操作规范进行，最大限度的避免上述并发症的出现。若出现出血、穿孔等并发症，我们将采取相应应急措施进行治疗。如果您有特殊的问题可向研究者咨询。

（5）病情进展为高级别上皮内瘤变的风险：慢性萎缩性胃炎为胃癌前疾病，临床随诊慢性萎缩性胃炎伴上皮化生胃癌年发生率为0.25%，异型增生胃癌年发生率为0.6-6%。不排除部分患者在研究过程中出现病情进展为胃黏膜高级别上皮内瘤变。临床胃镜及病理随诊是监测癌变的重要手段，因此请您务必配合每次治疗结束后对胃镜、病理活检及血清胃蛋白酶原检查，以便密切监测您的病情变化。
知情同意书

基于真实世界的健脾和胃活血解毒法治疗慢性萎缩性胃炎的临床观察研究

结果试验过程中您的病情发生变化，研究人员将评估您的病情，必要时终止试验。

（6）其他风险：如果您在研究中出现任何不适，或病情发生新的变化，或任何意外情况，不管是否与药物有关，均应及时通知研究人员。本研究将启动应急预案对此做出医疗处理。研究人员将尽全力减少本研究可能给您带来的伤害。

8. 重要提示

由于缺乏药物对胚胎毒性的相关数据，如您是妊娠期、哺乳期或近期有生育意向的妇女，则不宜参加本研究。育龄期妇女或配偶为育龄期女性，应在研究期间进行可靠避孕，建议采用1-2种避孕措施，避免受孕。若受孕则马上中止并退出临床研究，且联系您的主诊医师和专业的妇产科医生采取相应处理措施。

9. 终止您参加试验的理由

（1）研究期间出现新发属于排除标准的疾病，如胃黏膜高级别上皮内瘤变。

（2）研究者发现严重安全问题。

（3）研究经费不足难以完成研究。

（4）行政主管部门撤销试验。

10. 个人信息是保密的吗？

您参加本研究的所有医疗记录将以电子版和纸质版的形式完整地保存在我中心，研究者会将化验检查结果记录在您的研究报告表上。研究者、本院伦理委员会和科研管理部门将被允许查阅您的医疗记录。任何有关本项研究结果的公开报告将不会披露您的个人身份。我们将在法律允许的范围内，尽一切努力保护您个人医疗资料的隐私。

11. 怎样获得更多的信息？

您可以在任何时间提出与本项研究有关的任何问题。您的医生将留下他的电话号码。

如果在研究过程中有任何重要的新信息，可能影响您继续参加研究的意愿时，您的医生将会及时征求您的书面意见。

12. 您可以自愿选择参加研究和中途退出研究

是否参加研究完全取决于您的自愿。您可以拒绝参加此项研究，或在研究过程中的任何时间退出本研究，签署了知情同意书而决定退出时，研究人员会尊重您的选择。这都不会影响您和主诊医师间的关系，都不会影响对您的医疗或有其他方面
利益的损失。

13. 您决定参加研究，怎么办？

如果您完全理解医师对本研究的解释并自愿参与，您需要签署一份知情同意书。再决定参与研究之前，您可以与您的亲属、朋友讨论这件事情。将会给您一份同意签字页的副本。
知情同意书签字页

研究医师告知：
我作为研究医师，确认我已经向受试者明确地解释了《广东省教育厅高水平大学团队资助项目（基于疑难病的调理脾胃方药作用机制研究）的子课题—基于真实世界的健脾和胃活血解毒法治疗慢性萎缩性胃炎的临床观察研究》的性质、目的、可预见的风险等。他/她已经阅读并保留了一份受试者知情告知页和同意签字页的副本。他/她自愿同意参加本试验。

受试者知情理解：
我已经阅读了上述有关本研究的介绍，而且有机会就此项研究与医生讨论并提出问题。我提出的所有问题都得到了满意的答复。
我知道参加本研究可能产生的风险和受益。我知晓参加研究是自愿的，我确认已有充足时间对此进行考虑，而且明白：
我可以随时向医生咨询更多的信息。
我可以随时退出本研究，而不会受到歧视或不公正待遇，医疗待遇与权益不会受到影响。
我同样清楚，如果我中途退出研究，特别是由于药物的原因使我退出研究时，我若将病情变化告诉医生，完成相应的体格检查和化验检查，这将对我本人和整个研究十分有利。
如果因病情变化我需要采取任何其他的药物治疗，我会在事先征求医生的意见，或在事后如实告诉医生。
我同意参加本研究，谨遵医嘱。我已经收到了一份受试者知情告知页和同意签字页的副本。

受试者签名：
日期：__ __ __ __年 __ __月 __ __日

身份证号码：
联系电话：

受试者联系人：
联系电话：

我确认已向患者解释了本试验的详细情况，包括其权利以及可能的受益和风险，并给其一份签署过的知情同意书副本。

医生签名：
日期：__ __ __ __年 __ __月 __ __日

医生工作电话：

受试者投诉部门：广州中医药大学第一附属医院伦理委员会
受试者投诉电话：020-36588667（周一、周三 14:30-17:30）/020-36591965