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Protocol

Chinese medicine JQ granule combined with half-dose omeprazole for nonerosive reflux disease: A multicenter, randomized, double-blind, placebo-controlled trial study protocol

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ABSTRACT

Introduction: Nonerosive reflux disease (NERD) is a kind of esophageal disease manifesting mainly as heartburn and regurgitation. The prevalence of NERD in patients with gastroesophageal reflux disease is up to 70%, and it significantly affects the quality of life of patients. In China, besides proton-pump inhibitors (PPIs), a herbal formula is widely used in nonerosive reflux disease, which can improve intestinal and extra-intestinal symptoms of patients. This study will evaluate in a large, independent, randomized controlled trial (RCT) the comparative effectiveness of a specific type of Chinese herbal granule with half-dose PPI and full-dose PPI in managing nonerosive reflux disease.

Methods and analysis: This trial will be a multicenter, randomized, double-blind, placebo-controlled RCT. A total of 204 participants will be enrolled and randomized (1:1) to each group: herb granules plus 10 mg omeprazole plus 10 mg dummy omeprazole; and dummy herb granules plus 20 mg omeprazole. The efficacy measures will be the changes in scores in the Gastroesophageal Reflux Disease Questionnaire, the Short-Form 36, the Patient Report Outcome, the 17-item Hamilton Depression Scale, and the Signs and Symptoms Scale.

Discussion: This study will focus on the quality control of a Chinese medical formulation. The RCT research procedure will be conducted under the supervision of the Good Clinical Practice (GCP) center. This trial will reduce the routine dosage of omeprazole while adding Jianpi Qinghua JQ granule, with the aim to discuss the safety and effectiveness of the Chinese herbal granule on esophageal and extraesophageal symptoms while meeting the ethical requirements.

1. Introduction

Gastroesophageal reflux disease (GERD) is one of the most common diseases in gastroenterology. GERD is characterized by symptoms resulting from the reflux of gastric contents into the esophagus, oral cavity, larynx, or lung. Based on the results of esophagoscopy, GERD can be classified into two types according to the erosion of the esophagus: nonerosive reflux disease (NERD), which is without erosions, and reflux esophagitis (RE) with erosions. The prevalence estimates show considerable geographic variations. The range of GERD prevalence estimate is 18.1%–27.8% in North America and 8.8%–25.9% in Europe, but only East Asia shows estimates consistently lower than 10% [1]. GERD is prevalent worldwide, and the disease burden has increased. The typical symptoms of GERD are heartburn and regurgitation. Atypical symptoms, including dyspepsia, epigastric pain, chest pain, bloating, nausea, and belching, may be indicative of GERD but overlap with other conditions [2]. A retrospective study found that the frequency of regurgitation and heartburn had an incremental negative impact on health-related quality of life [3]. The patients had an increase in time off work and decrease in work productivity and physical functioning.

To treat GERD, lifestyle intervention is the first choice. It contains weight loss, tobacco and alcohol cessation, avoidance of late-night meals, and cessation of high-glucose and high-fat diet that can

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aggravate reflux symptoms. Patients failing in lifestyle interventions can try medical treatments including antacids, histamine-receptor antagonists (H_2RA), or proton-pump inhibitor (PPI) therapy. However, a Cochrane systematic review demonstrated that PPIs were more effective than H_2RAs in relieving symptoms of heartburn in patients with GERD [4]. At present, PPIs have a definite effect and are the most widely used drugs for treating GERD.

However, adverse events concerning PPIs have received increasing attention in recent years. The main adverse events include headache, diarrhea, and dyspepsia. Other potential adverse reactions include vitamin and mineral deficiencies, pneumonia and diarrhea, hip fractures and osteoporosis, and cardiovascular events in patients using clopidogrel. A research found that PPIs are likely to encourage the growth of some gut microflora and increase susceptibility to pathogenic bacteria [5]. The American Gastroenterological Association suggested that the dose of long-term PPIs should be reevaluated periodically to guarantee the lowest-effective PPI dose that can be prescribed to adapt to the treatment protocols [6]. Further, during maintenance PPI therapy, patients with GERD sometimes complain of upper gastrointestinal symptoms. A study found that upper gastrointestinal symptoms were more severe in patients with NERD than in patients with RE. These patients with NERD paid more attention to their upper GI symptoms, wanted to change PPI therapy [7], and had severe epigastric pain or burning symptoms, severe depression, and less therapeutic response compared with patients with RE [8]. Although PPIs are the most commonly used medical treatment for GERD, they cannot resolve all GERD symptoms; a part of the patients are not satisfied with the PPI therapy [9].

The use of herbal decoction is prevalent in clinic in China. Jianpi Qinghua (JQ) granule is often used in the gastroenterology department for patients with NERD. It is used as a granulated extract obtained by spray drying the hot water extract of a mixture of 10 crude herbs. The combination of herbs in the JQ granule is based on traditional Chinese medicine (TCM) theories and the clinical experience of TCM practitioners (meanwhile, the JQ granule is being reviewed by the China National Intellectual Property Administration). The herbs in the JQ granule have different effects, including protective effects on gastric mucosa [10,11], antispasmodic effects [12], accelerating gastric emptying and intestinal transit [13,14], anti-inflammatory effects [15], and even antidepressant effects [13]. The dosage is within the safe limit specified in *the Chinese Pharmacopoeia* (2015 edition).

This study will be performed to evaluate the comparative safety and effectiveness of omeprazole and JQ granule in treating NERD. The full-dose omeprazole will compared the combination of JQ granule with half-dose omeprazole. The results of the study may provide reference and clinical evidence for treating NERD with a combination of JQ granule and lower-dose omeprazole in clinical practice.

2. Materials and methods

The SPIRIT checklist will be used while compiling the report [16].

2.1. Study setting

This trial is a multicenter two-arm, parallel-group, placebo-controlled randomized controlled trial (RCT), involving 204 adults with NERD. Three tertiary hospitals in Beijing will enroll participants. The primary efficacy measure will be the change in the total score on the Gastroesophageal Reflux Disease Questionnaire (GerdQ) [17] from baseline to endpoint, and the secondary efficacy measures will be the changes in scores on the Short-Form 36 (SF-36), the Patient Report Outcome (PRO), the 17-item Hamilton Depression Scale (HAMD17), and the Signs and Symptoms Scale (SS) based on *the Clinical Guideline of New Drugs for Traditional Chinese Medicine* [18]. Before the trial begins, the chief physician will organize investigators to study and familiarize the aforementioned five scales and learn the skills to guide participants to complete the scale. All drugs will be taken orally in the trial, and the participants' use will be prescribed and overseen by the respective chief physician and ethics committee.

2.2. Participants

2.2.1. Inclusion criteria

The diagnostic criteria of NERD will be in accordance with *the China Consensus Opinion on Gastroesophageal Reflux Disease, 2006 edition.* Participants aged between 18 and 70 years who meet the following diagnostic criteria will be included: typical symptoms of heartburn and regurgitation appearing at least 1 day a week; elimination of RE, Barrett's esophagus, and other upper gastrointestinal diseases revealed by esophagogastroduodenoscopy (EGD) in recent 1 month; participants' score on GerdQ no less than eight; and participants willing and able to give informed consent.

2.2.2. Exclusion criteria

The exclusion criteria will be as follows: potential participants with severe primary disease of other systems or cancer; women who are pregnant, breastfeeding, or preparing for pregnancy; people currently using drugs that interacted with PPIs and reduced their effectiveness, or involved in another clinical trial; and people allergic to any herb in the JQ granule.

2.2.3. Participant timeline

The participants will be enrolled for a total of 6 weeks (4 weeks for the treatment phase and 2 weeks as the follow-up period). During the prescreening and screening period, the participants need to discontinue the NERD-related drugs, including PPI, H_2RA, antacids, antidepressants, and any herbs; complete the EGD safety test; and sign the informed consent form (the specific content of informed consent form can be found in online supplementary appendix 1). During the baseline phase, the participants need to complete the first assessment and be randomly assigned to one group. During the treatment phase, they will be guided how to take medicines, followed by assessment after 2 and 4 weeks for compliance and outcome. The follow-up phase will be 2 weeks after completion of the treatment.

2.2.4. Recruitment

Potential participants will be identified through gastroenterology clinics, the hospital's WeChat official publicity and recruitment advertisements, and the health- and medical-related TV programs. They will be screened by the chief physicians in clinics.

The flow chart for participant selection through the trial is summarized in Fig. 1, and the details of the data collection schedule are summarized in Table 1.

2.2.5. Dropout criteria

Participants will be entitled to quit at any time if they suffer from a severe adverse effect, aggravation of disease, and hypersensitivity towards the research medication. The study will be terminated under the following conditions: presence of serious adverse events related to the experimental medication and no obvious practical value of the medication.

2.2.6. Patient and public involvement

Every research hospital has a specialized clinic for NERD, which highlighted this as a priority topic. In the outcome indicators mentioned later, the PRO scale was a scale developed by the team after 2 years of collecting, screening, and optimizing the clinical symptoms of patients with chronic gastrointestinal diseases in China; it included surveys on patients with NERD. Some patients have given suggestions on how to introduce the specific content of the scales to the participants so that they could better understand the scales.

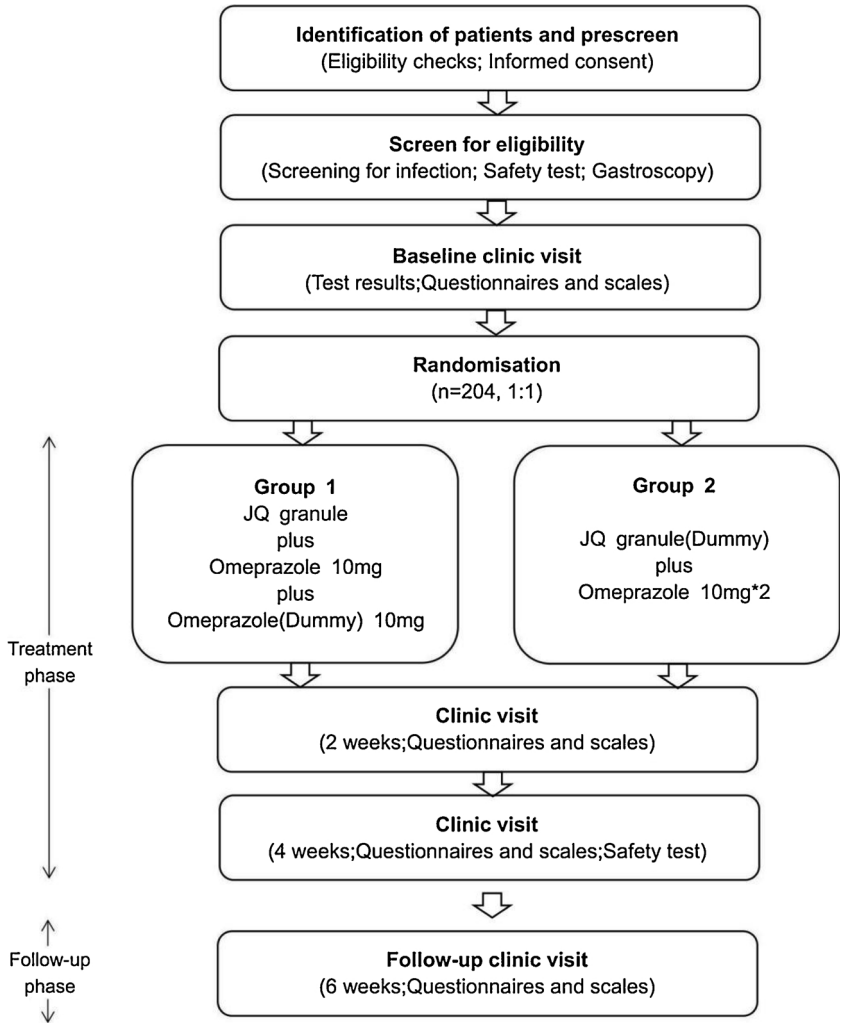

Fig. 1. Flow chart for participant selection through the trial.

2.3. Randomization and blinding

The participants in three hospitals will be randomized to one of two treatment groups by block randomization in a ratio of 1:1 as follows:

Group 1: JQ granules plus omeprazole 10 mg × 1 tablet plus dummy omeprazole 10 mg × 1 tablet

Group 2: Dummy JQ granules plus omeprazole 10 mg × 2 tablets

Random numbers will be generated by the Statistical Analysis System 9.2 (SAS 9.2) and based on the allocation sequence. Every number will be put in a brown envelope, and the envelope sequentially numbered and retained by the clinical research coordinator. After screening, the envelopes will be distributed among the participants, and the order of envelopes

Table 1
Timetable of trial assessments.

Outcome collected	Prescreen	Visit 1 –2 weeks Screening	Visit 2 0 week (baseline)	Visit 3 2 weeks (Treatment)	Visit 4 4 weeks (Treatment)	Visit 5 6 weeks (Follow-up)
Eligibility checks	√	√	√			
Informed consent	√					
Safety test		√			√	
Screening for infection		√				
EGD		√				
Safety test results			√			√
EGD result			√			
Baseline characteristics			√			
Vital signs			√	√	√	√
Questionnaires and scales			√	√	√	√
Randomization			√			
Medication administration				√	√	
Adverse reactions				√	√	√
Treatment adherence				√	√	
Withdraw the rest medicines					√	

will be the same as that of recruitment. The investigators then assign the numbered medicines according to the randomization number in the envelope (medicines are packaged in the pharmaceutical factory and the serial number consistent with the randomization number). All numbers will be manipulated by independent statisticians of the Good Clinical Practice (GCP) center of Xiyuan Hospital (the GCP center is available at: www. xyhospital. com/index. php?id = 571).

The statisticians analyzing the final data, investigators, and participants related in the study will be blinded to treatment allocation. The whole blinding procedure will be verified by the authorized contract research organization, and the blind codes remained in the GCP center.

2.4. Interventions

2.4.1. JQ granule

The herbal granule is a granulated extract obtained by spray drying the hot water extract of a mixture of 10 crude herbs: *Dangshen* (*Codonopsis Radix*), *Cangzhu* (*Atractylodes lancea*), *Zisuye* (*Folium Perillae*), *Peilan* (*Eupatorii herba*), *Zhiqiao* (*Fructus Aurantii*), *Huangqin* (*Scutellariae Radix*), *Huanglian* (*Coptidis Rhizoma*), *Haipiaoxiao* (*Sepiae Endoconcha*), *Shenqu* (*Medicated Leaven*), *and Doukou* (*Amomi Fructus Rotundus*). The granule composition and herb efficacy are summarized in Table 2. Each herb was quality-controlled, and the result is presented in Table 3. The participants will be asked to dissolve a bag of granules (17.4 g) in 100 mL of water and take the mixture orally twice a day, 1 h after breakfast and dinner, for 4 weeks.

2.4.2. Omeprazole tablet

The participants in group 1 need to take one tablet (10 mg per tablet), and the participants in group 2 will take two tablets, once a day before breakfast for 4 weeks.

2.4.3. Dummy JQ granule and dummy omeprazole tablet

The dummy omeprazole tablet is made of cyclodextrin (80%), rice (15%), bittering agent (5%), and food colorants. Its taste, color, smell, and texture is similar to those of the original one. The dummy JQ granule is made of cyclodextrin and 5% real JQ granule to imitate the color and smell of the original one.

Both granules and dummy medicines are manufactured by Beijing Tcmages Pharmaceutical Co., Ltd. (No. 5, Beijing, China) according to the standards of the Good Manufacturing Practice. All medications are packed in aluminum bags, labeled with the treatment number, stored, and distributed by investigators. The participants receive medicines at visit 2. To improve adherence to intervention protocols, the medicines will be returned at visit 4.

2.4.4. Measures following adverse events

The participants will be notified that they can abort the treatment if they experience any side effects (whether related to the trial treatment or not) and contact the local investigator (telephone or clinic). The modification of treatment is at the discretion of the chief physician and ethics committee. The local investigator can contact with the GCP center to access the blind-break system if necessary. The blind-break process required the participation of the local investigator and the supervisor of the GCP center and need to record the time and cause of blind-break. In the event of trial-related injuries, the participants might receive treatment and appropriate insurance compensation through ethics committee regulations.

2.5. Outcomes

2.5.1. Primary outcome

The primary outcome is the change in the total score on GerdQ from baseline (visit 2) to endpoint (visit 4). GerdQ was developed through the integration of validated questionnaires reflecting psychological problems (GSRS [28], GIS [29], and RDQ [30]) and the data of diagnoses of GERD in primary and secondary medical institutions. GerdQ was used for the diagnosis and management of GERD with good authenticity and reliability [31,32]. GerdQ has six items: heartburn, regurgitation, abdominal pain, nausea, sleep disorders, and use of OTC medications. The score is evaluated according to the frequency of every item in recent 1 week: 0 day, 1 day, 2–3 days, 4–7 days, respectively, assessed to the score of 0, 1, 2, and 3 in the items of heartburn, regurgitation, sleep disorders, and use of OTC medications; 0 day, 1 day, 2–3 days, and 4–7 days, respectively, assessed to the score of 3, 2, 1, and 0 in the items of abdominal pain and nausea.

2.5.2. Secondary outcomes

The secondary efficacy measures will be the changes in the scores on the SF-36, PRO, HAMD17, and SS. The SF-36, which contains 36 items in eight dimensions, is the most commonly used tool to assess the health status and reflect the effect of experimental medication. HAMD17 has been most commonly used for the clinical evaluation of depression.

PRO, which is short for the Patient Report Outcome Based on

Table 2
Ingredients and efficacy of Chinese herbal medicine in the JQ granule.

Ingredients	Crude herbal dose (g/d)	Efficacy (pharmaceutical study)
Dangshen (*Codonopsis Radix*)	18	Protective effect on gastric mucosa [19]; strengthening the immune system [20]; anti-inflammatory activity [21]
Cangzhu (*Atractylodes Lancea*)	15	Enhancing gastrointestinal hypofunction; anti-inflammatory activity; neuroprotective activity; immunomodulatory activity [14]
Zisuye (*Folium Perillae*)	12	Antispasmodic effect [12]
Peilan (*Eupatorii Herba*)	12	Recorded by *the Chinese Pharmacopoeia* (2015 edition): The main ingredient was essential oil; its main effect was stimulation of appetite
Zhiqiao (*Fructus Aurantii*)	12	Antidepressant effect; anti-immobility effect [13]
Huangqin (*Scutellariae Radix*)	9	Enhancing gut barrier function [22]; anti-inflammatory activity [23]
Huanglian (*Coptidis Rhizoma*)	6	Antibacterial activity [24]; anti-inflammatory activity [25]
Haipiaoxiao (*Cuttlebone*)	30	Antibacterial activity [26]; anti-inflammatory activity [27]
Shenqu (*Medicated Leaven*)	15	It was made by the fermentation of spicy polygonum, sweet wormwood, almond, and flour; its main effect was to promote food digestion.
Doukou (*Amomi Fructus Rotundus*)	6	Recorded by *the Chinese Pharmacopoeia* (2015 edition): The main ingredient was essential oil; its main effects were the prevention of nausea and vomiting and the stimulation of appetite

Table 3
Quality control of JQ herbal granules.

Herb	Thin-layer identification *(reference standard)*	Testing			Extract (standard quantity)	Infrared fingerprint	Microbial limit		Control bacteria examination
		Moisture content (%)	Particle size (%)	Solubility			Aerobic quantity (cfu/g)	Mold and yeast quantity (cfu/g)	
Doukou	√ (*Eucalyptol*)	1.2	3.0	√	11.6% (≥5.0%)	√	150	50	√
Dangshen	√ (*Lobetyolin*)	3.6	3.0	√	30.0% (≥20.0%)	√	10	< 10	√
Cangzhu	√ (*Atractylodes lancea*)	2.9	4.0	√	25.3% (≥21.0%)	√	50	50	√
Shenqu	√ (*Artemisia apiacea*)	3.3	4.0	√	17.0% (≥12.0%)	√	40	10	√
Peilan	√ (*Eupatorii Herba*)	3.8	3.0	√	31.2% (≥26.0%)	√	50	< 10	√
Zisuye	√ (*Folium Perillae*)	3.8	4.0	√	22.9% (≥9.0%)	√	50	< 10	√
Zhiqiao	√ (*aurantiamarin and Aurantii Fructus*)	1.9	4.0	√	79.9 mg/g (Naringin ≥ 40.0 mg/1 g)	√	< 10	< 10	√
Huangqin	√ (*Scutellariae Radix, Baicalin, Baicalein, Wogonin*)	1.9	3.0	√	205.2 mg/g (baicalin ≥100.0 mg/1 g)	√	10	< 10	√
Huanglian	√ (*Berberine hydrochloride, Coptidis Rhizoma*)	3.1	4.0	√	Berberine 150.2 mg/g (≥80.0 mg/1 g); epiberberine 20.2 mg/g (≥15.0 mg/1 g); coptisine 34.9 mg/g (≥15.0 mg/1 g); palmatine 39.4 mg/g (≥25.0 mg/1 g)	√	< 10 cfu/g	< 10 cfu/g	√
Haipiaoxiao	Physiochemical identification: √	3.6	5.0	Uniformly suspended		√	< 10 cfu/g	< 10 cfu/g	√; No salmonella; Gram-negative bacteria(resistant to bile salts) < 10 cfu/g

Identification: √ means met the requirement; moisture content: less than or equal to 6%; particle size: less than or equal to 13%; dissolubility: √ means that all the particles dissolved; infrared fingerprint: √ means conforming to the infrared fingerprint of herbal granules; microbial limit: the quantity of aerobic bacteria < 2000 cfu/g, the quantity of molds and yeasts < 200 cfu/g; control bacteria examination: *Escherichia coli* should not be detected.

Chronic Gastrointestinal Diseases, is developed by the digestive diseases department of Xiyuan Hospital of Chinese Academy of Traditional Chinese Medicine. Considering the clinical characteristics of patients with chronic gastrointestinal diseases in China, 2 years were spent to collect measurement indicators, screen and optimize items, implement presurvey of small samples and field survey, and finally formulate the current PRO. It contains 35 items in 6 dimensions (regurgitation, dyspepsia, physical status, ability to life, defecation situation, and mental state). The analysis of 274 questionnaires showed that the PRO had good reliability and validity in reflecting the status of chronic gastrointestinal diseases. Relevant results were published in the China National Knowledge Infrastructure, and the specific contents were reflected in appendices. Every item in the PRO has five levels of discomfort (never, occasionally, sometimes, often, and always), and they, respectively, represented the scores of 0, 1, 2, 3, and 4 (PRO details can be found in online supplementary appendix 2).

SS is based on *the Clinical Guideline of New Drugs for Traditional Chinese Medicine*. It is used to evaluate the discomfort of the gastrointestinal system based on the TCM theory. It contained 15 items of TCM terminology, which are used to assess the severity of physical discomfort (0 = absent; 1 = mild; 2 = moderate; 3 = severe). The main concerns of these items include stomach distension, stomachache, appetite decrease, heartburn, acid regurgitation, sputum increase, feeling of obstruction in pharynx, feeling thirsty but not wanting water, feeling of distention on both sides of the lower abdomen, limb weakness, shortness of breath, feeling weak and unwilling to speak, somatosensory heaviness, feeling afraid of the cold, and having loose stools (SS details can be found in online supplementary appendix 3).

All questionnaires and scales will be collected at baseline, during the treatment period, and during the follow-up period.

2.5.3. Safety outcomes

Data on vital signs (pulse, respiration, temperature, and blood pressure) and laboratory tests (blood routine test, urine routine test, stool routine test, liver and kidney function test, blood glucose, erythrocyte sedimentation rate, and 12-lead electrocardiogram) will be collected at baseline and during visit 4. Adverse events will be recorded by investigators during the trial.

2.6. Data analysis

2.6.1. Sample size

This study is a noninferiority trial. It revealed that 60% of patients with NERD showed significant relief on PPI therapy [2]. The team has experience in using herb formulas for more than 20 years, and the granule formula has been used in the clinic for several years. Combined with other clinical efficacy studies on similar formulas (in the other three provinces of China), this study estimated that the efficacy rate of omeprazole combined with the granule formula in treating NERD was 70%–80%. With the sample size review by the Data Monitoring Committee, the efficacy rate was eventually estimated to be 74.5%. After consultation between statistical experts and clinical investigators, the noninferior boundary value (Δ) was decided to be 0.6 (1/10 of the effective rate of the omeprazole group). One-sided alpha was 0.025. The ratio of two samples was 1 ($K = 1$). The dropout rate was 20%. The PASS software was used for sample size calculation. The final sample size was 204 participants (102 participants per group).

The sample size is based on the noninferiority design (Fig. 2).

$$n_c = \frac{\left[\mu_{1-\alpha}\sqrt{\bar{p}(1-\bar{p})(1+1/k)} + \mu_{1-\beta}\sqrt{p_T(1-p_T)/k + p_C(1-p_C)}\right]^2}{[(p_T - p_C) + \Delta]^2}$$

$$n_t = kn_c$$

Fig. 2. Sample calculation formula of the noninferiority test.

2.7. Statistical methods

All demographic information, questionnaires, and scales are included in the Case Report Form (CRF). The participants filled out the CRFs under the guidance of investigators. All data from CRFs will be entered into the Drug & Clinical Trial Data Management Platform (developed by the GCP center: http://www. xyedc. com/) twice by the other two different investigators (double data entry). This platform could help in saving data permanently, and the original CRFs will be preserved for at least 5 years after finishing the study. The statisticians in the GCP center will download data from the platform for analysis (the data will be exported in Excel format).

Analyses will be conducted in a blinded manner by independent statisticians and based on the intention-to-treat principle. A two-sided *P* value of less than 0.05 will be considered to be statistically significant. The baseline characteristics will be compared using either the chi-square test or the Student *t* test. The primary and secondary outcomes will be analyzed using nonparametric statistics, median (1 st to 3rd quartile), and Mann–Whitney *U* test. Adverse events will be calculated and compared using the chi-square test or Fisher's exact test.

2.8. Interim analyses

No planned, interim between-group analyses will be conducted.

3. Discussion

The use of herbal formula is very common in China. Chinese herbal compounds are widely used for treating digestive system diseases. In China, many clinical studies have been performed on TCM, most of which were reported in the form of case report and clinical experience but lacked high-quality research, especially RCT research. The statistical findings showed that clinical studies reporting program registration, ethical review, and informed consent signature accounted for a relatively low proportion of the total number of studies. In the methodological aspect of RCT, reports of randomized sequence generation, allocation concealment, and blind implementation of clinical studies accounted for a smaller proportion. Many difficulties have been encountered in RCT research of TCM. Besides the strict procedure and supervision mechanism of RCT research itself, the quality control of Chinese medicine formulation is also very important. This study will try to ensure good RCT supervision and drug quality control.

In the quality control of compound granules, the cooperative pharmaceutical factories have done a good job in controlling the source of herbs. In China, different provinces produce different herbs, and the corresponding herbs contain the best active ingredients. The pharmaceutical factories have strict regulations on the area, year, and method of herbal picking. After the herbal medicine is processed into granules, the granules are tested, including the color, odor, TLC identification, moisture, granularity, solubility, content of active ingredients, and microbial examination, to control the effectiveness and safety of the medicine. With regard to dosage form, granules are chosen. In Chinese outpatient clinics, most of the herbal medication is taken home with crude pieces, and it takes the patient 1–2 h to cook and take the medicine every day. This method is time-consuming, and quality control is difficult to achieve. These troubles are avoided with granules, which are easy to preserve and increase patient compliance.

The design of RCTs originates from actual clinical observation. A large number of overlapping gastrointestinal symptoms are observed, and hence it is difficult for a single drug to achieve a satisfactory therapeutic effect. Present knowledge shows that the NERD group comprises a majority of patients (up to 70%) with GERD [33]. A Cochrane systematic review showed that PPIs were the preferred treatment for NERD [34]. In clinic, a large number of patients with NERD also had the symptoms of indigestion, while a high-frequency use of PPIs could inhibit the secretion of gastric acid and aggravate the

symptoms of indigestion. Some ancient Chinese medicine combinations could accelerate gastrointestinal peristalsis [35] while neutralizing gastric acid [36], such as *Banxia xiexin* decoction derived from *Shanghanlun*, and even had a good effect in reducing visceral hypersensitivity and improving gastrointestinal function [37], such as a well-known formula of *Sijunzi* decoction. Combining the ancient formulas and clinical experience, this JQ granule and RCT were designed. Considering the side effects of the long-term use of PPIs, attempts were made to reduce the routine dosage of PPIs, add JQ granule, and observe the improvement in various upper gastrointestinal symptoms in patients with NERD. The gut–brain axis theory emphasizes the interaction between the brain and the gastrointestinal system. Patients with gastrointestinal diseases often have problems in their emotional state, resulting in a significant decline in their quality of life [38]. Previous studies on PPI treatment of NERD have paid less attention to the mental state of patients. Therefore, this study aimed to observe the changes in the mental state and quality of life of patients with NERD after taking JQ granule and explore whether JQ granule had an effect on symptoms outside the gastrointestinal tract.

In conclusion, the findings of this randomized, placebo-controlled trial will provide evidence to support the use of JQ granule for treating patients with NERD.

Contributors

Tang XD and Wang FY are the Chief Investigators and lead investigators. Lv L, Ma XX, Zhang BH, Bian LQ, Chen T, and Zhao YP contributed to the design of the study. Gao R, Lu F, Zi MJ, Li BS, and Li ZH were responsible for the ethical approval and the supervision and guidance of the entire project. Zhao Y will be responsible for the statistical analysis. Li F, Yin XL, Che H, Xie JY, Wu HM, Li X, Ma JX, Ma W, Zhang M, Zhou B, and Zhang C will be responsible for managing the trial. All authors reviewed and approved this manuscript.

Trial status

The trial is ongoing. The first participant was randomized into the trial in January 2017 and the recruitment is anticipated to be completed by June 2019.

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Ethics and dissemination

Before the start of recruitment, approvals were granted by the Ethics Committee of Xiyuan Hospital of China Academy of Chinese Medical Sciences (2016XLA146-3). Before the trial began, investigators got informed consents from the participants. The paper version of all informed consents were reviewed by the ethics committee and kept by the lead investigator. In the process of the clinical trial, the ethics committee approval and the informed consent were the main measures to protect the rights and interests of participants. The composition and work of the ethics committee was relatively independent of any participant.

Declaration of Competing Interest

The authors declare no competing interests. Funding agencies and any external organizations were not involved in the research design or manuscript preparation. All the authors participated in the design and development of the experimental scheme. All authors read and approved the final manuscript.

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