The efficacy and safety of Shenzhu Guanxin Recipe Granules for treatment of patients with coronary artery disease: protocol for a double-blind, randomized controlled trial

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Keywords: Coronary artery disease, traditional Chinese herbal, randomized controlled trial, intermediate coronary lesions

Abstract

Background Coronary artery disease (CAD) is one of the most common types of the cardiovascular diseases, previous pilot trials suggested that Traditional Chinese Medicine brought clinical benefits for patients with CAD. We will conduct this trial to determine the efficacy and safety of Shenzhu Guanxin Recipe Granules for treatment of patients with coronary artery disease. Patients and Methods This randomized controlled trial recruited 194 patients who were diagnosed CAD by clinical manifestations and examinations, in which coronary computed tomography angiography (CCTA) showed 50-70% of stenosis, with soft or mixed plaque. The included participants were randomly assigned to the case group and control group with a 1:1 allocation ratio; patients in the case group received SGR and usual care, and those in the control group received placebo (6 g/day for 6 months) and usual care. The endpoint of the study included calcium coverage score (CCS), C-Reactive protein (CRP), and the levels of blood lipids, tumor necrosis factor-α (TNF-α), interleukin-1 (IL-1), interleukin-6 (IL-6), and ATP-binding membrane cassette transporter A1 (ABCA1) were calculated before recruiting at6th month. The indicators were Seattle Angina Questionnaire (SAQ) and TCM syndrome questionnaire scores at 0th, 3rd, and 6th months. Discussion This clinical trial may provide a reliable evidence regarding the clinical effectiveness and safety of SGR therapy for patients with CAD by clinical manifestations and examinations, in which coronary computed tomography angiography (CCTA) showed 50-70% of stenosis, with soft or mixed plaque.

Introduction

Coronary artery disease (CAD) is one of the most common types of the cardiovascular diseases[1], resulting in over 9.5 million deaths worldwide[2], that has remarkably increased globally from 5.2 million deaths in 1990[3]. Intermediate coronary lesions (ICL), which was defined by luminal narrowing with a diameter stenosis of 40-70%, continues to be a therapeutic dilemma for cardiologists[4]. Although previous studies have indicated that diameter stenosis of 40-70% has been used as indication for percutaneous coronary intervention (PCI), however, the treatment of ICL has still remained controversial [5, 6]. In non-left main lesions, the guideline published by the American College of Cardiology (ACC)/American Heart Association (AHA) for PCI recommended ≥ 70% stenosis as the criterion for significant stenosis[7], while the guideline released by European Society of Cardiology expressed 50% stenosis with documented ischemia as the criterion for revascularization. Consequently, recruitment of a conservative treatment or aggressive revascularization strategy to perform PCI is still a main challenge for patients with ICL.

Regarding the possible side effects of PCI, some patients with ICL select a conservative treatment strategy. In addition, drugs play an important role in the conservative treatment of ICL. Although antiplatelet therapy and anticoagulation therapy are cornerstones for treating coronary heart disease (CHD) [8], however, traditional Chinese herbal products possess several benefits for patients with CHD, especially the relief of clinical symptoms [9-11]. Based on the theory of traditional Chinese medicine (TCM), CHD belongs to the category of "chest pain" and "heart pain" in TCM, which was mainly caused by

"Qi stagnation", "blood stasis" and "phlegm turbidity". Shenzhu Guanxin Recipe Granules (SGR), a traditional Chinese herbal product, including Radix Ginseng, Rhizoma Atractylodis, Radix Notoginseng, Rhizoma Pinelliae, Hirudo medicinalis, Radix Panacis quinquefolium, and Folium Nelumbinis, have been proved to accelerate blood circulation, enhance qi, and eliminate intravascular phlegm, all playing critical roles in pathogenesis and progress of CAD in traditional Chinese medicine (TCM) [12, 13]. A previous study revealed that SGR was effective and safe to improve Seattle Angina Questionnaire (SAQ) and Chinese medicine (CM) symptom scores, and decrease adverse events, such as death, restenosis and other emergency cases in patients receiving a standard Western medicine treatment after PCI in southern China [13].

Based on previous clinical and experimental evidences, we hypothesized that SGR may provide an alternative therapeutic strategy for patients with ICL who prefer to receive a conservative treatment in lieu of an aggressive revascularization strategy. Therefore, we performed a multicenter, randomized, double-blind, placebo parallel controlled clinical trial to further investigate the efficacy of the mentioned treatment strategy.

Patients And Methods

This study mainly investigated the curative effects and possible mechanism of SGR on CAD patients. In this study, patients with CAD were randomly assigned to the case group and control group; the patients in case group received SGR, and those in the control group received placebo twice-daily for 6 months. As soon as the patients were recruited to the trial, they underwent laboratory examinations and fulfilling SAQ. The laboratory examinations mainly included alanine amino transferase (ALT), aspartate amino transferase (AST), blood urea nitrogen (BUN), serum creatinine level, and blood lipids. The patients were followed-up for 12 months with repeated questionnaires for every 3 months. At 6 months follow-up, the participants underwent repeated laboratory examinations, including coronary computed tomography angiography (CCTA). At the beginning of the study, all patients signed informed consent forms, which were informed about the risks and benefits of the treatment strategy. A flow diagram of the trial is shown in Figure1.

Inclusion and Exclusion Criteria

The inclusion criteria were as follows: (1) the age of the subjects should be over 18 and less than 75 years old; (2) living in Guangdong province for long-time (total duration of residency > 3 years, annual duration of residency > 9 months); (3) patients were aware of the study and agreed to sign informed consent forms; (4) patients had been diagnosed with CAD by clinical manifestations and examinations, and CCTA showed 50-70% of coronary atherosclerotic stenosis, with soft plaque or mixed plaque; (5) the patients did not undergo PCI surgery and coronary artery bypass grafting (CABG); (6) Phlegm and blood stasis syndrome (PBSS) due to syndrome of qi deficiency. Syndrome differentiation will be determined by

two qualified TCM cardiologists dependently according to diagnostic criteria for TCM differentiation (Table1).

The exclusion criteria were as follows: (1) patients were complicated with other serious diseases, including malignant tumor, severe infection, and other significant life-limiting comorbidities; (2) pregnant and lactating women and those allergic to TCM; (3) poor compliance, and failure to visit regularly; (4) Valvular heart disease; (5) patients with congenital metabolic abnormalities or immune diseases.

Dropout criteria

The included patients have the right to stop treatment and withdraw from the research project for any reason at any time, and the reason why they want to quit the research project will be recorded in their CRF. Participants who do not complete the research project with the following reasons should be considered as dropped out. (1) The patient chooses to quit the research project. (2) loss to follow-up. (3) Poor compliance. (4) The participant develops another severe disease that needs to be treated during the study.

Recruitment Strategies

In order to recruit patients, advertisements were placed in a broad range of media outlets, including the flyers within the hospital, as well as website of Chinese Clinical Trial Registry. Patients who were interested in the trial received information about the study. Each potential participant was informed that the participation is fully voluntary and refuse to participate in the research has no negative effect on their treatment. Those who would like to join the study were later assessed to determine whether they meet the inclusion criteria or not.

Randomization and Blinding

A random number generator in SAS 6.12 software (SAS Institute, Cary, NC, USA) was used to generate a random number in a 1:1 randomization ratio by DME (Design, Measurement, and Evaluation in Clinical Research) Center of Guangzhou University of Chinese Medicine (Guangzhou, China). The research team members, except for the clinical research methodology personnel, will be blinded to the treatment and the group assignment. Participants were informed about the information of case group and control group, while were not told their group assignment, thereby allowing blinding of the participants between the treatment groups. Both the SGR and placebo granule were manufactured by the Jiangyin Tianjiang Pharmaceutical Co., Ltd. (Jiangyin, China), and the placebo was identical compared with SGR in color, size, shape, and taste. The study code will not be revealed until the end of the study, unless there is a serious adverse event (AE).

Intervention

After a recruitment period prior to baseline assessment, the included participants were randomized to the case group and control group, in which the patients in case group received SGR and those in the control group received placebo (6 g/day for 6 months). Simultaneously, the included patients also received usual care according to patients' conditions, including aspirin, clopidogrel, angiotensin converting enzyme inhibitors or beta-blockers, calcium channel blockers, and nitrate esters irrespective of the initial randomization assignment. All the treatments were under the responsibility of physicians according to the clinical guidelines. Study medication (including both placebo and SGR) will be dispensed by the Hospital Central Pharmacy as a set of boxes at the beginning of each study month. In order to check the compliance of patients, the patient was asked to bring the box back. The treatment prescriptions and conditions of patients were recorded in the case form. Details of study procedures of the trial are given in Table 2.

Outcome measures

Before starting the intervention, at 3 months intervention, after completing the intervention (6 months after treatment), and 1 year intervention, all the patients had to complete a questionnaire related to quality of life. Additionally, all the patients underwent laboratory examinations and CCTA at baseline (prior to starting either intervention) and at 6 months follow-up. During the follow-up period, any enrolled participants who were unable to continue the study during the treatment remained in their randomized group to perform intention-to-treat (ITT) analysis.

Primary outcomes

The primary endpoint of the study was CCTA, that mainly included calcium coverage score (CCS). CCS represents the percentage of coronary arteries affected by calcific plaque, which was detected with cardiac CT (CCT). CCS has been shown to be reliable, reproducible, and predictive of cardiovascular risk, and also was highly associated with the risk of CAD[14-16]. A study revealed that a twofold increase in CCS was associated with a 34% (P⬚0.001) increase in the risk of a hard CAD event, in addition to a 52% (P⬚0.001) increase in the risk of any CAD event [17].

Secondary outcomes

Secondary outcomes were as follows: (1) concentration of ATP-binding membrane cassette transporter A1 (ABCA1), tumor necrosis factor-α (TNF-α), interleukin-1 (IL-1), and interleukin-6 (IL-6); (2) the level of serum lipids; (3) the level of high sensitivity C-reactive protein (CRP); (4) the SAQ score; (5) scores of CM symptoms; (6) evaluation of the occurrence and composite of major adverse cardiac events (MACE). The SAQ was used to assess the patients' quality of life from five aspects, i.e. the level of limitation of physical activity, steady-state angina pectoris, condition of angina pectoris attacks, satisfaction level of

treatments, and cognition level of disease (DP)[18]. The scores of CM symptoms included the following aspects: chest pain, sense of suppression in the chest, attack inducement, and shortness of breath, fatigue, palpation, and spontaneous perspiration [19] (Table 3).

Follow-up protocol

The first follow-up was carried out at 3 months after receiving treatment, and the patients' health condition was assessed by inspecting medical records, which were acquired by completing the case report form. The second follow-up was undertaken at 6 months after receiving treatment, in which the eligible participants underwent CCTA and laboratory examinations, and the researchers also needed to assess the participants' physical conditions according to the SAQ scores and scores of TCM syndrome questionnaire. The third follow-up was performed at 12 months, the eligible participants had to complete SAQ and TCM syndrome questionnaire.

Adverse events (AEs)

All drugs may have side effects or allergic reactions, although no adverse reactions of SGR have been reported yet. Any discomforts or unexpected situations that happen during the experiment period were taken as AEs into account regardless of whether they are related to the study intervention or not. All the AEs were recorded in case report form in detail. Serious AEs, including death, life-threatening or severely or permanently disabling events, were immediately reported to the principal investigator. The ethics committee assessed whether an AE was related to the experimental drug or not.

Data management

To ensure strict adherence to the study protocol and familiarity with the trial administration process, an independent committee will be formed by the principal research members prior to the beginning of the study. Data management personnel of the committee should be qualified, effectively trained and familiar with the functions of data management. A designated person is responsible for the data management of this clinical trial. When the patients are recruited to the research project, the demographic and baseline characteristic data will be collected by researchers. A standard case report form was used to collect data. Before start of recording, data were de-identified. Clinical outcomes, the results of SAQ, TCM syndrome questionnaire, adverse events, and the reasons why participants drop out of the study will be recorded in detail on case report forms (CRFs). In order to decease errors, data of the CRFs will be entered by two researchers independently. They will check each other's input values and only the consistent data can they be stored in the database. Paper files were kept in a locked filing cabinet in the hospital. With respect to the electronic documents, the results of laboratory tests and CCTA were stored on a password-protected computer, and access was restricted only to the principal investigator.

Determination of the sample size

The calculation of sample size was undertaken based on the results of our pilot study. We hypothesized that the expected difference in the primary outcome (coronary artery calcification score) between the SGR group and placebo group was estimated to be 10%. To calculate the sample size, we employed the "pwr.t.test" function in R package "pwr" (R package version 1.2-2. https://CRAN.R-project.org/package=pwr)[20]. As an example, say we want to be able to detect a difference of at least 6.2 in the mean CCS (about 10% decreases in CCS) with a common standard deviation of the two groups to be 10. Therefore our effect size is 6.2/10 = 0.62 according to Cohen (1988) [21]. For a desired power of 80%, Type I error tolerance of 0.05, and a hypothesized effect size of 0.62, we should sample at least 84 participants per group, i.e., a total of 168 participants. If assuming there will be a dropout rate of 15% within 6 months, then 194 participants can eventually be recruited.

Statistical analysis

All data analysis will be conducted by qualified statisticians in a double-blind manner according to the intention-to-treat principle. The database will be built by EpiData 3.1 software. In this study, SPSS 22.0 software (IBM, Armonk, NY, USA) was used to perform statistical analysis. Continuous variables were expressed as mean ± standard deviation (SD) or median, and categorical variables were reported as numbers and percentages. Student's t-test was used for making comparison between the two groups as well. Besides, one-way analysis of variance (ANOVA) was applied for making comparison between the groups. Pearson's chi-squared test was applied to sets of categorical data to evaluate how likely it is that any observed difference between the sets arose by chance. P-value < 0.05 was considered statistically significant.

Discussion

Although the treatment of CAD has remarkably advanced, the treatment of ICL has still remained controversial. Chinese herbs had been proved to have definite curative effects on CAD and gradually attracted scholars' attention in clinical trials[22-24]. Furthermore, SGR had been proved to be effective for patients with angina pectoris after PCI, and it can also upregulate the expression of platelet/endothelial cell adhesion molecule-1 (PECAM-1)/CD31 and vascular endothelial growth factor (VEGF), thereby promoting myocardium angiogenesis in myocardial infarction rats [25].In this study, we attempted to further investigate the efficacy and safety of SGR in patients with ICL, in which CCS was used as an indicator to evaluate the efficacy. Blood profile was associated with atherosclerosis, which was one of the most important risk factors of CAD. The serum concentration of high-density lipoprotein-cholesterol (HDL-C) was detected as a strong, independent and inverse predictor of atherosclerotic cardiovascular disease (ASCVD), in particular, CAD [26, 27]. Genes had been proved to be associated with the serum concentration of HDL-C, including ABCA1, which can modulate the concentration of HDL-C and catalyze the transfer of lipids from various tissues and cells to apolipoprotein A-I (apo A-I)[28, 29]. In this trial, in

order to further reveal whether SGR can affect the metabolism of blood lipids, the concentration ABCA1 was also calculated in addition to the concentration of blood lipids.

Numerous studies have reported a relationship between the elevated levels of circulating inflammatory markers and adverse cardiovascular events [30]. TNF-α induces the production of IL-6, that can activate hepatocyte production of CRP [31]. Among myriads of inflammatory markers, CRP was found as a valuable biomarker in refining risk assessment [32, 33]. In the present clinical trial, the influence of SGR on inflammatory markers, such as TNF-α, IL-1, IL-6, and CRP were assessed as well.

This study not only evaluated the efficacy and safety of SGR therapy for patients with ICL, but also discussed the potential mechanisms of SGR for the treatment of CAD. To minimize bias of the trial, a rigorous set of methods were conducted, including randomization, in which the blinding method and statistical analysis were carried out according to the ITT.

There are some limitations in this study. Firstly, although we recruited patients with PBSS due to qi deficiency, however, this Chinese medicine syndrome can dynamically change after the intervention. Secondly, the calculation of sample size was based on a pilot study and clinical observations, in which a larger sample size may result in different achievements.

In summary, the present study has provided a solid foundation for the clinical treatment of CAD, in which further evidence can be achieved regarding the application of TCM for the treatment of CAD.

Trial status

This research has been registered on Chinese Clinical Trial Registry (No. ChiCTR1900020501), and the first patient in this trial was enrolled on 1 January 2015. The trial has already enrolled participants: 50 patients have been recruited, and 40 patients had completed. The recruitment will be completed by 12 December 2019.

Declarations

Ethics approval and consent to participate

This study was approved by the Ethics Committee of the Guangdong Provincial Hospital of Traditional Chinese Medicine (Guangzhou, China) (Approval No. B2016-042-01), and we will not begin recruiting at other centers in the trial until local ethical approval has been obtained". All patients were informed about the risks and benefits of the treatment strategy and signed informed consent forms at the beginning of the study.

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Availability of data and materials

Data sharing is not applicable to this article because no datasets were generated or analyzed during the study

Competing interests

The authors declare that they have no competing interests.

Consent for publication

Not applicable.

Authors' contributions

XJ drafted the manuscript and participated in designing the trial. DPX planned the protocol and revised the manuscript. BXW and YKL recruited and screened eligible patients in the inpatient department. XJD was responsible for generating and distributing the random numbers. GQL participated in designing the outcome measurements and assessing the outcomes. HLW participated in assessing treatment efficacy and collected clinical data. XW was the study coordinator. All the authors have read and approved the final manuscript.

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Not Applicable

Abbreviations

CAD: coronary artery disease; TCM: traditional Chinese medicine; PCI: percutaneous coronary intervention; SGR: Shenzhu Guanxin Recipe Granules; TCM: traditional Chinese medicine; SAQ: Seattle Angina Questionnaires; ITT: intention-to-treat; CABG: coronary artery bypass grafting; CCS: calcium coverage score, CRP: C-Reactive protein; MACE: major adverse cardiac events; ANOVA: analysis of variance; HDL-C: high-density lipoprotein-cholesterol; CCTA: coronary computed tomography angiography; ABCA1: ATP-binding membrane cassette transporter A1;TNF-α: tumor necrosis factor-α.

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Tables

Table 1. Diagnostic criteria of TCM syndromes

Diagnostic criteria of TCM syndromes

main symptoms	1.chest pain
	2. sense of suppression in the chest
	The included patients need to have one of the main symptoms.
qi deficiency syndrome	1.palpitation and shortness of breath
	2. fatigue
	3. spontaneous sweating
	4. pale complexion
	5. pale tongue
	6. corpulent tender tongue with indentation in margin of the tongue
	7. weak pulse
	The included patients need to have two or more of the above symptoms.
blood stasis syndrome	1.dark purple lips, complexions or claws
	2.purple, dark or bruised tongue
	3.enlarged sublingual venation
	4.uneven pulse
	The included patients need to have two or more of the above symptoms.
phlegmy turbidity syndrome	1.being overweight
	2. Thick and greasy tongue
	3.slippery pulse
	The included patients need to have two or more of the above symptoms.

Table 2. Study Procedures of the Trial

	Study procedures	Baseline	Treatment period	Follow-up period	
	time point	0	3-month	6-month	12-month
	outcome measures				
	clinical data	√			
	Coronary artery CT	√		√	
	CRP	√		√	
Therapeutic evaluation	Blood lipids	√		√	
	SAQ	√	√	√	√
	scores of CM symptoms	√	√	√	√
	ALT, AST	√		√	
	creatinine, serum urea nitrogen	√		√	
Safety indicators	blood glucose	√		√	
	drug Interaction	√	√	√	√
	adverse event		√	√	√
	compliance observation		√	√	√
	medicine treatment	√	√	√	√

Note: CRP= C reactive protein, SAQ =The Seattle Angina Questionnaire, CM=Chinese medicine,

ALT= alanine aminotransferase, AST=aspartate aminotransferase.

Table 3. Primary and Secondary Outcomes

Primary endpoints	Coronary artery calcification score, Change of area of non-calcified plaque, and the proportion of non-calcified plaques to total plaques
Secondary endpoints	1. Concentration of gene ABCA1 and TNF-, IL-1, IL-6
	2. Level of serum lipids
	3. Level of high sensitivity C-Reactive protein (CRP)
	4. Seattle Angina Questionnaire (SAQ) score
	5. Change of Traditional Chinese Medicine (TCM) syndrome
	6. Evaluation of occurrence and composite of major adverse cardiac events (MACE)

Note: ATP-binding membrane cassette transporter A1 (ABCA1), TNF-α= tumor necrosis factor-α (TNF-α), IL-1= interleukin-1 (IL-1), IL-6= interleukin-6

Figures
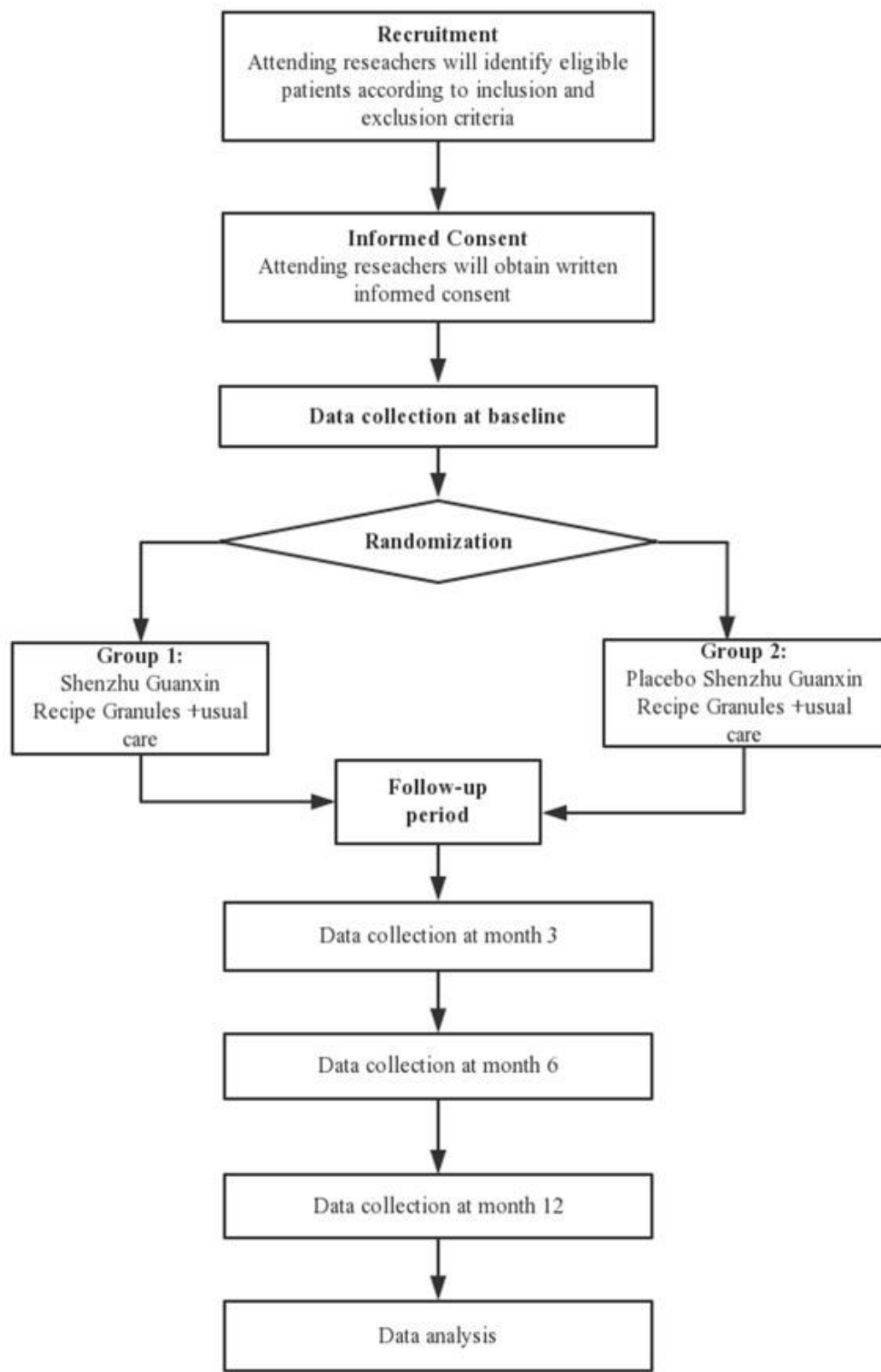
Figure 1

Flow diagram of the trial