The effect of Sang-qi Granules on blood pressure and endothelial dysfunction in stageI or II hypertension: study protocol for a randomized double-blind double-simulation controlled trial

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Study protocol

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Abstract

Background Hypertension is an important worldwide public health challenge because of its high prevalence and concomitant risks of cardiovascular disease. It induces half of the coronary heart disease and approximately two-thirds of the cerebrovascular disease burdens. Vascular endothelial dysfunction plays important roles in the pathophysiology of essential hypertension. Sang-qi Granules (SQG), a Chinese herbal formula, is used to treat I or II hypertension. Several animal experimental studies have shown that SQG can lower blood pressure and myocardial fibrosis by suppressing inflammatory responses. However, there is no standard clinical trial to confirm this and whether SQG can improve endothelial cell function is unknown.Methods In this randomized, double-blind, double-simulation controlled trial, 300 patients with stage I or II hypertension will be recruited and randomly allocated in a 1:1:1 ratio to group A(treatment with SQG and placebo of Cozaar), group B (treatment with Cozaar and placebo of SQG), and group C (treatment with SQG and Cozaar). SQG (or its placebo) will be administrated twice a day at the doze of 10g each time, and 50mg Cozaar(or its placebo) will be administrated once in the morning. The primary endpoint is the drug efficiency of the each three groups. The secondary endpoints are the change of average systolic and diastolic blood pressure during the day and the night, the change of blood pressure drop rate at night, target organ damage assessment (heart rate variability, ankle-brachial index and pulse wave velocity), symptoms improvement assessment (hypertension symptom scale, TCM syndrome integral scale, Pittsburgh sleep quality index scale, Self-Rating Anxiety Scale, Self-Rating Depression Scale and the Short Form-36 Health Survey), blood lipids, serum indicators of vascular function (changes in serum ET-1, TXA2, NO, PGI2 values) and safety indicators.Discussion This study will provide clinical evidence for the efficacy and safety of SQG in the treatment of hypertension. Meanwhile, the possible mechanism of SQG for lowering blood pressure will be further explored by observing the protective effect of SQG on vascular endothelial function, as well as its effect on related clinical symptoms, risk factors and target organs of hypertension.

Background

Hypertension, a major cause of cardiovascular disease, has become a leading global health challenge. It has been shown in meta-analyses of observational studies that hypertension is associated with an increased risk of cardiovascular disease (CVD), end-stage renal disease, subclinical atherosclerosis, and all-cause mortality[1]. Although there are significant advanced strategies for treating hypertension, such as evidence-based methods to treat risk factors and implementation of angiotensin-converting enzyme inhibitors, β-blockers, etc., the results are still not optimistic—hypertension is not completely being controlled. Evidence of 38276 adults from the National Health and Nutrition Examination Survey has demonstrated that age-standardized prevalence of hypertension decreased from 48.4% in 1999–2000 to 45.4% in 2015–2016, however, absolute burden of hypertension consistently increased, from 87.0 million in 1999–2000 to 108.2 million in 2015–2016[2]. While, among Chinese adults, more than one forth have hypertension and the prevalence has increased significantly during recent decades[3].

As a complex condition, the precise cause of essential hypertension is unknown[4]. One potential mechanism is endothelial dysfunction. Endothelium is a tissue that plays a vital role in regulating vascular tone, cell growth and the interaction between the leukocytes, thrombocytes and the vessel wall[5]. Endothelial cells can produce a variety of substances critical for the maintenance of vascular homeostasis, with nitric oxide (NO) being the most important one[6].When NO is released from endothelial cells, it causes smooth muscle relaxation and subsequent vasodilation. A plenty of studies have implicated that endothelial dysfunction is an early event in the pathophysiology of essential hypertension that may contribute to subclinical target organ damage and progression of atherosclerosis[7]. Thus, endothelial dysfunction emerges as a promising therapeutic target of agents in hypertension.

Hypertension was mentioned early enough in Yellow Canons Internal Medicine, a classic literature of TCM (Traditional Chinese Medicine), but it was classified as ‘headache’ and ‘vertigo’ in ancient China. At that time, traditional Chinese herbal medicine was used to treat the disease, but there was no effective evidence-based medical research. Sang-qi Granules（SQG）is a compound forming from traditional Chinese herbs used to treat hypertension. Its main ingredients are loranthus parasiticus(Sangjisheng), lycium barbarum L. t (Gouqizi), Catsia tora Linn (Juemingzi), Dendranthema indicum (Yejuhua) and Salvia miltiorrhiza Bunge (Danshen). Our team has conducted an Nano LC-MS/MS analysis of SQG to evaluate its chemical components, and found that it mainly contains betaine, chlorogenic acid, rutin, montfermanin, hesperidin, tanshinone and quercetin. It has been proved in our previous animal studies that SQG can lower blood pressure and myocardial fibrosis by suppressing inflammatory responses, such as upregulating the expression of PPAR and downregulating the expression of TNF-α, MCP-1, and TGF-β1/Smads signaling molecules relevant to myocardial fibrosis pathogenesis in cardiomyocytes[8]. Studies have confirmed that inflammation leads to the development of hypertension, and is also a key factor of endothelial dysfunction[9]. Therefore, SQG has the possibility to further regulate vascular endothelial function and plays a role in lowering blood pressure by inhibiting inflammatory response (Fig.1). Consequently, we designed a clinical study to assess the efficacy and safety of SQG on treating endothelial dysfunction in hypertension.

Methods/design

Objective

Our study aims to assess the clinical effect of SQG on vascular endothelial dysfunction in patients with stage I or Ⅱ hypertension, to provide a reliable experimental basis for the early prevention and treatment of target organ damage in hypertension, and to observe whether TCM plus western medicine can obtain better curative effect than western medicine alone.

Design

This study is a randomized, double-blind, double-simulation controlled trial, and participants will be recruited from China-Japan Friendship Hospital by using notices at the hospital and newspaper

advertisements.

In this clinical trial, patients with stage I or □ hypertension will be analyzed to determine the efficacy and safety of SQG, and basic analysis will be conducted in terms of the examination results. The study participants will voluntarily sign an informed consent and all examinations and tests will be carried out based on the clinical trial plan. Eligible subjects will be chosen based on specific inclusion and exclusion criteria. Participants will be randomized before the first treatment. Three hundred subjects with stage I or II hypertension will be randomly assigned to three groups (in a 1:1:1 ratio): group A(treatment with SQG and placebo of Cozaar), group B (treatment with Cozaar and SQG placebo), and group C (treatment with SQG and Cozaar). Recruited patients will receive an 8-week treatment (SQG and placebo of SQG will be given twice a day in the morning and evening, 10g every time, and the Cozaar and placebo of Cozaar will be administrated at 50mg every morning). The SQG and its placebo produced in China in accordance with the China Pharmacopoeia standard of quality control, will be used in this study. Upon completion of the 8-week treatment, follow-up tests will be conducted at weeks 2, 4, 6 and 8 after randomization (Fig. 2). This study was registered at the institute 'Chinese Clinical Trial Registry', which is a registry in the WHO Registry Network (ChiCTR1800016427).

Recruitment

Patients with hypertension, recruited at clinic and ward of China-Japan friendship hospital through advertisements and referrals, will be screened. The principle investigator (PI), together with a well-trained attending physician, will identify potentially eligible patients based on the eligibility criteria. Then, a researcher will inform the patient face to face of the whole schedule, including the aim, procedures, possible side effects and benefits of the study SQG in detail. If the patient agrees to take part in the study, he must sign an informed consent before randomization.

The inclusion, exclusion and withdraw criteria will be seen in Fig.3.

Ethics

Our protocol (version identifier: V1.0 (2018.3.30)) was approved by the clinical research ethics committee of China-Japanese Friendship Hospital (Approval No.2018-59-K43). And we also registered our trial at Chinese Clinical Trial Registry (ChiCTR1800016427), complies with the principles of the Declaration of Helsinki and the principles of Good Clinical Practice[11-12]. Every participant will sign an informed consent before enrollment and they will have right to withdraw from the trial at any time.

Randomization and blinding

One sealed opaque envelope with random series was prepared. The random series was generated by Statistical Analysis System(SAS, Version 9.4)by statisticians in the Scientific Research Department of China-Japanese Friendship Hospital. Three hundred participants will be randomly assigned to three groups to obtain the clinical trial plan corresponding to the random number.

There are three hundred sealed opaque envelopes, each of which contains information of one participant: group number, treatment, possible adverse events and emergency measures. The envelopes are kept by a special person, rather than the researchers, participants, clinical trial pharmacists, data managers or statisticians, and neither of whom knows the location nor the treatment plan. The drug is similar to its placebo in each group. The manufacturer labeled the random codes on the package according to the principles of GCP.

Intervention

Eligible participants will be randomly assigned to three groups to obtain the clinical trial plan corresponding to the random number. Group A will be given SQG and placebo of Cozaar, group B will be given Cozaar and placebo of SQG and group C will be given SQG and Cozaar. SQG (or its placebo) will be administrated twice a day at the doze of 10g each time, and 50mg Cozaar (or its placebo) will be administrated once in the morning. SQG (production batch number: 181201), placebo of SQG (production batch number: 181201), and placebo of Cozaar (production batch number: 181001) were produced and packed in a single batch by Jiangxi Puzheng Pharmaceutical Co., Ltd. (Social unified code: 91360823744294486X). The test results of drug quality are consistent with the Chinese Medicine Standards of the State Food and Drug Administration (SFDA). SQG is composed of original drug flow paste 200 kg and dextrin 180 kg. The placebo of SQG is composed of caramel 5 kg, dextrin 120 kg and original drug flow paste 25 kg. The main component of Cozaar placebo is dextrin. Cozaar was bought from Pharmaceutical Branch of China Pharmaceutical Holdings Beijing Co., Ltd. (Social unified code 91110101101297579G).

Endpoint measurements

Primary endpoint

Comparison of drug efficiency between the three groups

(Efficiency needs to meet the following two points).

(1) Blood pressure: The change of blood pressure needs to reach a valid standard according to *Guiding Principles for Clinical Research of New Chinese Medicines*[13].

(2) Flow-mediated dilation (FMD): Its value needs to increase by at least 2%[14].

Secondary endpoints

1. The change of average systolic and diastolic blood pressure during the day and the night, the change of blood pressure drop rate at night: Above indicators will be assessed by 24-hour blood pressure monitoring.

2. Target organ damage assessment:

(1) Heart rate variability (HRV): Analysis of HRV based on routine 24-hour Holter recordings provides a sensitive, noninvasive measurement of autonomic input to the heart.[15]

(2) Ankle-brachial index(ABI) and pulse wave velocity (PWV): The ABI is the ratio of the systolic blood pressure which measures the brachial arteryat the ankle[16]. The PWV is defined and calculated as the distance between the two arterial sites divided by the time delay between the two arterial point sites [17].

3. Symptom improvement assessment

(1) Hypertension symptom scale：Hypertension symptoms of all patients will be assessed through hypertension symptom scale (Additional file 2).

(2) TCM syndrome integral scale：TCM syndrome of all patients will be assessed through TCM syndrome intergral scale (Additional file 3).

(3) Pittsburgh sleep quality index scale: Sleep quality of all patients will be assessed through Pittsburgh sleep quality index scale[18-19].

(4) Self-Rating Anxiety Scale (SAS): Patients' anxiety condition will be assessed through Self-Rating Anxiety Scale [20].

(5) Self-rating depression scale (SDS): Patients' depression condition will be assessed through Self-Rating Depression Scale [21].

(6) The Short Form-36 Health Survey (SF-36): Changes in patients' health-related quality of life will be assessed through SF-36 [22-23].

4. Blood lipids: Changes of total cholesterol, triglyceride, low density lipoprotein and high density lipoprotei will be assessed at baseline and treatment endpoint..

5. Serum indicators of vascular function: Changes of serum ET-1, TXA2, NO, PGI2 values will be assessed at baseline and treatment endpoint.

6. Safety indicators: Creatinine, blood glucose, homocysteine, uric acid (UA), blood routine, urine routine will be tested at baseline and treatment endpoint.

Laboratory tests

1. Creatinine, blood glucose, blood lipids, homocysteine, uric acid (UA), blood routine, urine routine will be tested at the Clinical Laboratory, China-Japanese Friendship Hospital Beijing, China. Creatinine, blood glucose, blood lipids, homocysteine, uric acid (UA), Ang-II, hs-CRP will be tested by Chemistry Analyzer(Instrument name and model: BECKMAN COULTER Chemistry Analyzer AU5800, Beckman Kurt Co., Ltd, US). Blood routine will be tested by Blood Routine Analyzer (Instrument name and model: Sysmex blood routine analyzer Xn90, SYSMEX Co., Ltd., Japan) and urine routine will be tested by Urine

Analyzer(Instrument name and model: Fully Automated Urine Analyzer AUTION MAX AX-4030, Aikolai Co., Ltd.,Japen).

2. ET-1, TXA2, NO, PGI2 will be sent to the Clinical Research Center of China-Japan Friendship Hospital (2~6°C transportation) within 10 min. After the blood is centrifuged, the supernatant fluid will be pipetted and stored in a cryotube, and stored in a -80℃ refrigerator.

3. The cryopreserved supernatant fluid will be tested by using an ELISA kit or chemical kit within six months. Serum ET-1, TXA2 and PGI2 levels will be tested by enzyme-linked immunosorbent assay (ELISA) using Human ET-1, TXA2 and PGI2 ELISA kit. Serum NO levels will be measured by Nitrate reductase method using the Nitric Oxide (NO) assay kit. The experimental procedure, referring to the instructions of the kit, will be carried out by a professional technician. Instruments will be used during the experiment: electronic balance (Model: YP30001, Shanghai Guangzheng Medical Instruments Co., Ltd, China), minishaker (Typ: MS1 Minishaker, IKA (Guangzhou) Instruments and Equipment Co., Ltd, China), Desktop low-speed automatic balancing centrifug (Model: LDZ5-2, Beijing Jingli Centrifuge Co., Ltd, China), Electric constant temperature water tank (Model: HW. W21.600, Beijing Changfeng Instrument and Meter Company, China), and Multi-function microplate reader (Model: SpectraMax M2, Meigu Molecular(Shanghai) Instruments Co., Ltd, China).

Data collection and management

Each participant will get CRF for collecting relevant data. There will be an evaluation for every participant every 14 days during the trial (day -17 ± 0, day 14 ± 2 days, day 28 ± 5days, day 42 ± 5 days and day 56 ± 5days). Every evaluation will include physical examination, symptom improvement record, the use and recovery and distribution of the test drugs, combined medication record, adverse events record. Blood samples, 24-hour blood pressure monitoring will be collected only at the first and last time. Trials (SPIRIT) flow-chart of the trail can be found in Fig.4.

Data will be input into clinical data management system (CDMS) with the website (http://www.cardiar.com/zryygxy) by two research staff. The CDMS will be managed by Beijing Cardiar Technology Co., Ltd.(Social unified code: 91110 10655 68170 240). All data supporting the conclusion of this trail will be available in this system. There will be a password to control access. To ensure the data integrity and easiness of storage, we will use data rules, valid values and scope checks. Missing data and specific errors will be found by our system. The changes of document will be available but the changes trails will be audited. Auditing trial conduct will be carried out by Beijing Inruida Pharmaceutical Technology Co., Ltd.(Social unified code: 91110105MA00H1U54L), the procedures mentioned above will be kept completely independent from investigators and the sponsor. All personnel involved in data entry and management will sign a confidentiality agreement to prevent data leakage and the participant's personal information will be fully protected. Original CRF will be kept for 5 years after the end of this trial.

Adverse events (AEs)

Adverse events are defined as accidents or any signs of discomfort, symptoms or diseases. These adverse events include hypertensive emergencies, bleeding, hematoma, syncope, severe pain and local infection. If any adverse event occurs during the observation period, all details should be written down on the CRF, and the clinical research must report the adverse events to the research leader, sponsor, the ethics committee within 24 hours. Ethics committee needs to give treatment advices according to the corresponding adverse events.

Statistical analysis

Sample size calculation

There will be an superiority trial between group B(treatment with Cozaar and placebo of SQG) and group C(treatment with SQG and Cozaar), and there will be an non-inferiority trial between the group A(treatment with SQG and placebo of Cozaar) and group B(treatment with Cozaar and placebo of SQG).

The sample size was estimated based on clinical research literature and preliminary clinical basis of blood pressure and FMD of hypertensive subjects. Given a type-Ⅰ error rate of α=0.05 and a type-Ⅱ error rate of β=0.2. The efficiency of the group C was estimated at 90%, and the group B at 70%. The calculation result was 78 patients each group by PASS 11 software, 156 patients for three groups. After considering the expulsion rate and the requirement of minimum case number of the GCP(A randomized controlled clinical trial requires at least 100 patients each group). We estimated 100 patients in group B and group C. Group A was an exploratory trail with the above two groups, 100 patients initially identified. Above all, we decided to recruit 300 patients during the trail.

Data analysis

Data entry and management will be completed by an independent data administrator to ensure data accuracy. A professional statistician will perform the data analysis for the results. We will use the intent-to-treat principle to analyze the efficacy and safety of SQG. For continuous variables, the independent two-sample Student's t test will be used for comparisons between the two study groups, and the paired test will be used for intra-group comparisons. The χ^2 test will be used for categorical variables. When continuous data distribution is not normal, the Wilcoxon test will be used. $P < 0.05$ is considered to be statistically significant, and all tests are two-tailed.

Discussion

Hypertension is an important risk factor of cardiovascular [24]. However, data from a recent national survey in the United States demonstrates that the blood pressure of about one-half of all hypertensive adult patients is not controlled[25], which contributes to widespread morbidity and mortality worldwide[26]. Therefore, it is necessary to seek more treatment methods. That is why we choose SQG to conduct the research. According to the studies, SQG can promote the expression of PPAR pathway and inhibite the expression of TNF-α, MCP-1, and TGF-β1/Smads signaling molecules to suppress

inflammatory responses. And futhermore, SQG plays a certain role in reducing blood pressure as well as protecting target organs of hypertension[8]. Vascular endothelial dysfunction is also a factor of development of hypertension by contributing to increased systemic vascular resistance, and inflammation may be a potential mechanism of endothelial dysfunction. For example, ligand-activated PPAR-γ decreases the inflammatory responses in cardiovascular cells, particularly in endothelial cells[27]. TNF has been proved to attenuate NO production by destabilising eNOS mRNA, and restore endothelial-dependent vasodilation[28]. However, there is a lack of high-quality evidence-based medical research of SQG. So we designed this trial to validate its efficacy and safety for the treatment of hypertension. To ensure the quality of this study and reliability of our conclusions, the experimental design and study implementation have been conducted under strict quality control. Statisticians were involved in the study design to conduct sample size estimation, random allocation sequence generation, randomization concealment, and blinding. A training session has been held to explain the study protocol, and clarify the SOPs. Specialized laboratories will process the biochemical measurements. Additionally, the trial progress and quality will be monitored by a trained CRO.

High-quality evidence on the efficacy and safety of SQG in treating hypertension will be provided by this trial, thus offering reliable reference for the clinical application of SQG.

Trial status

Our protocol(version identifier: V1.0 (2018.3.30)) has been approved by the clinical research ethics committee of China-Japanese Friendship Hospital(Approval No.2018-59-K43), Beijing, China in May 2018. The study started in 13th February 2019, and twenty patients had been recruited. The study will be finished by December 2020.

Abbreviations

SQG: Sang-qi granules; CVD: cardiovascular disease; TCM: Traditional Chinese medicine; GCP: good clinical practice; HRV: heart rate variability; ABI: ankle brachial index; PWV: pulse wave velocity; SAS: Self-Rating Anxiety Scale; SDS: Self-rating depression scale; SF-36: 36-Item Short Form Survey Instrument; BMI: body mass index; UA: uric acid; ET-1: endothelin 1; TXA2: thromboxaneA2; NO: nitric oxide; PGI2: prostaglandin I2; Ang-II: angiotensin II; hs-CRP: high-sensitivity C-reactive protein; SPIRIT: Standard Protocol Items; CDMS: clinical data management system; CRF: case report form; SFDA: State Food and Drug Administration; SOP: standard operating procedure; CRO: clinical research organization; AEs: Adverse events.

Declarations

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Availability of data and materials

Not applicable

Authors' contributions

HYS and DSY contributed equally to this study LL and LH are in charge of for the study and the supervision the study. HYS and DSY conceived the study and participate in its initial design, LH participated in the final design. HYS and DSY participated in the design of the intervention and statistical design and sample size calculation. HYS advised recruitment strategy. DSY completed the registry of this trial. LH and JJQ helped our study to be approved by the clinical research ethics committee of China-Japanese Friendship Hospital. DSY, JJQ, RS participated in the design of the outcome measurements and assessment of the outcomes. DSY, JJQ, RS, RHL, CLZ, RQJ will participate in data acquisition and its interpretation. LPL participated in the blood sampling. HYS and DSY wrote the initial draft of the manuscript and all authors read and approved the final manuscript.

Ethics approval and consent to participate

Our protocol(version identifier: V1.0 (2018.3.30)) had been approved by the clinical research ethics committee of China-Japanese Friendship Hospital(Approval No.2018-59-K43),where the study will take place. And we had also registered at Chinese Clinical Trial Registry(ChiCTR1800016427), complied with the principles of the Declaration of Helsinki and the principles of Good Clinical Practice. Every participant will sign the clinical trial consent forms before enrollment and they have right to with draw from the trial at any time.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

Publisher's Note

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Additional Files

Additional file 1: SPIRIT Checklist. (DOC 119kb)

Additional file 2: Hypertension symptom scale. (DOC 18kb)

Additional file 3: TCM syndrome integral scale. (DOC 23kb)

Figures

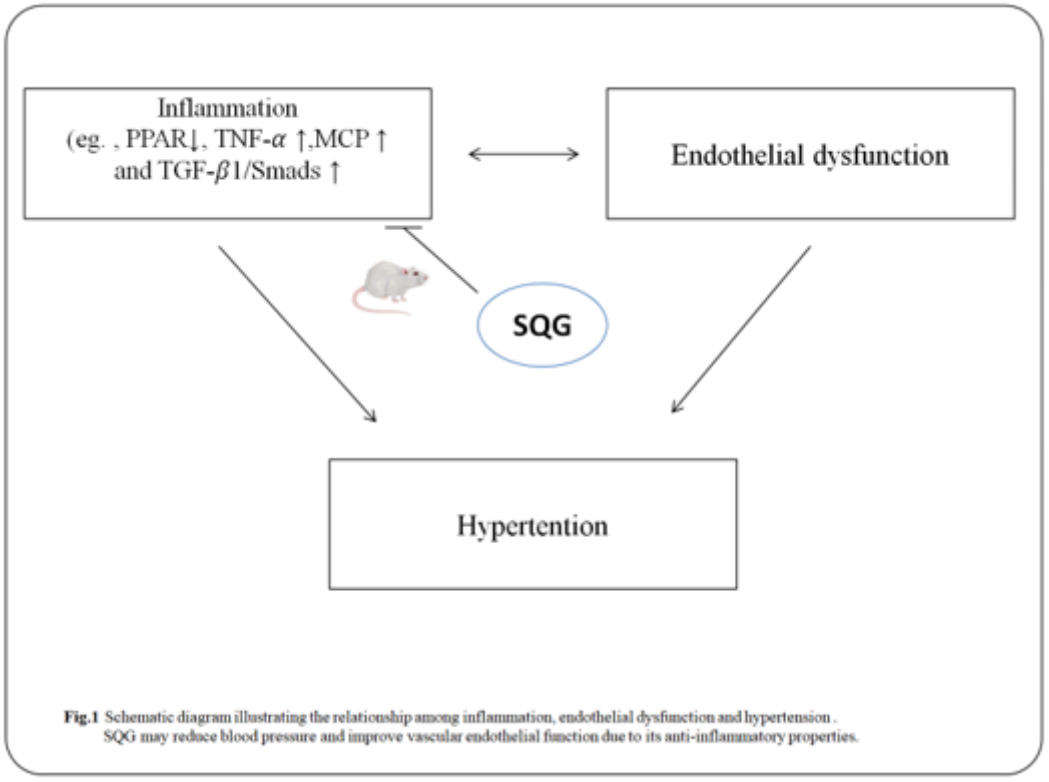


Fig.1 Schematic diagram illustrating the relationship among inflammation, endothelial dysfunction and hypertension . SQG may reduce blood pressure and improve vascular endothelial function due to its anti-inflammatory properties.

Figure 1

Schemematic diagram illustrating the relationship among inflammation, endothlial dysfunction and hypertension. SQG may reduce blood pressure and improve vascular endothelial function due to its anti-inflammatory properties

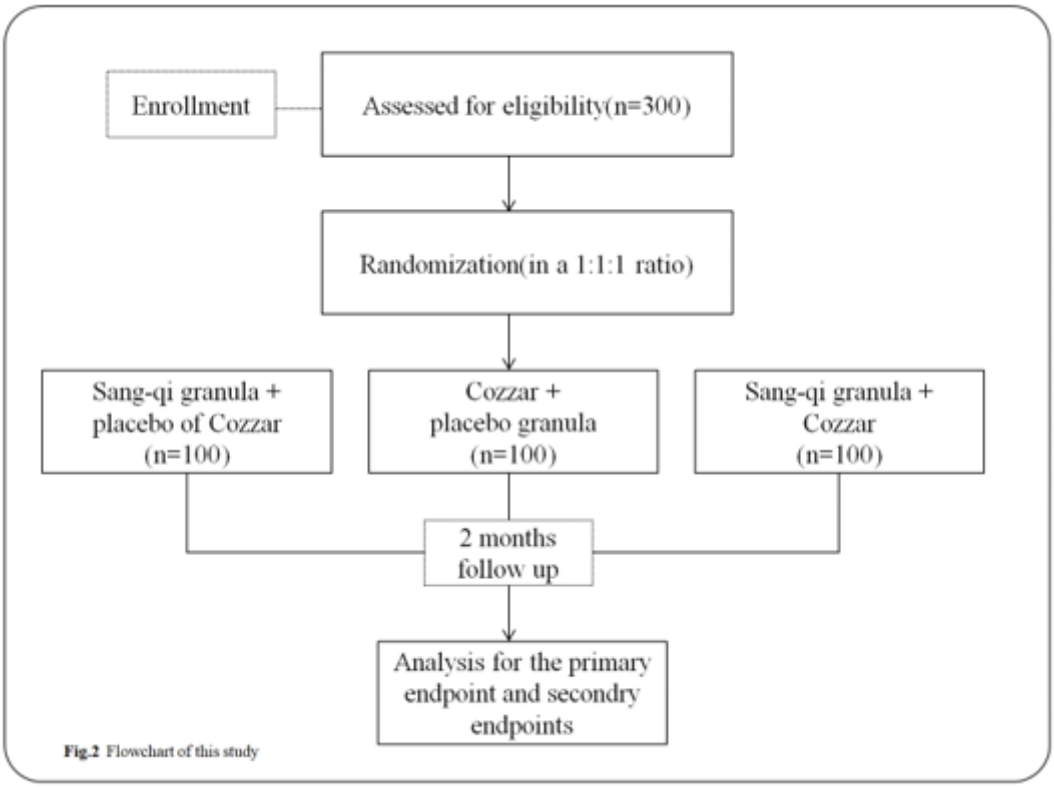
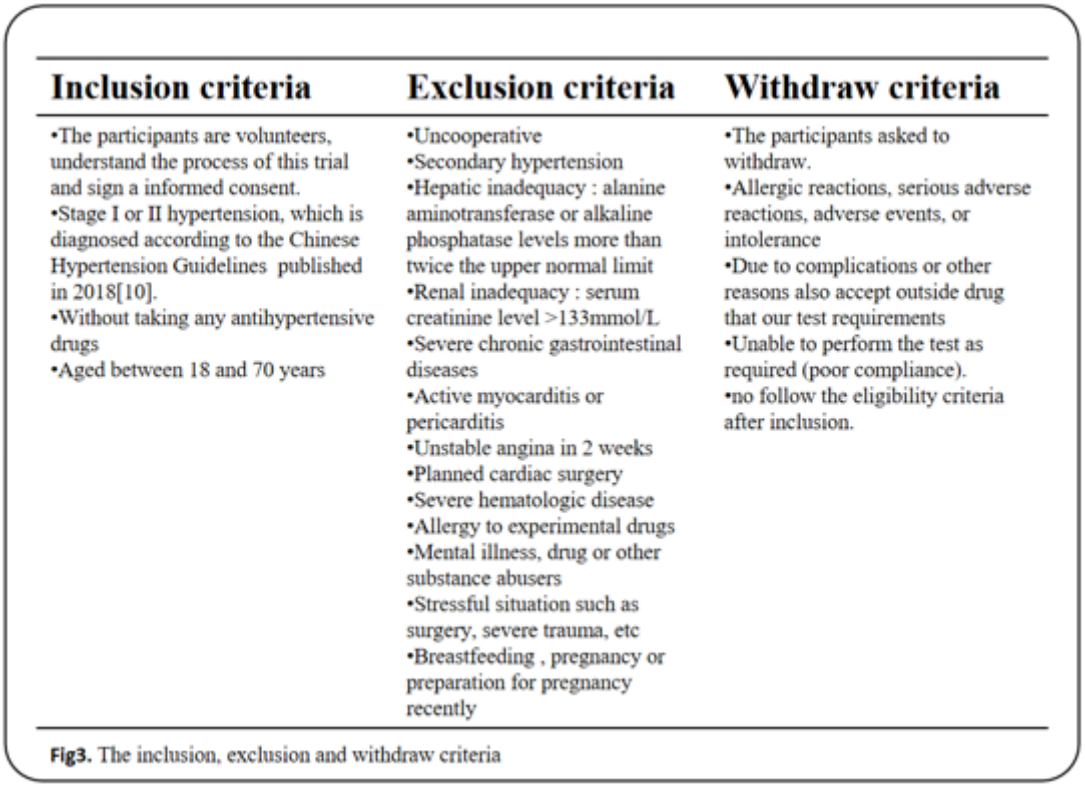


Fig.2 Flowchart of this study

Figure 2

Flowchart of this study

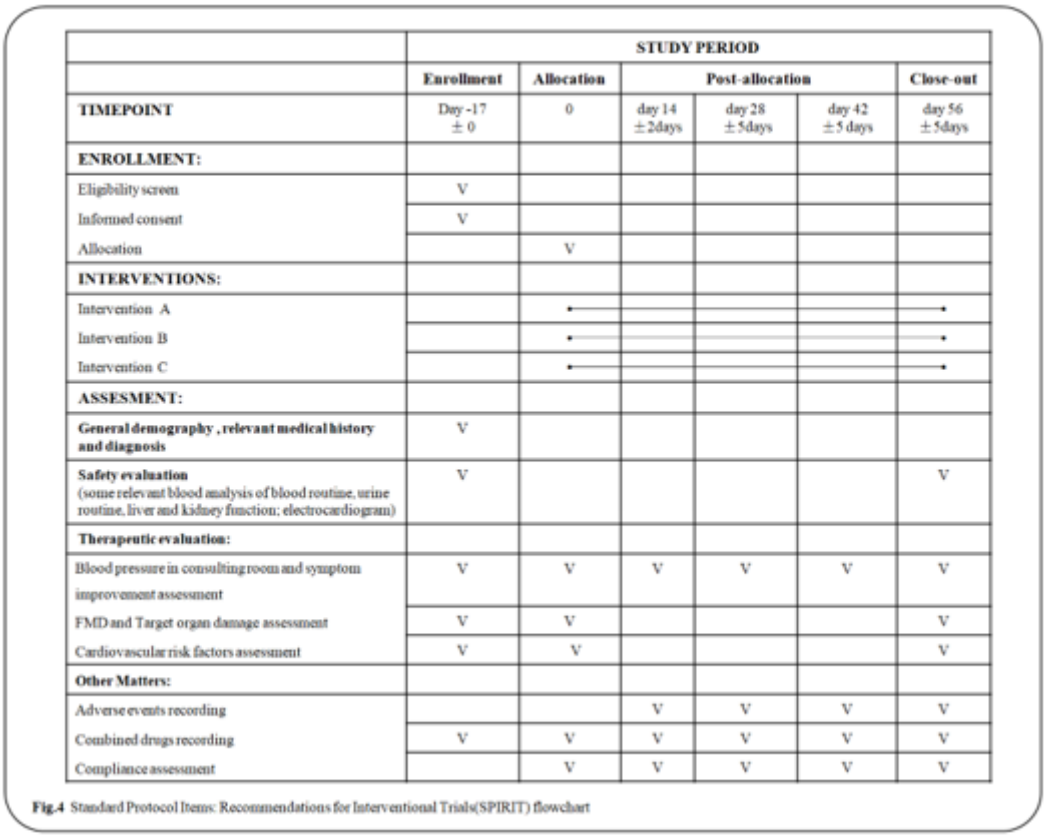


Inclusion criteria	Exclusion criteria	Withdraw criteria
•The participants are volunteers, understand the process of this trial and sign a informed consent. •Stage I or II hypertension, which is diagnosed according to the Chinese Hypertension Guidelines published in 2018[10]. •Without taking any antihypertensive drugs •Aged between 18 and 70 years	•Uncooperative •Secondary hypertension •Hepatic inadequacy : alanine aminotransferase or alkaline phosphatase levels more than twice the upper normal limit •Renal inadequacy : serum creatinine level >133mmol/L •Severe chronic gastrointestinal diseases •Active myocarditis or pericarditis •Unstable angina in 2 weeks •Planned cardiac surgery •Severe hematologic disease •Allergy to experimental drugs •Mental illness, drug or other substance abusers •Stressful situation such as surgery, severe trauma, etc •Breastfeeding , pregnancy or preparation for pregnancy recently	•The participants asked to withdraw. •Allergic reactions, serious adverse reactions, adverse events, or intolerance •Due to complications or other reasons also accept outside drug that our test requirements •Unable to perform the test as required (poor compliance). •no follow the eligibility criteria after inclusion.

Fig3. The inclusion, exclusion and withdraw criteria

Figure 3

The inclusion, exclusion and withdraw criteria



	STUDY PERIOD					
	Enrollment	**Allocation**	**Post-allocation**			**Close-out**
TIMEPOINT	Day -17 ± 0	0	day 14 ±2days	day 28 ±5days	day 42 ±5 days	day 56 ±5days
ENROLLMENT:						
Eligibility screen	V					
Informed consent	V					
Allocation		V				
INTERVENTIONS:						
Intervention A		•	—	—	—	•
Intervention B		•	—	—	—	•
Intervention C		•	—	—	—	•
ASSESMENT:						
General demography , relevant medical history and diagnosis	V					
Safety evaluation (some relevant blood analysis of blood routine, urine routine, liver and kidney function; electrocardiogram)	V					V
Therapeutic evaluation:						
Blood pressure in consulting room and symptom improvement assessment	V	V	V	V	V	V
FMD and Target organ damage assessment	V	V				V
Cardiovascular risk factors assessment	V	V				V
Other Matters:						
Adverse events recording			V	V	V	V
Combined drugs recording	V	V	V	V	V	V
Compliance assessment		V	V	V	V	V

Fig.4 Standard Protocol Items: Recommendations for Interventional Trials(SPIRIT) flowchart

Figure 4

Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) flowchart

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- TCMsyndromeintegralscale.docx
- SPIRITChecklist.pdf
- Hypertensionsymptomscale.docx