Efficacy and Safety of Qushi Huayu Granule For Hyperlipidemia: Study Protocol For a Randomized, Double-Blind, Placebo-Controlled Trial

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Abstract

Background: Hyperlipidemia has become a common chronic disease worldwide in recent years. Studies shown that hyperlipidemia patients, especially those with a high level of serum low-density lipoprotein cholesterol (LDL-C), have a significantly higher prevalence of atherosclerosis, leading to coronary heart disease. Previous basic experiments and clinical studies have shown that Qushi Huayu granule (QSHY) can reduce blood lipids in patients with non-alcoholic fatty liver disease (NAFLD) accompanied by hyperlipidemia, but lack of clinical efficacy evaluation for patients with hyperlipidemia. This study aims to investigate the efficacy and safety of Qushi Huayu granule for Hyperlipidemia.

Methods: This is a randomized, double-blind, placebo-controlled trial. 210 hyperlipidemia participants will be enrolled and randomized into QSHY or placebo granule groups in equal proportions, and receive treatment for 24 weeks. The primary outcome is the percentage change of LDL-C from baseline to week 12. Secondary outcomes are other serum lipid biochemical markers levels, life quality measuring health surveys, and Traditional Chinese Medicine (TCM) Pattern Scale. All related tests will be measured at baseline, week 12 and 24 after enrolment. Adverse events and safety of intervention will be monitored and evaluated.

Discussion: We design a clinical trial of hyperlipidemia management with QSHY, a TCM formula. The results of this trial will present the efficacy and safety of QSHY in patients with hyperlipidemia, and provide clinical evidence for the treatment of hyperlipidemia.

Trial registration: Chinese Clinical Trial Registry, ID: ChiCTR2000034125. Registered on June 25, 2019.

Introduction

Background

Due to the change of lifestyle and diet, the incidence rate of hyperlipidemia has increased significantly(1). 53% of adults, or more than 100 million people in the United States, have elevated levels of serum LDL-C (2). The prevalence of dyslipidemia in Chinese adults is as high as 40.40%(3)and 45% of the prevalence is in Russia(4). Hyperlipidemia usually refers to elevated serum cholesterol and/or triglycerides (5) levels due to the disorder of systemic lipids metabolism. Among them, the increase of LDL-C is the main risk factor of atherosclerosis(6, 7) leading to coronary artery disease, myocardial infarction(MI), and stroke (8, 9). In addition, studies showed the relationship between the control of blood lipids and the progress of diseases such as osteoporosis(10), chronic kidney disease(11, 12), acute pancreatitis(13).

The treatment of hyperlipidemia is based on lifestyle change therapy, which is generally required to improve the diet structure and lifestyle, but has little effect on blood lipids level when used alone(14). Further, cooperate with western medicine, and start drug treatment according to the risk of atherosclerotic cardiovascular disease (ASCVD)(15, 16). At present, statins in clinical application are used as the cornerstone of lipid-lowering medicines (17). Other medicines including fibrates, ezetimibe, proprotein

convertase subtilisin/kexin type 9 (PCSK9) inhibitors, bile acid sequestrants, niacin, and other recent therapies including gene therapy of small interfering RNA, antisense oligonucleotides, viral vector-mediated and non-coding RNA therapy(18–20) are still in the stage of laboratory research, or not been widely used in clinical. In clinical, the lipid-lowering drugs represented by statins have certain limitations, the incidence of adverse reactions of statins is relatively high(21, 22). The main adverse reactions are gastrointestinal reaction, thrombocytopenia(23), liver and kidney function damage, myopathy, hyperglycemia, and neurotoxicity(24), Myopathy was the most common adverse reaction. Rhabdomyolysis occurred in severe cases(25), and even statin-induced necrotizing autoimmune myopathy (SINAM)(26). With the deepening of related researches, several studies suggest that statins have a risk of diabetes(27).

Traditional Chinese medicine (TCM) has a good effect on hyperlipidemia(28). In the 2002 version of the "Guiding Principles for Clinical Research of New Chinese Medicines", hyperlipidemia is classified as the "phlegm" category of Chinese medicine. Phlegm and blood stasis are the main pathological products of hyperlipidemia, and the syndrome of phlegm and blood stasis is a common syndrome type of hyperlipidemia(29). Although existing research reports suggest that TCM formulas or some herbal ingredients have a good therapeutic effect on hyperlipidemia in preclinical researches, currently, only Xuezhikang capsules(30), Zhibituo(31), and Zhibitai capsules(32) are the final products of Chinese patent medicines with clear indications for lipid-lowering applications in the market. Therefore, the treatment of hyperlipidemia by TCM lacks evidence-based medicine data support and market transformation.

Qushi Huayu granule (QSHY) prescription is an empirical prescription of TCM, which is composed of five herbs. QSHY has been proven to alleviate liver steatosis and inflammatory damage in patients with nonalcoholic fatty liver disease (NAFLD) and obese rodent models(33–36). QSHY treatment significantly reduced the elevation of serum LDL-C, TC, TG, ALT, and AST in NAFLD rodent models induced by HFD(35, 37), the related mechanism is that QSHY could regulate the dysbiosis of intestinal microbiota and inhibit hepatic lipogenesis(37, 38). Although the experimental evidence indicates that QSHY could be used in the administration of hyperlipidemia, there is still a lack of evaluation of the effect of QSHY in the treatment of patients with hyperlipidemia compared with placebo. Therefore, this study will investigate the efficacy and safety of QSHY and provide clinical evidence for the administration of hyperlipidemia.

Methods/design

This study will investigate the efficacy and safety of QSHY as a treatment for Hyperlipidemia diagnosed with Phlegm-blood Stasis Syndrome. This is a randomized, double-blind, placebo-controlled trial. The flow diagram of this trial is shown in Figure. 1. This study will be conducted in Shuguang Hospital Affiliated to Shanghai University of Traditional Chinese Medicine.

The visit in this trial are designed as 5-time points during 24 weeks of intervention: Baseline, 6 weeks $\pm$ 5 days after enrolment, 12 weeks $\pm$ 5 days after enrolment, 18 weeks $\pm$ 5 days after enrolment, 24 weeks $\pm$ 5

days after enrolment. At each visit time point, participants will have tests according to the study schedule, and data of vital signs will be recorded. The detailed flow path information is shown in Figure.2.

Sample size

According to the previous results from a single center clinical observation, after treated with QSHY decoction, the fasting serum TC level decreased by 23.84% compared with baseline, and the fasting serum TC level in the control group decreased by 12.71% compared with baseline. It is expected that the decrease of fasting LDL-C level in the QSHY granule group will increase by 15% compared with placebo. Assuming $\alpha = 0.05$, $\beta = 0.2$, $n_T: n_C = 1:1$, $\delta = 0$, $\pi_C = 0.155$, $\pi_T = 0.305$, according to the formula of the optimal sample size, 94 samples in each group will be obtained. Considering the leakage rate of 10%, there will be at least 105 cases in each group.

$$n_T = n_C = \frac{(z_{1-\alpha} + z_{1-\beta})^2 [\pi_T(1 - \pi_T) + \pi_C(1 - \pi_C)]}{[(\pi_T - \pi_C) - \delta]^2}$$

Inclusion criteria

☑For patients who meet the diagnostic criteria of Chinese and Western medicine for hyperlipidemia. The diagnostic criteria for hyperlipidemia refer to the Chinese Guidelines for the Prevention and Treatment of Dyslipidemia in Adults (2016 Revised Edition)(39). TCM diagnosis, syndrome differentiation criteria, and their basis refer to the TCM diagnosis and treatment criteria for dyslipidemia formulated by the heart disease branch of the Chinese society of TCM(40).

☑Aged over 18 years;

☑Participates without ASCVD, $3.4\text{mmol/L} < \text{LDL-C} < 4.9\text{mmol/L}$; ASCVD patients, $2.6\text{mmol/L} < \text{LDL-C} < 4.9\text{mmol/L}$;

☑Patients with fasting TG $< 5.7 \text{ mmol/L}$;

☑BMI $< 35 \text{ kg/m}^2$;

☑Willing and able to follow the scheduled visit plan, diet and exercise instructions, laboratory tests and other procedures.

☑Patients who signed informed consent.

Exclusion criteria

☑The patients who used other lipid-lowering drugs 4 weeks before enrollment;

☑Patients with uncontrolled endocrine or metabolic diseases that may interfere with blood lipids levels;

- ☒Patients taking oral corticosteroids;
- ☒Patients with a history of alcohol or narcotic drug abuse within 1 year before screening;
- ☒Patients with high or very high risk of arteriosclerotic cardiovascular disease;
- ☒Patients with congestive heart failure, unstable angina, MI, stroke, coronary artery bypass surgery or angioplasty, or unstable/serious peripheral artery disease in the past 6 months;
- ☒Patients who have undergone gastrointestinal surgery in the past year or who have taken weight-loss drugs in the past 3 months and have lost more than 10% of their body weight;
- ☒Pregnant or lactating female patients;
- ☒Patients with serious primary diseases or other major diseases such as malignant tumors.

Randomization and concealment

Randomization and allocation

The consecutive random sequence of 2 groups will be provided by the clinical medicine center with SAS Version 9.1 statistical software. Eligible participants will be randomly allocated into the QSHY group or the placebo group in a 1:1 ratio. Random sequence will be sealed in opaque envelopes and locked in the independent clinical medicine center. The allocation concealment will be maintained until the all data of each participant in each visit had been uploaded and locked.

Blinding

Blind editing and blind bottom preservation: All patients and researchers will be blinded to the treatment assignments until the trial is completed. Personnel unrelated to this clinical trial completes the preparation of drug blinding and emergency letters. Duplicate blinding is adopted in this study. All the data will be uploaded into the electronic database in double copies, and the final statistical plan is confirmed by question answering, verification, and blind review, the database will be locked. After that, the first unblinding will be carried out and the results of the undefined group information corresponding to random number for necessary statistical analysis can be obtained. After the analysis, the main researcher will perform the second unblinding with the identification of two groups. All the unblinding processes will be recorded. In case of emergency, the reason, time, and place of blindness breaking will be recorded, and the cases will be treated as missing cases.

Recruitment

The investigators will be experienced physicians familiar with the trial process. A printed standardized protocol and an informed consent form will be presented during the investigation. The enrolment will be performed after the investigators fully introduce the detailed trial process, probable benefits and potential

risks to eligible participant. The investigators will fulfill the case report form (CRF) with participants data after the participants have signed informed consent form. All data collected from participants including personal information will be kept confidential in this trial.

Participants can withdraw at any time and will be recorded the reason for withdrawal. The investigation with the curative effect after medication and the relationship with the trial will be recorded in detail as the evaluation index at the time of termination. The original data of all withdrew and terminated cases should be kept and recorded for further analysis. If adverse events occur, the researchers should judge its relationship with the trial, and take necessary measures to ensure the safety and rights of participants. The severe adverse event should be timely report to the drug regulatory department.

Interventions

Included participants in the treatment group will receive QSHY granule, while QSHY simulated granule as placebo will be applied in the control group. Both groups of participants will receive regular health education, including diet control, exercise, and behavior modification. ¶diet adjustment: diets with low sugar, low fat and high vitamin will be recommended, of which the fat content is less than 30%, protein content accounts for 15%-18%, and carbohydrate accounts for 52%-55% of the daily total energy; ¶Strengthen physical exercise: moderate metabolic equivalent exercise will be recommended for more than 30 minutes each time, 4 times a week; ¶Adjust emotion and keep a good mood.

The QSHY are compound preparations of 5 Chinese herbs, *Artemisiae scopariae herba*(Yin Chen), *Polygoni cuspidati rhizome et radix*(Hu Zhang), *Curcumae longae rhizome*(Jiang Huang), *Gardeniae fructus* (Zhi Zi), and *Herba hyperici japonici*(Tian Jihuang), packaged in consecutively numbered drug containers. The number was distributed according to the randomized number. The placebo will have a identically packaged appearance, weight, and taste compared to the QSHY granule. Both QSHY granule and placebos will be produced by Jiangyin Tianjiang Pharm Co. Ltd (approval number AH20160363), Jiangsu, China. Participants will be advised to take one pack after-meal, twice a day. The drugs are stored in the clinical trial base certified by Good Clinical Practice(GCP) and are managed and distributed in an independent clinical medicine center. The number of drugs received, taken, and returned by the patients will be recorded in detail by the research doctors at each visit. During the experimental period, Non-pharmacologic care is permitted but other TCM herbs and Western medication for lipid-lowering or fatty liver treatment will be prohibited.

Participants will be provided the information of the treatment orally and an informed consent form. Participants will be advised not to take concomitant medications or change the dose and frequency of drugs autonomously. To facilitate completion, participants are suggested to contact the arranged physicians for any questions raised about this trial. The drugs left over will be returned and the related medication compliance will be calculated. Any combination of medications will be recorded in detail. Participants will be recommended to visit the outpatient clinic regularly for post-trial care.

Outcomes

The primary outcome in this study is the percentage change of LDL-C from baseline to week 12. The secondary outcomes are the changes in fasting serum TC, TG, HDL-C, non-HDL-C, apolipoprotein (Apo) A-I, ApoA-II, ApoB and fasting blood glucose at 12-week assessment and 24-week assessment, the change in the ratio of TC/HDL-C at 12-week assessment and 24-week assessment. All mentioned serum biochemical markers will be measured at baseline, 12-week and 24-week after randomization. The measurement of life quality will be assessed by Medical Outcomes Study item short-form health survey (SF-36) questionnaire. The changes in the syndrome of TCM for participants will be measured using four TCM diagnostic methods and the Scores of TCM syndrome Scale. Other outcomes are blood pressure, heart rate, body mass index (BMI), and waist-to-hip ratio (WHR).

Safety indexes are blood and urine routine examination, results of serum liver function test including AST, ALT, alkaline phosphatase (ALP), and serum renal function test including creatinine (CR) uric acid (UA), and blood urea nitrogen (BUN). Adverse events that occurred in the trial period will be monitored at each visit. All collected adverse events and their degree will be recorded with followed medical intervention in the CRF.

The clinical trial protocol was jointly agreed upon by the main researcher and the sponsor, and has been approved by the IRB of Shuguang Hospital affiliated with Shanghai University of TCM before implementation(Ethics approval number: 2019-780-135-01). If the protocol is revised in the process of clinical trial implementation, it needs reapproval from the ethics committee.

Data management

Data management will be applied by an electronic data capture system (EDC). Two data administrators will input and proofread the data independently. Divergences raised about the CRF and data proofread will be generated as a concentrator data ready queue (DRQ). Data administrators will send the DRQ to the researchers through the clinical supervisor. The researchers deal with the DRQ and return it as soon as possible. The data administrators will confirm the modification and enter the new data according to the responses of the researchers, and issue DRQ again if necessary. After reviewing and confirming the correctness of the database, the main researchers, applicants, and statistical analysts will lock the data. The locked data file will not be changed. Any problems found after data locking will be corrected. The demographic and clinical information of participants will be kept by doctors confidentiality. The results of this trial will be submitted for publication in peer-reviewed journals and can be disseminated through conference presentations.

Statistical analysis

The statistical analysis will be performed by an independent statistician. After the trial protocol is determined, the statistician is responsible for formulating the detailed statistical analysis plan in consultation with the principal investigator. Statistical analysis will be conducted using SAS Version 9.1 statistical software. Full analysis set (41) including participants who met the inclusion and exclusion criteria and receiving at least one evaluation at least once after randomization will be statistically

analyzed. Per-protocol set (PPS) including participants who had good compliance (80% – 120% of the trial drugs were used), did not take prohibited drugs during the trial, and completed the CRF will be statistically analyzed. Safety analysis will be conducted based on a safety analysis set including participants who have received at least one intervention and safety evaluation. Continuous variables are presented as mean $\pm$ standard deviation (42) or median with quartile range, according to the distribution. An independent t-test or the Mann-Whitney U test will be conducted to compare the differences between groups. Dichotomous variables will be presented as frequency and percentage and analyzed with the chi-square test or Fisher's exact test. Subgroup analyses will be performed based on groups with high heterogeneity if necessary.

Discussion

Hyperlipidemia is a companion to a lot of diseases, such as NAFLD and coronary heart disease. According to previous studies, QSHY can improve liver function and blood lipid including TC, LDL-C, and TG of HFD rodent models(34), and no obvious adverse reactions were found(35, 37). Three previous clinical trials performed in China(33, 34, 43) have shown that QSHY can significantly reduce ALT and AST in patients with NAFLD, and can reduce serum TG and TC with a high mean value at baseline. This indicates that QSHY has a therapeutic effect on patients with NAFLD and hyperlipidemia. However, the data presented are all based on the inclusion criteria of NAFLD patients, precise data of QSHY for hyperlipidemia is still lacking. We designed this protocol to find out whether QSHY is an effective treatment of hyperlipidemia.

Although no symptom occurs in hyperlipidemia, high level of LDL-C, not only a biomarker, appears to be a causal factor of the pathophysiology of ASCVD. According to the guidelines for the management of dyslipidaemias issued by European Society of Cardiology / European Atherosclerosis Society (ESC/EAS) in 2019 (44), serum LDL-C level is recommended as the main outcome for screening, diagnosis, and management lipid modification to reduce cardiovascular risk. Thus, we set LDL-C, not TC or TG to be the main research object in this trial. According to the 2002 guiding principles of clinical research on new drugs of traditional Chinese medicine, participants are recruited according to the conventional TCM syndrome identification before randomization.

This protocol set up five visits after enrolment to supervise the six months of the treatment period. Observation items designed will be measured and recorded in the CRF. Participants will have propaganda and education on diet control and exercise. However, due to the autonomy of patients, quantitative and accurate quality control cannot be achieved, and the potential interference caused by lifestyle differences cannot be eliminated.

This protocol presents a rigorously designed, double-blind, placebo-controlled RCT, objective to study the therapeutic effect and safety of QSHY, especially for hyperlipidemia patients, to provide effective clinical evidence for the administration of hyperlipidemia

Trial Status

The final version of this protocol is 2.0 on 23 December 2019. Recruitment began on 23 June 2020 and will be completed on 23 December 2022. 102 patients have been enrolled.

Declarations

Acknowledgments

Not applicable.

Authors' contributions

YYH and YZ were involved in the study concept and design. YLS, NH, GFC, YYH, and YZ participated in the generation of the study protocol. YLS drafted the manuscript. All authors reviewed and approved the final manuscript.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Ethics approval and consent to participate

The study has been approved by the ethics committee in Shuguang Hospital (Ethics approval number: 2019-780-135-01). Patients are included after giving written informed consent.

Consent for publication

We will give informed consent for the publication of the dataset from patients at the point of recruitment to the Trials. All the patient details will be strictly confidential. Any information that is published will not reveal the identity of the participants.

Competing interests

The authors declare that they have no conflict of interests.

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Figures

Figure 1

Flow diagram of this study protocol

	STUDY PERIOD					
	Enrolment	Allocation	Post-allocation			
TIME POINT(week)	-3~0	0	6	12	18	24
ENROLMENT:						
Eligibility screen	X					
Informed consent	X					
Demographic data	X					
Medical history	X					
Allocation		X				
INTERVENTIONS:						
QSHY granule plus primary treatment			←————→			
Placebo plus primary treatment			←————→			
ASSESSMENTS:						
Vital signs		←————→				
Propaganda and education of diet and exercise		←————→				
Efficacy Assessment						
LDL-C	X			X		X
TC, TG, HDL-C, non-HDL-C	X			X		X
ApoA-I, ApoA-II, ApoB	X			X		X
FBG	X			X		X
SF-36	X			X		X
TCM syndrome score	X			X		X
BMI, WHR	X			X		X
Safety Assessment	X			X		X
Blood and urine routine examination	X			X		X
Hepatic and renal functions	X			X		X
Adverse events			X	X	X	X
HCG	X					

Figure 2

Study schedule of enrolment, interventions, and assessments. Abbreviations: QSHY, Qu-Shi Hua-Yu granule; LDL-C, Low-density lipoprotein cholesterol; TC, Total cholesterol; TG, Triglyceride; HDL-C, High density lipoprotein cholesterol; Apo, apolipoprotein; FBG, fasting blood glucose; SF-36, Medical Outcomes

Study item short-form health survey; TCM, Traditional Chinese Medicine; BMI, Body mass index; WHR, Waist-to-hip ratio; HCG, Human chorionic gonadotropin.

Supplementary Files

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

- [ClinicalTrialsRegistryPlatform.png](#)
- [SPIRITFillablechecklist.doc](#)