YLTZ in the treatment of primary hyperlipidemia (phlegm-turbid obstruction type): study protocol for randomized, double-blind, parallel dose control and multi-center phase II a dose exploration

Xiaohui Zeng
Guangdong province engineering technology research institute of TCM
Juncheng Zhuo
Guangdong province engineering technology research institute of TCM
Xuejun Huang
Guangdong province engineering technology of TCM
Haining Gan
Guangdong province engineering technology research institute of TCM
Dake Cai
Guangdong province engineering technology research institute of TCM
Dane Huang
Guangdong province engineering technology research institute of TCM
Nan Yao
Guangdong province technology engineering insititute of TCM
Leyi Li
Guangzhou University of Chinese Medicine
Yuxing Chen
guangdong province engineering technology research institute of TCM
Dongmei Sun (simao37@163.com)
Guangdong Yifang Pharmaceutical co.,LTD.

Study protocol

Keywords: Yinlan Tiaozhi Capsule (YLTZ), primary hyperlipidemia (HLP), blood lipids level

Posted Date: April 27th, 2021

DOI: https://doi.org/10.21203/rs.3.rs-38442/v1

Abstract

Backgrounds: Yinlan Tiaozhi Capsule (YLTZ) is a prescription of traditional Chinese medicine (TCM) based on clinical experience. YLTZ have been used for the treatment of primary hyperlipidemia (HLP) in China, performing the disorder of blood lipids level, but few clinical studies have been conducted to assess its efficacy and safety in the treatment of primary HLP. Here, we designed a clinical trial combining Western Chinese medicine and TCM evaluation systems to evaluate the efficacy and safety of primary HLP.

Methods: The study is designed as a randomized, double-blind, parallel dose control and multi-center clinical trial. Eligible subjects (n=120) will be allocated after satisfying the criteria (western medicine). Subjects will be randomized to receive YLTZ, or a placebo for 12-week treatment and with follow-up after treatment to record symptoms and signs and to collect serum samples for detecting the lipids level. At the same time, the syndrome differentiation criteria of TCM, such as body mass index, furred tongue and palpitation, will be recorded as determined by doctors of both Western and Chinese medicine. Participants will be instructed to comply with the protocol and to keep a daily record of symptoms. The primary and secondary outcomes and safety indicators will be used to evaluate the efficacy and safety of YLTZ in the treatment of primary HLP based on both Western Chinese medicine and TCM evaluation systems.

Discussion: Previous studies were expected to evaluate whether the addition of YLTZ to standard routine treatment would enhance the treatment effectiveness and improve the primary HLP. However, this trial is focused on the outcome of lipids level, and we chose a range of outcome measurements to assess the improvement of relevant symptoms and signs. This trial is the first study designed to define and optimize the outcome measurements of lipids level of YLTZ in the treatment of patients with primary HLP.

Trial registration: The trial has also been registered with the Center for Drug Evaluation (CDE, CTR20190061) and the China Clinical Trials Registry (ChiCTR1900021326).

Introduction

Background and rationale

HLP is a chronic metabolic disease caused by abnormal metabolism of lipids, which mainly refers to a disorder of blood lipid metabolism in which total cholesterol (TC), triglyceride (TG), low density lipoprotein-cholesterol (LDL-C) and/or high density lipoprotein-cholesterol (HDL-C) in plasma are too high and/or too low[1].

Numerous studies have demonstrated a consistent and linear association between the magnitude and the duration of the exposure to high LDL-C levels and the risk of developing atherosclerotic cardiovascular diseases (ASCVD) which is noted as a high-risk fatal diseases[2–4]. How to carry out lipid-lowering therapy has become an important topic in the field of treatment of ASCVD[5 6].

Generally, it was classified into two type, including primary HLP and secondary HLP[7]. In perspective of diagnosis of HLP, except that bad lifestyles (such as high energy, high fat, high sugar diet, excessive drinking, etc.) are associated with dyslipidemia, most primary HLP is caused by single or multiple gene mutations which has family aggregation and obvious hereditary tendency, so it is usually called familial HLP in clinic[7]. Secondary HLP refers to dyslipidemia caused by systemic diseases, such as diabetes mellitus, nephrotic syndrome hypothyroidism and polycystic ovary syndrome, etc[8].

However, there is no conception of HLP in TCM. According to its clinical manifestations, it can be classified as "vertigo", "chest obstruction", "stroke", "blood stasis" and "phlegm-dampness"[9 10]. Most TCM physicians believe that the basic pathological changes of HLP belong to the deficiency of the liver, spleen and kidney, and the deficiency of phlegm and blood stasis[10 12]. Hence, lipid-regulating therapy should be based on the principles of smoothing the liver, invigorating the spleen and tonifying the kidney. Recently, in terms of the analysis of literature reports, many clinical practices and experimental studies of TCM have proved that it has unique advantages in regulating lipid[13 14]: it can regulate the function of viscera, enhance the metabolism of the body to clear the source of the root, and has no drawbacks of the decline of western medicine, the gradual increase of drug withdrawal and many side effects.

YLTZ, consisted of Pummelo Peel, Ginkgo biloba, Gynostemma Pentaphyllum and propolis, was clinically used to treat HLP for ten years. It was comprehensively considered to replenish qi to invigorate the spleen, promote blood circulation and remove blood stasis and eliminate phlegm and dampness based on TCM theory, and previous pharmacological experiments evidenced these functions[15–17], thereby resolving the root causes and symptoms of HLP in the theory of TCM[18]. In addition, it was approved by the State Food and Drug Administration for clinical trial in 2012, the batch number is 2012L01011.

At present, this trial is planned to carry out a phase IIa exploration, Beijing Hospital of Traditional Chinese Medicine affiliated to Capital Medical University is the head of the clinical trial group, coupled with other 7 qualified research hospitals. The efficacy and safety of YLTZ in the treatment of primary HLP (phlegm turbidity obstruction type) are preliminarily evaluated, and the optimal clinical dose is explored to provide the basis for the next phase of clinical trial.

According to the Regulations on Drug Registration Management, GCP, Technical Requirements for Clinical Research of New Chinese Medicines and Guiding Principles for Clinical Research of New Chinese Medicines, this clinical trial plan was formulated based on the data of pre-clinical research, main components of prescriptions and main functions of YLTZ.

Objetives

With LDL-C as the main evaluation index, the efficacy and safety of YLTZ in the treatment of primary HLP (phlegm turbidity obstruction syndrome) were evaluated by randomized, double-blind, dose-parallel control and multi-center clinical trial design.

Trail design

This study is a double-blind, randomized, parallel-dose, placebo-controlled, multi-center clinical trial comparing YLTZ and placebo capsules (PC) in people with HLP. A brief flow chart of the study protocol is shown in figure1. The study complies with the principles of the Declaration of Helsinki and Good Clinical Practice guidelines. Its reporting will be guided by the CONSORT statement and the relevant extensions related to herbal medicine interventions.

The trial will be lead and organized by Beijing Traditional Chinese Medicine Hospital Affiliated to Capital Medical University (Beijing, China), and will be conducted together with other 7 hospitals. A total of 120 participants will be recruited. After acquiring consent from the participants and their parents/legal guardian by investigators, the participants will be enrolled for a trial period of 16 weeks and will be required to attend a total of 5 visits during the trial. The study consists of a 4-week run-in period and a 12-week treatment period. The duration for the run-in and treatment was decided based on our previous systematic reviews.

Potential participants will undergo preliminary screening for eligibility during visit 1 by investigators, which will include a registered medical practitioner. Initial assessments for baseline data collection will be conducted if the participants are eligible, which includes the Chinese Medicine Questionnaire, measurement of primary outcome, second outcome and safety assessments. A daily diary will then be given to record the occurrence of adverse events and use of topical treatments during the 4-week run-in period. The treatment period will start after that, participants will be randomly assigned to either the treatment (YLTZ) groups or the control (PC) group. During the treatment period, the outcome measurements will be collected once per 4 weeks, and participants will also be required to record their medication intake, including trial interventions and occurrence of adverse events to assist with compliance monitoring and acceptability of intervention.

Methods

Settings and participants

We will recruit participants in two ways. (1) Through the screening of patients in the hospital case bank, find patients who meet the inclusion standard. (2) Recommendation through other clinic departments; (3) Recruit eligible patients through hospital or community free clinics; (4) Recruitment through recruitment advertisement or publication of leaflets; (5) Recruitment through recruitment advertisements published on the website of research institutes. (6) Initiate the patients who have already been admitted to the group to recommend other patients who have the same disease.

A total of 120 patients will be enrolled at one of the following three hospitals in China: (1) Beijing Traditional Chinese Medicine Hospital Affiliated to Capital Medical University, (2) Taizhou Hospital of Traditional Chinese Medicine, (3) Second Affiliated Hospital of Hunan University of Traditional Chinese Medicine, (4) Fifth Affiliated Hospital of Xinjiang Medical University, (5) Nanchang Hongdu Hospital of Traditional Chinese Medicine, (6) Luoyang First Hospital of Traditional Chinese Medicine, (7) Baoding First Hospital of Traditional Chinese Medicine, (8) Wenzhou Traditional Chinese Medicine Hospital.

Western medicine diagnosis and syndrome differentiation of HLP

Refer to the guiding principles of clinical research on the treatment of HLP with TCM and the guidelines for prevention and treatment of dyslipidemia in adults in China (Revised Edition 2016).

Under normal diet, the serum lipid level after fasting for 12 hours was measured, which met the following criteria of blood lipid level stratification. TC or TG increased, or HDL-C decreased.

Table 1. Quantitative limits of HLP level

	TC	LDL-C	HDL-C	Non HDL-C	TG
Ideal level		<2.6mmol/L (100mg/dl)		<3.4mmol/L (130mg/dl)	
Appropriate level	<5.2mmol/L (200mg/dl)	<3.4mmol/L (130mg/dl)		<4.1mmol/L (160mg/dl)	<1.7mmol/L (150mg/dl)
Edge elevation	≥5.2mmol/L (200mg/dl) and <6.2mmol/L (240mg/dl)	≥3.4mmol/L (130mg/dl) and <4.1mmol/L <160mg/dl>		≥4.1mmol/L (160mg/dl) and <4.9mmol/L <190mg/dl>	≥1.7mmol/L (150mg/dl) and <2.3mmol/L (200mg/dl)
Elevation	≥6.2mmol/L (240mg/dl)	≥4.1mmol/L (160mg/dl)		≥4.9mmol/L <190mg/dl>	≥2.3mmol/L (200mg/dl)
Reduction			<1.0mmol/L (40mg/dl)		

Table 2. Clinical classification of HLP

	TC	TG	HDL-C	WHO type
Hypercholesterolemia	↑			a
Hypertriglyceridemia		↑		
Combined Hyperlipidemia	↑	↑		b
Low-density lipoproteinemia			↓	

Chinese medicine diagnosis and syndrome differentiation

Refer to the Guiding Principles for Clinical Research of New Chinese Medicine in the Treatment of HLP (2002 edition). The main symptoms of phlegm turbidity obstruction syndrome are obesity, heavy head, chest tightness, nausea, spitting and salivation, heavy limb numbness; the secondary symptoms are palpitation, insomnia, tastelessness, loss of appetite; fat tongue, greasy coating, slippery pulse string. There are two main symptoms and one minor symptoms, which can be differentiated into Phlegm-Turbid obstruction syndrome combined with dialectics of tongue and vein.

Table 3. Quantitative grading of TCM syndromes

Main symptoms		
Obesity	Description	Score
Normal:	None	0
Mild:	Body mass index□25	2
Medium:	Body mass index□30	4
Severity:	Body mass index□35	6
Heavy head	Description	Score
Normal:	None	0
Mild:	Micropharyngeal sinking	2
Medium:	Dizziness	4
Severity:	Head heavy and tight	6
Chest tightness	Description	Score
Normal:	None	0
Mild:	Mild chest constriction	2
Medium:	Obvious tightness, sometimes too much breath	4
Severity:	Suffocating chest tightness	6
Nausea, spitting and salivation	Description	Score
Normal:	None	0
Mild:	Nausea and occasional sparse phlegm	2
Medium:	Thick phlegm in retching	4
Severity:	Excessive vomiting and sputum	6
Limb numbness and heaviness	Description	Score
Normal:	None	0
Mild:	Slight limb anesthesia, occasionally heavy lower limbs	2
Medium:	Limb anesthesia is sometimes heavy and sometimes light, frequent lower limb distress	4
Severity:	Significant limb anesthesia and severe lower limb distress	6
Secondary symptoms		
Palpitation	Description	Score
Normal:	None	0
Mild:	Occasionally mild palpitations	1
Medium:	Palpitations occur from time to time	2
Severity:	Palpitation and panic	3
Insomnia	Description	Score
Normal:	None	0
Mild:	Easy to wake up, or wake up early, mildly affect work	1
Medium:	Sleeping less than 6 hours a day, affects work.	2
Severity:	Sleeping less than 4 hours a day, affects work	3
Tastelessness	Description	Score
Normal:	None	0
Mild:	Slightly tasteless in the mouth	1
Medium:	A heavy tastelessness	2
Severity:	Tastelessness and no appetite for food	3
Loss of appetite	Description	Score
Normal:	None	0
Mild:	A slight reduction in diet	1
Medium:	Decreased diet	2
Severity:	A marked reduction in diet	3

Tongue and pulse images are only described and not scored.

Inclusion criteria

(1) Age between 18 and 75 years old;

(2) TCM syndrome differentiation of phlegm and turbidity obstruction syndrome;

(3) The introduction period conforms to the diagnostic criteria of Western medicine for primary HLP, and 3.4 mmol/L (130 mg/dl) = LDL-C < 4.9 mmol/L (190 mg/dl);

(4) Therapeutic life-style change(TLC) intervention for four weeks during the introduction period (maintaining a balanced diet and living habits, and discontinuing all drugs affecting blood lipid, see attached. Record 1) The fasting blood lipids were still in accordance with the above diagnostic criteria after the end of the import period, and the difference between the import period and the baseline period was not more than 12% (based on the higher value);

(5) Those whose baseline dietary score was less than 5 points;

(6) Voluntary signing of informed consent.

Table4. Dietary evaluation of patients with hyperlipidemia

	Quires	Scores
1	Have you eaten meat less than 75g/d in the past week?	0=no 1=yes
2	What kind of meat do you eat?	0=lean meat 1=fat lean meat 2=fat meat 3=viscera
3	Number of eggs you have eaten in the past week	1=0-3 eggs per week 2=4-7 eggs per week 3=more than 7 eggs per week
4	Number of fried foods you have eaten in the past week	0=not eaten. 1=1-4 times per week. 2=5-7 times per week. 3=more than 7 times per week
5	How many times have you eaten butter cakes in the past week?	0=not eaten 1=1-4 times per week 2=5-7 times per week

Note: The total score < 3 is qualified; the total score is 3-5 is mild malnutrition; the total score > 6 is severe malnutrition.

Exclusion criteria

(1) Patients who suffered from acute myocardial infarction, cerebrovascular accident, severe trauma or major surgery within six months;

(2) Patients with HLP caused by other diseases, such as nephrotic syndrome, hypothyroidism, gout, severe hepatobiliary diseases (viral hepatitis, cholecystitis, cholelithiasis), etc., have been diagnosed as secondary HLP. Patients with HLP and known homozygous hypercholesterolemia caused by drugs (phenothiazines, beta-blockers, adrenocorticosteroids and some contraceptives, etc.);

(3) Patients who are using hormones, thyroxine and other drugs affecting blood lipid metabolism and those who have taken other lipid-lowering measures in the past two weeks;

(4) Patients who have undergone PCI and CABG in one year and a half Patients, patients with acute coronary syndrome, patients with cardiac function of three or more levels within six months;

(5) Allergic constitution or allergic to known drug ingredients;

(6) Patients whose blood pressure (> 180/110 mmHg) has not been controlled by systemic hypotension therapy;

(7) Patients with triglyceride (> 5.7 mmol/L) (500 mg/dl);

(8) Patients who smoked more than five cigarettes a day in the first three months of screening, or more than five cigarettes a day during the experiment;

(9) Patients with abnormal liver and kidney function (ALT and/or AST (> 1.5 times of the upper limit of normal value, Scr > the upper limit of normal value) and their fabrication. Patients with severe diseases of the blood system;

(10) Patients (including male patients's pouses) had pregnancy plans, pregnant or lactating women during the trial period and within 6 months after the last medication;

(11) Patients requiring long-term anticoagulation and adrenocorticosteroids;

(12) Type 1 diabetes mellitus and type 2 diabetes mellitus (systemic hypoglycemic therapy, random blood sugar (> 11.0 mmol/L), glycosylation after the introduction period. Patients with hemoglobin (> 9%);

(13) Patients with malignant tumors, chronic alcoholism, drug dependence or mental illness;

(14) Those who have participated in or are participating in other clinical trials in the past three months;

(15) Those who are not considered suitable to participate in clinical trials by researchers.

Suspension criteria

In the course of the study, the whole experiment will be terminated in many centers for the following reasons:

(1) The researchers find serious safety problems;

(2) The efficacy is too poor to continue the experiment;

(3) The scheme has major failures;

(4) The bidder has major financial or management reasons;

(5) The administrative department could cancel the experiment, and all the experiments could be stopped in the middle of the study;

Randomization and blinding

The method of stratified block randomization was adopted, and the center was taken as stratified factor for random grouping. Professional statisticians use SAS statistical software to generate random number grouping tables and complete the blindness of experimental drugs.

In this experiment, a double-blind design was used to package YLTZ and PC in the same way. The experiment was designed by two-stage blind method. The random coding table is set up by the statistical unit and sealed in two copies. It is submitted to the responsible unit of clinical trial and the bidding unit for proper preservation. Each trial drug has an emergency letter with the corresponding drug code, which is distributed to the centers. Emergency letters can only be opened when an emergency occurs in the subjects, and the emergency management must depend on the understanding of the type of test drug, so that it can be broken blindly. All emergency letters can be retrieved after the end of the trial.

Sample size

According to the "Drug Registration Management Measures" and the requirements of CDE, it is decided that this experiment is an exploratory study, and the number of cases drafts into the group is 120, inclusive of 20% dropout compensation. Among them, there are 30 cases in high dose, middle dose, low dose and PC group.

Trial interventions

The treatment interventions are YLTZ and matching PC, which are identical in appearance, taste and odor. The capsule of drug and placebo are both produced by Guangdong Yi Fang Pharmaceutical Co., Ltd, and the drug is provided by Guangdong Province Engineering Technology Research Institute of T.C.M.

The concrete administration method includes introduction period and treatment period.

Introduction period for 4 weeks:

- PC were given orally, 6 capsules per time, 3 times per day.

Treatment period for 12 weeks:

- Low dose group: 2 YLTZ per time + 4 PC per time, 3 times per day.
- Medium dose group: 4 YLTZ per time + 2 PC per time, 3 times per day.
- High dose group: 6 YLTZ per time, 3 times per day.
- PC group: 6 PC per time, 3 times per day.
- Introducing period: 4 weeks. Treatment period: 12 weeks of continuous medication.

All drugs will be taken orally after meals. All the drugs are concealed in the same sealed and opaque packages. The label of the package contains the drug name, the approval number, functions, usage, dosage, storage conditions, expiration date, and the name of the manufacturer. Participants will be informed that they would be randomly assigned to receive either YLTZ or PC. They will be encouraged to contact the investigators if they have any uncomfortable feeling or if they think the drugs are not helpful. Participants in both groups can continue their prior routine treatments, with the exception of Chinese herbal medicine. The details of these routine treatments will be recorded in the case report forms (CRFs).

During the trial, the following drugs will be prohibited. Once the prohibited drugs are used, the subjects will be informed to drop out of the study. Any natural and synthetic statins (such as lovastatin, etc.), beta (such as fenofibrate), nicotinic acid (such as nicotinic acid), cholic acid chelating agent (such as colenemide), ezymeb, probucol, n-3 fatty acid preparations, other traditional Chinese medicines with phlegm-resolving effects, Chinese herbal tablets or Chinese patent medicines that have the same or similar functions as YLTZ, as well as pharmaceuticals and herbal decoctions containing phlegm-resolving effects.

Outcomes measures

The primary outcome measures include the evaluation of the relative baseline changes of LDL-C in 12th weeks of administration.

Secondary outcome measures include the level of LDL-C, TG, TC, HDL-C and non-HDL-C , as well as the observation of therapeutic effect of TCM syndromes. Participants will be asked to compelete the evaluation of the relative baseline changes of LDL-C in 4th and 8th weeks of administration, evaluation of the relative baseline changes of TG, TC, HDL-C and non-HDL-C(once in the 4th, 8th and 12th week of medication), therapeutic effect of TCM syndromes and therapeutic effect of single symptom of TCM(once in the 4th, 8th and 12th week of medication).

Safety evaluation

The indices of vital signs, cardiopulmonary signs and electrocardiography will be compared before and after the treatment to assess for safety. Additionally, research interviewers will keep in touch with each participant to monitor safety.

(1) Vital signs(blood pressure, breathing, heart rate, body temperature)

(2) Blood routine, urine routine + microscopy, stool routine + OB;

(3) Liver function (ALT, AST, TBIL, AKP, gamma-GT), renal function (Scr, eGFR, urinary NAG enzyme, urinary microalbumin);

(4) Four coagulation items (APTT, PT, TT, FIB);

(5) Creatine kinase (CK);

(6) Fasting blood sugar;

(7) 12-lead ECG;

(8) Adverse events

Detect and record before and after treatment, participants whose assessments are normal before treatment, yet are abnormal after treatment, should be periodically reviewed to the end of follow-up.

Any adverse events will be recorded in a CRF with details, including occurrence time, severity, duration, effective measures and the outcomes. According to the judgement of severity, the investigators will decide whether the participants should be suspended or withdrawn from the trial. When SAEs occur, such as severe haemorrhage, hepatic failure, renal failure or death, the investigator will report to the principal unit and ethics committee, and the investigator can open the patient's emergency envelope to determine the group allocation..

Statistical analysis

All statistical analyses will be performed by an independent statistician blinded to the allocation, using the Statistical Analysis System (SAS, Version 9.4, Institute Inc., Cary, NC, USA). The main contents of the statistics include the following parts: the actual number of subjects enrolled in each group, the situation of dropped and excluded cases, demographic and other baseline characteristics, compliance, efficacy analysis and safety analysis.

All statistical tests are carried out bilaterally, and the difference between the two tests will be considered statistically significant if the P value is less than or equal to 0.05. The description of quantitative indicators will calculate the mean, standard deviation, median, minimum, maximum, lower quartile (Q1), upper quartile (Q3), and classification indicators will describe all kinds of cases and percentages. The comparison of general situation among groups will be analyzed by appropriate methods according to the types of indicators. The comparison of quantitative data between groups will be conducted by group t test or Wilcoxon rank sum test, the classification data by chi-square test or exact probability method, the rank data by Wilcoxon rank sum test or CMH test, and the comparison of multiple groups of data by variance analysis or Kruskal-Wallis test.

Full analysis set (FAS) refers to the ideal set of subjects as close as possible to the intentional analysis principle (the main analysis should include all randomized subjects). This data set is obtained after all randomized subjects are eliminated with the smallest and reasonable method, including all randomized subjects who have used the research drug once. For the estimation of the missing values of the main variables, the results closest to the first observation (last observation carry forward) are used to carry forward to the missing place of the test data. Per Protocol Set (PPS) is a subset of FAS data set that is more compliant with the protocol, requirements refer to the case set that conforms to the inclusion criteria, does not conform to the exclusion criteria, and completes the treatment protocol, that is, there is no serious violation of the protocol (including the inclusion criteria), good compliance (compliance between 80% and 120%), and complete the CRF requirements (no lack of main efficacy indicators) for PP analysis. Safety data set (SS), which is treated at least once, has actual data recorded by safety indicators. Safety missing value does not need to be carried forward.

Discussion

This study protocol was designed to investigate the efficacy and safety of YLTZ in the treatment of primary HLP (phlegm turbidity obstruction syndrome), and would be conducted under the principle of

random, double-blind, parallel dose control and multiple-center.

In this trial, combined with the outcome measurement of biochemical indexes, dietary evaluation and quantitative grading of TCM syndromes, we mainly investigate the effect of YLTZ on primary HLP which is also characterized as phlegm and turbidity obstruction syndrome, coupled with the LDL-C level is between 3.4 mmol/L (130 mg/dl) and 4.9 mmol/L (190 mg/dl).

For statistical analysis, PP analysis and FAS analysis were carried out for the primary outcome at the same time. Covariance analysis model was used to estimate LSmean and 95% CI of LDL-C before and after treatment. 95% confidence interval of the difference of LDL-C between high, medium and low dose groups and control groups was calculated. In order to investigate the consistency among the centers, a covariance analysis model with center-grouping interaction terms will be considered on the basis of the above-mentioned covariance analysis model, and whether the interaction terms are meaningful will be judged at 0.10 level. Secondary outcomes, including TC relative baseline change value, TG relative baseline change value, HDL-C relative baseline change value, non-HDL-C relative baseline change value, TCM syndromes efficacy and TCM single symptoms efficacy, will be compared between groups using the above general statistical methods on the basis of descriptive statistics.

Nevertheless, there are some challenges. The enrollment will meet some difficulties, because the run-in period is sufficiently long for patients to lower their lipid levels by taking exercise and balancing diet. In addition, 6 capsules per time might increase the reluctance and therefore decreasing the compliance. Hence, the measurements we probably take is expanding the source of patient recruitment, such as community hospitals, and increase the frequency of formal explanation of the danger of primary HLP to enhance the voluntariness of taking medicine.

The results of this trial will provide clinical data on the efficacy and safety of YLTZ in decreasing the content of LDL-C and improving the quality of life of patients with HLP. Positive results from the trial can lead to a better management of primary HLP to help patients. This investigation will also contribute to the understanding and treatment of primary HLP from Chinese medicine perspectives.

Quality control

Quality control will be performed as follows

1. Clinical trial records

Researchers should fill in all cases according to the design requirements of "original medical record form". The original medical record is the original record and cannot be changed. When making any correction, the original record should not be blacked out but only a horizontal line shall be drawn at the modified place, and the reason should be explained by adding a description. The doctor participating in the clinical trial shall sign and date it.

Laboratory data in clinical trials should be recorded and the original report (or copy) should be attached to the original medical record. The significant deviation or data beyond the clinical acceptable range should be verified, and the doctors participating in the clinical trial should make necessary explanation.

2. Training researchers

The personnel involved in clinical trials must have professional qualifications, receive training on relevant work of the trial, and have sufficient experience to complete the tasks they are responsible for. Before the start of clinical trial, the personnel participating in the clinical trial shall be trained uniformly. The training documents of clinical trial (one set for each person) include: the researcher's manual, clinical trial protocol, informed consent, original medical records, trial drug use record form, and standard operating procedures formulated or modified for specific research projects, so as to enable the personnel to understand clinical trial protocol well.

3. Verification of data

The researcher should verify the significant deviation or data beyond the acceptable range, and the researcher shall make necessary explanation and sign to determine whether it has clinical significance. Each test item must indicate the unit of measurement adopted. All observations and findings in clinical trials should be verified to ensure the reliability of the data and ensure that all conclusions in clinical trials are derived from the original data.

4. Laboratory quality control requirements

The laboratory should establish standard operating procedures and quality control procedures. When the main indicators may be subject to subjective influence, consistency test should be carried out. When the test results of each central laboratory are significantly different or the normal reference value range is different, the normal value range of each center should be checked.

Abbreviations

AKP, Alkaline Phosphatase; ALT, Alanine Aminotransferase; APTT, ActivatedPartial ThromboplastinTime; AST, Aspartate Aminotransferase; BUN, Blood Urea Nitrogen; FIB, Fibrinogen; GCP, Good Clinical Practice; HDL-C high-density, lipoprotein cholesterol; HLP, Hyperlipidemia; LDL-C, low density lipoprotein-cholesterol; PCI, Percutaneous Coronary Intervention; PT, Prothrombin Time; γ-GT, R-glutamyl Transferase; Scr, Serum creatinine; TBIL, Total Bilirubin; TC, total cholesterol; TG, Triglyceride; TT, Plasma thrombin time; TLC, Therapeutic life-style change; CK, Creatine Kinase.

Trial Status

Protocol version number and date: 1.1, 2018-12-5.

Date of recruitment began: 2019-3-6

Approximate date of recruitment will be completed: 2021-6-30.

Declarations

Acknowledgements We gratefully acknowledge support from the Major New Drug Creation Projects of the Ministry of Science and Technology of China (No. 2016ZX09101076), National Natural Science Foundation of China(No. 81973508) and Guangdong Science and Technology Project(No. 2017A070701017). We are especially grateful to all the trial staff working at our research affiliates.

Contributors XHZ and JCZ have the same contribution to this paper. DMS is the corresponding author to this paper. XHZ, YXC and DMS designed the protocol and conceived the study. JCZ wrote the draft and XHZ revised the manuscript critically for important intellectual content. HNG and XJH edited the manuscript and contributed to the final draft. DEH and NY were responsible for all statistical analysis in this trial. All authors have carefully read and approved the final manuscript. The funding body supports this protoco. The costs, such as those for publishing the article and purchasing CPMs are supported by the funding body.

Funding The study is funded by the Major New Drug Creation Projects of the Ministry of Science and Technology of China (No. 2016ZX09101076), National Natural Science Foundation of China(No. 81973508) and Guangdong Science and Technology Project(No. 2017A070701017).

Competing interests None declared.

Patient consent Obtained.

Ethics and trial registration Any amendments to the study protocol has been submitted to the Human Research Ethics Committee (HREC) for approval. The trial has also been registered with the Center for Drug Evaluation(CDE, CTR20190061) and the China Clinical Trials Registry (ChiCTR1900021326).This study has been approved by the Medical Ethics Committee of Beijing Traditional Chinese Medicine Hospital Affiliated to Capital Medical University, and other 7 hospitals. If the protocol needs to be modified, we will reapply for ethical approval. All patients are required to sign an informed consent prior to participation, and the researcher is required to explain the procedures and the objectives of the research, including details regarding the methods to be used, the risks and benefits and the possibility of inclusion in a control or experimental group. The study follows the principle that all information related to patients is confidential; their names will not appear in any records.

References

1. Tan SM, Han E, Yu CQR, Singh SR, Gea-Sanchez M, Legido-Quigley H. A systematic review of community nursing interventions focusing on improving outcomes for individuals exhibiting risk factors of cardiovascular disease. *J Adv Nurs* 2019.

2. Howard BV, Roman MJ, Devereux RB, et al. Effect of lower targets for blood pressure and LDL cholesterol on atherosclerosis in diabetes: the SANDS randomized trial. JAMA. 2008;299:1678–89.
3. KANNEL WB, DAWBER TR, FRIEDMAN GD, GLENNON WE, MCNAMARA PM. RISK FACTORS IN CORONARY HEART DISEASE. AN EVALUATION OF SEVERAL SERUM LIPIDS AS PREDICTORS OF CORONARY HEART DISEASE. THE FRAMINGHAM STUDY. Ann Intern Med. 1964;61:888–99.
4. Ference BA, Ginsberg HN, Graham I, et al. Low-density lipoproteins cause atherosclerotic cardiovascular disease. 1. Evidence from genetic, epidemiologic, and clinical studies. A consensus statement from the European Atherosclerosis Society Consensus Panel. Eur Heart J. 2017;38:2459–72.
5. Judge C, Ruttledge S, Costello M, et al. Lipid Lowering Therapy, Low-Density Lipoprotein Level and Risk of Intracerebral Hemorrhage - A Meta-Analysis. J Stroke Cerebrovasc Dis. 2019;28:1703–9.
6. Huang R, Mills K, Romero J, et al. Comparative effects of lipid lowering, hypoglycemic, antihypertensive and antiplatelet medications on carotid artery intima-media thickness progression: a network meta-analysis. Cardiovasc Diabetol. 2019;18:14.
7. -. Familial Hypercholesterolemia: Advances in Recognition and Therapy. Prog Cardiovasc Dis. 2016;59:125–34.
8. Sandesara PB, Virani SS, Fazio S, Shapiro MD. The Forgotten Lipids: Triglycerides, Remnant Cholesterol, and Atherosclerotic Cardiovascular Disease Risk. Endocr Rev. 2019;40:537–57.
9. Wen CP, Fan YS, Wang XC, Li XY, Lu KD. Effect of detoxification, removing stasis and nourishing yin method on corticosteroid-induced hyperlipidemia in patients with systemic lupus erythematosus. Chin J Integr Med. 2007;13:180–4.
10. Xie W, Zhao Y, Du L. Emerging approaches of traditional Chinese medicine formulas for the treatment of hyperlipidemia. J Ethnopharmacol. 2012;140:345–67.
11. Geisler CE, Renquist BJ. Hepatic lipid accumulation: cause and consequence of dysregulated glucoregulatory hormones. J Endocrinol. 2017;234:R1–21.
12. Piao SH, Guo J, Hu ZP. [Clinical research of Chinese medicine syndromes of hyperlipidemia inpatients]. Zhongguo Zhong Xi Yi Jie He Za Zhi. 2012;32:1322–5.
13. Nie L, Song H, He A, Yao S. Recent Research Progress in Natural Bioactive Constituents against Lipid Metabolic Diseases. Curr Top Med Chem. 2016;16:2605–24.
14. Luo YZ, Zhao BW, Chen X, Gu Y, Zhang YL. [Lipid regulation mechanism and dosage form selection of Xixian Tongshuan Preparation based on molecular simulation methods]. Zhongguo Zhong Yao Za Zhi. 2019;44:1436–41.
15. Huyen VT, Phan DV, Thang P, Hoa NK, Ostenson CG. Antidiabetic effect of Gynostemma pentaphyllum tea in randomly assigned type 2 diabetic patients. Horm Metab Res. 2010;42:353–7.
16. Fukuda T, Fukui M, Tanaka M, et al. Effect of Brazilian green propolis in patients with type 2 diabetes: A double-blind randomized placebo-controlled study. Biomed Rep. 2015;3:355–60.

17. Yuxing C, Xuejun H, Du Tieliang, Xiaohui Z, Nan Y, Dane H. effect of YLTZ on lipid level in experimental hyperlipidemia rabbit model. *Chinese Traditional Patent Medicine* 2014:1518–1521.
18. Dongmei S, Silan Q, Xiaoli B, et al. Study on Fingerprint of YInlantiaozhi Capsule *2014 National Symposium on Traditional Chinese Medicine*, Hangzhou, Zhejiang, China 2014;5.

Figures

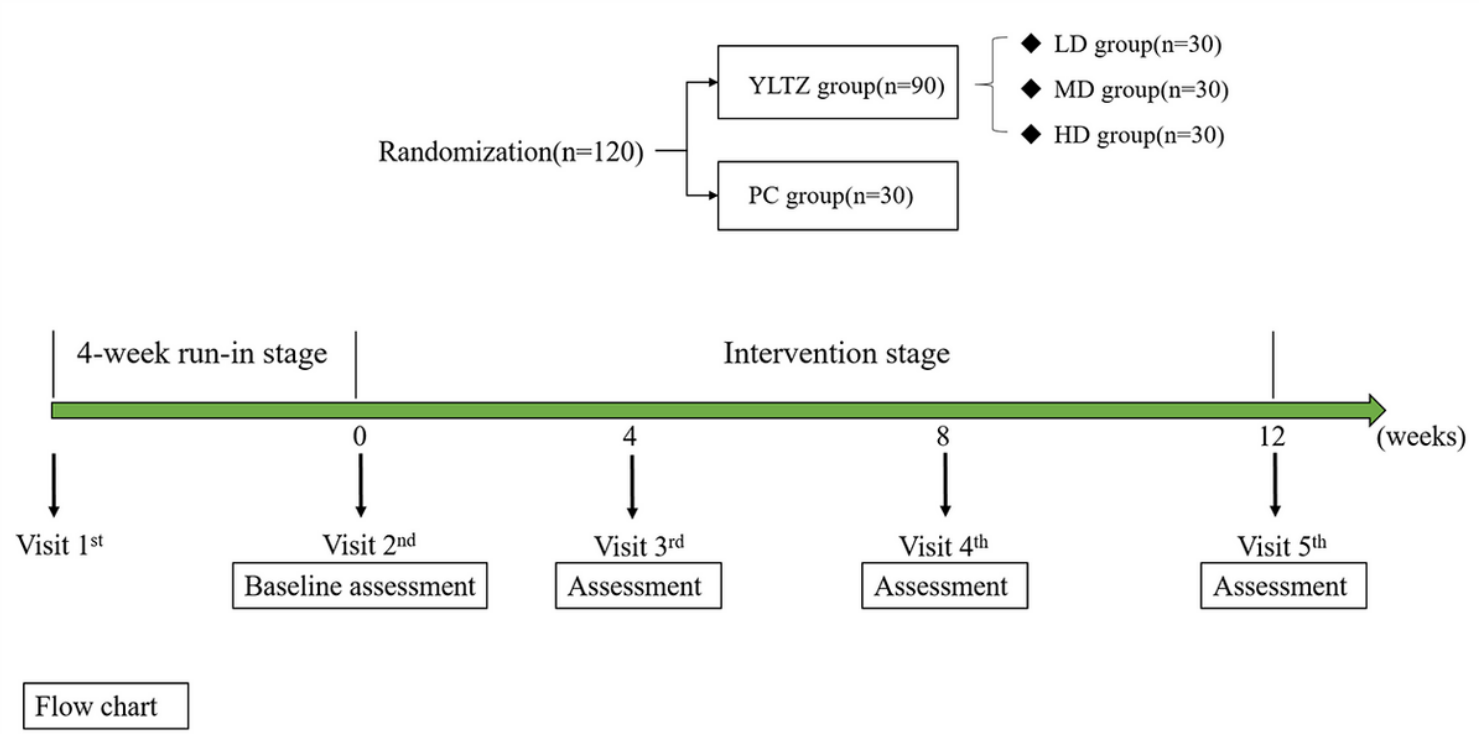

Figure 1

Brief flow chart of YLTZ protocol (LD, low dose; MD, middle dose; HD, high dose.)

STUDY PERIOD					
	Enrolment	Allocation	Post-allocation		
Visit frequency	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5
Time point	-28 day ±5 day	0	The 4th week ± 5 day	The 8th week ± 5 day	The 12th week ±5 day
Information collection					
Sign informed consent	√				
Diagnostic criteria	√				
Demographic data	√				
Included / excluded cases	√	√			
Medical and treatment history	√				
Concomitant treatment	√				
Intervention					
[YLTZ-HD]			◆———	———	———◆
[YLTZ-MD]			◆———	———	———◆
[YLTZ-LD]			◆———	———	———◆
PC			◆———	———	———◆
Assessments					
Vital signs	√	√	√	√	√
Safety assessments	√	√			√
Screening indicators					
Urine pregnancy test	√				
TSH	√				
glycosylated hemoglobin		√			
Dietary evaluation		√	√	√	√
Curative effect observation					
LDL-C	√	√	√	√	√
TC，TG，HDL-C	√	√	√	√	√
Quantitative grading of TCM syndromes		√	√	√	√
Single symptom of traditional Chinese Medicine		√	√	√	√
Efficacy of non HDL-C		√	√	√	√
Others					
Adverse events		√	√	√	√

Figure 2

Content for the schedule of enrolment, interventions, assessments and adverse events.

Supplementary Files

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

- SPIRITChecklistdownload8Jan13.doc