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Traditional Chinese Patent Medicine Qizhijiangtang Capsule for Non-Proliferative Diabetic Retinopathy: Study Protocol for a Randomized Controlled Trial

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Abstract

Background: Diabetic retinopathy remains a leading cause of vision loss globally. Here, we investigated the efficacy and safety of Qizhijiangtang Capsule (QZJC), a kind of traditional Chinese patent medicine, for patients with NPDR.

Methods: This study is a multi-center, randomized, controlled clinical trial. A total of 100 participants will be randomly assigned in a 1:1 ratio to QZJC group or QZJC placebo group. The treatment duration lasts 24 weeks. The primary outcome is the changes in the degree of retinal microaneurysm lesions assessed by fundus photography and fundus fluorescence angiography before and after treatment. The secondary outcomes include the changes in corrected visual acuity, blood glucose, glycosylated hemoglobin, urinary microalbumin excretion rate, the improvement of TCM syndromes and TCM symptoms.

Discussion: We postulate that NPDR patients will benefit from QZJC. If successful, this work will provide preliminary evidence that QZJC could delay the progress of DR.

Trial registration: Chinese Clinical Trial Registry no. ChiCTR1900023506.

Keywords: Traditional Chinese patent medicine; Qizhijiangtang Capsule; Non-proliferative diabetic retinopathy; Randomized controlled trial; Protocol

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Introduction

Diabetic Retinopathy (DR) is the most frequently occurring complication of Diabetes Mellitus (DM). The quantity of people suffered with DR has been estimated to increase from 463 million in 2019 to 700 million by 2045 [1]. It has been reported that DR is a primary cause of preventable blindness in labor age population globally. During the stage of Proliferative Diabetic Retinopathy (PDR), the patients may experience severe vision impairment, which is irreversible and dramatically affects the life quality of diabetic patients. Therefore, early prevention and treatment of DR is essential. Current therapies for DR mainly aimed at PDR or diabetic macular edema, drugs intervention for early stage are still limited. Traditional Chinese Herbal Medicine may provide an alternative and complementary therapy for targeting the early and potentially reversible retinal damage [2]. Qizhijiangtang capsule (QZJC), a kind of traditional Chinese patent medicine, which has been approved in China. QZJC consists of *Astragalus mongholicus* Bunge, *Rehmannia glutinosa* (Gaertn.) DC., *Polygonatum cyrtonema* Hua, and *Terminalia chebula* Retz. QZJC has been proven to regulate glucolipid metabolism, improve the insulin resistance, inhibit the glomerulosclerosis and renal interstitial fibrosis [3,4]. However, its effect on DR is still unclear. We will carry out a clinical

trial to investigate the efficacy and safety of QZJC targeting NPDR.

Methods

Ethics and permissions

The protocol has been approved by the Medical Ethics Committee of Guang'anmen Hospital of the China Academy of Chinese Medical Sciences (No. 2019-008-KY). (The protocol has registered at http://www.chictr.org.cn/showprojen.aspx?proj=39622. Trial registration number: ChiCTR1900023506).

Setting and participants

Six hospitals in China agree to participate in this study, including Guang'anmen Hospital of China Academy of Chinese Medical Sciences, Beijing Shijitan Hospital, Capital Medical University, Beijing Changping District Hospital of Chinese Medicine, Beijing Shunyi District Hospital of Chinese Medicine, Beijing Miyun District Hospital of Chinese Medicine, and Beijing Pinggu District Hospital of Chinese Medicine. All the participants will be provided with general information of the study and the possible risks and benefits, and the informed consent will be obtained from all participants prior to entry into the trial (Figure 1).

Eligibility Criteria

Diagnostic criteria

Diagnostic criteria for Type 2 Diabetes (T2DM) are based on the guideline for the prevention and control of T2DM in China [5], which is defined as: (1) In patients with classic diabetic symptoms of hyperglycemia, a random plasma glucose ≥ 11.1 mmol/L; or (2) Fasting plasma glucose ≥ 7.0 mmol/L; or (3) Two-hour plasma glucose ≥ 11.1 mmol/L after an oral glucose tolerance test.

Diagnostic criteria for DR are based on proposed International Clinical Diabetic Retinopathy and Diabetic Macular Edema Disease Severity Scales by American Academy of Ophthalmology. Diagnosis and classification of type 2 diabetic retinopathy is defined as: (1) Mild NPDR: Microaneurysm only; (2) Moderate NPDR: More than just microaneurysms but less than severe NPDR; (3) Severe NPDR: Any of the following: More than 20 intraretinal hemorrhages in each of 4 quadrants; definite venous beading in 2+ quadrants; prominent intraretinal microvascular abnormalities in 1+ quadrant; and no signs of proliferative retinopathy; (4) Proliferative DR: One or more of the following: Neovascularization, vitreous/preretinal hemorrhage [6].

TCM syndrome differentiation

Diagnosis of deficiency of dual qi and yin combined with blood stasis syndrome are based on Traditional Chinese medicine Clinical Pathway of *Xiaoke* disease [7].

Inclusion criteria

1. Participants should be between 30 and 70 years old;

2. Participants should meet the diagnostic criteria for T2DM.

3. Participants should meet the diagnostic criteria for DR and the stage of NPDR.

4. Participants should meet the diagnostic criteria of deficiency of dual qi and yin combined with blood stasis syndrome.

5. Participants should sign informed consent forms.

6. Anti-hyperglycemic drugs have been used steadily in the past three months and can be expected to remain unchanged throughout the study.

Exclusion criteria

1. Participants experience postoperative retinal photocoagulation, suitable photocoagulation therapy, or suffer with the stage of PDR (IV, V, VI stage), type 1 diabetic retinopathy, other ocular complications, such as glaucoma, severe cataracts, retinal detachment, and retinopathy not related to DM, etc.

2. Participants with s serious complications of heart, brain and kidney or with other serious primary diseases.

3. Participants with recurrent hypoglycemia, diabetic ketoacidosis and severe infection within recent months.

4. Participants with impaired liver and kidney function.

5. Pregnant, pregnant or lactating women, or those with a history of drug allergy.

6. Alcohol abuse and/or psychoactive substances, drug abusers and addicts.

Randomization, Concealment and Blind

A specific randomization sequence will be generated by an independent Clinical Research Organization (CRO) from the Institute of Basic Research in Clinical Medicine of the China Academy of Chinese Medical Sciences. Eligible participants will be randomized to the intervention group or the control group at a 1:1 ratio. The researchers will sequentially enroll patients based on randomization code. To ensure concealment, the block sizes will not be disclosed and not be available to both participants and researchers until the trial is end. In the event of a medical emergency, the participant's randomization code and treatment allocation can be identified. Both participants, investigators and the statistician will be blinded. In addition, QZJC and QZJC placebo will be manufactured as granules with the same color and smell, the appearance of them are identical. After production, study drugs will be packaged and transferred to numbered package in accordance with the randomization sequence.

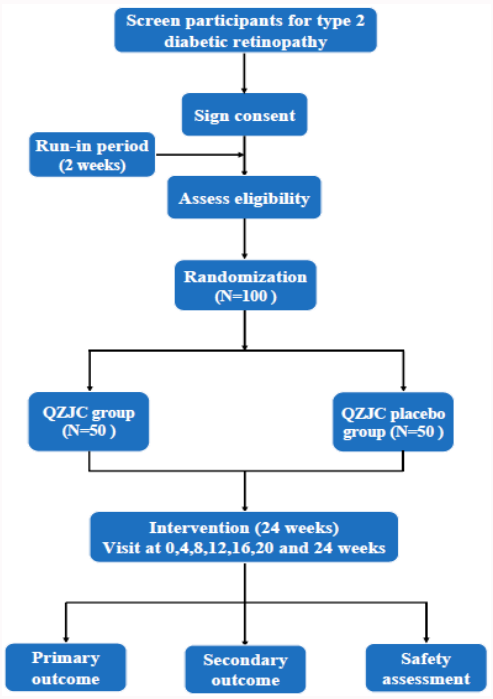
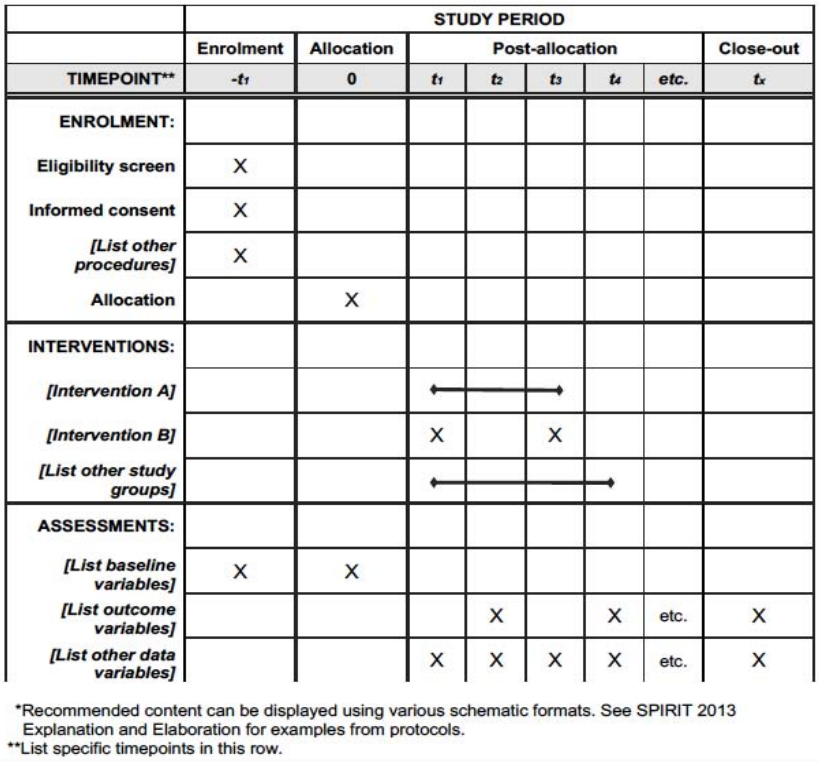


Figure 1: Flow diagram of enrollment, intervention and assessments.



	STUDY PERIOD							
	Enrolment	Allocation	Post-allocation					Close-out
TIMEPOINT**	$-t_1$	0	t_1	t_2	t_3	t_4	etc.	t_x
ENROLMENT:								
Eligibility screen	X							
Informed consent	X							
[List other procedures]	X							
Allocation		X						
INTERVENTIONS:								
[Intervention A]			←	—	→			
[Intervention B]			X		X			
[List other study groups]			←	—	—	→		
ASSESSMENTS:								
[List baseline variables]	X	X						
[List outcome variables]				X		X	etc.	X
[List other data variables]			X	X	X	X	etc.	X

*Recommended content can be displayed using various schematic formats. See SPIRIT 2013 Explanation and Elaboration for examples from protocols.
**List specific timepoints in this row.

Figure 2: Schedule of enrolment, interventions, and assessments.

Interventions

A total of 100 participants will be recruited and randomly assigned to either the intervention or the control group. All the participants will be treated with conventional treatment, including a healthy low-fat diet, moderate physical activity, anti-hyperglycemic, lipid-lowering and anti-hypertensive drugs, to ensure access to steady levels of body weight, blood glucose, blood lipids and blood pressure. On the basis, the intervention group used 2.5 g QZJC three times per day, while the control group used 2.5 g QZJC placebo three times per day, both of them are recommended to be taken after meals with boiled warm water. The treatment duration will be 24 weeks, and we will follow up for another 2 years.

Outcomes

Primary outcome

The primary outcome of the study is the changes in the degree of retinal microaneurysm lesions assessed by fundus photography and fundus fluorescence angiography before and after treatment. This will be determined according to the following scale: None, mild non-proliferative phase, moderate non-proliferative phase, severe non-proliferative phase, and proliferative phase, which are divided into aggravated, stable, and improved conditions. The aggravated condition is defined as retinal microaneurysm lesions with a degree of severity > grade 1 after treatment. The stable condition was defined as a degree of retinal microaneurysm lesions before and after treatment that is unchanged, while the improved condition is defined as a degree off retinal microaneurysm lesions that is reduced by >1 grade after treatment.

Secondary outcomes

Secondary outcomes are listed as the corrected visual acuity, fasting blood glucose, 2-h postprandial blood glucose, glycosylated hemoglobin, urinary microalbumin excretion rate, the improvement of TCM syndromes and TCM symptoms from baseline to 24 weeks.

Safety assessment and adverse events monitoring

Safety assessment outcomes are listed as vital signs, routine blood test, routine urine test and routine stool test, electrocardiogram, liver function, renal function will be performed at every 12 weeks from baseline. Adverse Events (AEs) will be documented at every visit, including the occurrence time, severity, duration, solution and transfer. AEs will be divided into three levels: Mild, moderate and severe, and the causality between TCPMs for trials and AEs will be judged. In case of any AEs, such as subjective discomfort of the patient and abnormal laboratory test, it will be taken measures immediately to protect the safety of the participants. Any serious AEs during the test must be reported to the Ethics Committee of the unit immediately, and notify the telephone number and contact person of the units listed in the CRF form. The "Severe Adverse Event (SAE)" form must be filled in. All AEs will be recorded, monitored, and treated until resolved.

Study Procedure

The study will include a 2-week washout period, a 24-week treatment period and a 2-year follow-up period. Subjects who are diagnosed with NPDR will be given a 2-week lifestyle intervention at run-in period, all of them will provide written informed consent prior to participation. After the intervention period begin, participant visits will conduct every 4 weeks. All data will be documented on the CRFs (Figure 2).

Sample Size Calculation

According to data from preliminary trial [8], the rate of retinal

microvascular disease was reduced by 2.9% in the placebo group, and we predicted that the rate of retinal microvascular disease would be reduced by 6.5% in the TCPM group. The standard deviation was set as 2.17. The superiority margin was assumed to increase 1.4 percentage on the basis of placebo. The ratio of the two groups was set as 1:1. The significance level is targeted at 0.025 for one-sided test. The power achieved to detect a difference is set as 0.9. Sample size will be calculated the independent proportions power analysis using PASS 11.0 software, approximately 45 participants in each group will be needed. The sample size used in our study was increased by an additional 10% in case of loss of follow-up. Hence, the final sample size is estimated to be 50 in each group.

Data Collection and Management

The researchers will record original data into the Case Report Form (CRF), the supervisor will check whether the trial is launched consistent with the protocol, and the data in the CRFs is identical with the original data, errors and inconsistencies will be timely corrected. Before data entry, the data administrators will check the CRFs again to ensure the accuracy of the data, the data administrator will also record the coding process in the coding book. Duplicate entry is adopted for inputting the data. If problems are found in the input process, they will be registered and reported in time, so as to deal with the problems quickly. The data administrator will write the computer programs and input data. After entering the data, the CRFs need to be filed and saved. The researchers will keep the clinical trial data until 5 years after the end of the clinical trial.

Statistical Analysis

Analysis subjects

Three analysis sets will be used in this trial, including Full Analysis Set (FAS), Per Protocol Set (PPS) and Safety Set (SS). FAS includes all randomized subjects and drop-out subjects who have been treated at least once and excluded for reasonable reasons. For the subjects who failed to observe the efficacy, the principle of the Last Observation Carried Forward (LOCF) will be applied to handle with the missing outcome data. PPS is a set of compliance protocol, including that the participants have good compliance of using 80% to 120% quantity of the study drugs; the baseline characteristics are not missing, and the data of the primary outcome can be obtained; and it does not run counter to the protocol. SS is a set that received at least one-time treatment and has data recorded with safety assessment.

Statistical method

Statistical analysis will be completed by the third-party statisticians using SAS 9.3 software. Continuous data will be expressed as the mean, median, standard deviation, minimum value, and maximum value, while categorical data will be expressed as the number of cases and percentages. To compare baseline characteristics between the two groups, independent *t* tests will be used to analyze continuous data, and chi-squared test or Fisher exact test will be used for categorical data. With regard to outcome analysis, the classified variables will be performed using the chi-squared test or Fisher exact test, and continuous variables will be performed using t test for normally distributed data and Wilcoxon rank sum test for non-normal distribution data. Moreover, repeated measures Analysis of Variance (ANOVA) will be applied to determine to further investigate the effects of treatment and time course. A two-tailed test will be applied, and $P<0.05$ will be considered to indicate a statistical significance.

Discussion

In the UPLC-QE-Orbitrap-MS analysis, a total of 52 compounds were identified in QZJC capsules, many of the compounds have been proved by modern pharmacological studies to have the effect of improving related symptoms of DM and its complications, reflecting the characteristics of synergistic action of multiple components in QZJC [9]. In the previous experiments, QZJC has been demonstrated that ameliorated retinal vascular permeability and inhibited retinal neovascularization *via* up-regulating Prostacyclin 2 (PGI2) and down-regulating VEGF and von Willebrand Factor (vWF); it also attenuated inflammation *via* promotion of Nitric Oxide (NO) and Superoxide Dismutase (SOD) expression [10]. Currently, we therefore design a randomized and controlled multicenter clinical trial to assess the efficacy and safety of QZJC. We hypothesize that QZJC could have a potential retinal protective effect on NPDR patients. If successful, the findings of this trial may provide an alternative treatment for NPDR patients. It may also provide scientific evidence for delaying the progress of DR. This trial also has some limitations. Firstly, as the test instruments of each research center are different, the error of test results is inevitable. Secondly, there might be several individual differences in the subjects, possibly leading to different efficacy of the drug. The improvements need to be seen in the future.

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Authors Contribution

Conception and design: PB and NQ; Administrative support: GH; Provision of study materials or patients: HHJ, SY and CAM; Collection and assembly of data: LCQ and ZWH; Data analysis and interpretation: FS and ZYY.

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