The Immediate And Long-Term Effects of Shexiang Tongxin Dropping Pill On Coronary Slow Flow: Study Protocol For A Randomized Double-Blind Placebo-Controlled Trial

Birong Liu
Beijing University of Chinese Medicine Affiliated Dongzhimen Hospital
Yong Liu
Beijing University of Chinese Medicine Affiliated Dongzhimen Hospital
Liyong Ma
Beijing University of Chinese Medicine Affiliated Dongzhimen Hospital
Jia Liu
Beijing University of Chinese Medicine Affiliated Dongzhimen Hospital
Jingen Li
Beijing University of Chinese Medicine Affiliated Dongzhimen Hospital
Kailin Huang
Beijing University of Chinese Medicine Affiliated Dongzhimen Hospital
Qiang Fu
Beijing University of Chinese Medicine Affiliated Dongzhimen Hospital
Xiangying Zheng
Beijing University of Chinese Medicine Affiliated Dongzhimen Hospital
Yi Pan
Beijing University of Chinese Medicine Affiliated Dongzhimen Hospital
Wei Zhang
Beijing University of Chinese Medicine Affiliated Dongzhimen Hospital
Qun Gao
Beijing University of Chinese Medicine Affiliated Dongzhimen Hospital
Jiaqi Ye
Beijing University of Chinese Medicine Affiliated Dongzhimen Hospital
Yuqing Liu
Beijing University of Chinese Medicine Affiliated Dongzhimen Hospital
Xuezeng Hao
Beijing University of Chinese Medicine Affiliated Dongzhimen Hospital
Meng Li (15201328277@163.com)

Beijing University of Chinese Medicine Affiliated Dongzhimen Hospital https://orcid.org/0000-0001-9695-6493

Lijing Zhang

Beijing University of Chinese Medicine Affiliated Dongzhimen Hospital

Study protocol

Keywords: Shexiang Tongxin Dropping Pills, Coronary slow flow, Immediate and long-term effects, Role mechanism, Trial protocol

Posted Date: June 28th, 2021

DOI: https://doi.org/10.21203/rs.3.rs-467743/v1

Abstract

Background: Coronary slow flow (CSF) is a phenomenon characterized by delayed contrast medium progression in angiography in the absence of obstructive coronary epicardial disease. However, there is currently no definite effective therapy. A small sample self-controlled study had suggested an immediate improvement in coronary slow blood flow by Shexiang Tongxin Dropping Pills (STDP). But high-quality evidences on drug dosage, medication cycle and long-term effects are still lacking while the mechanism of STDP remains unclear.

Methods: This study is a randomized, double-blinded, and placebo-controlled clinical trial. A total of 64 CSF patients diagnosed by coronary angiography will be randomly allocated into the test group, using STDP, and the control group, using placebo. The main efficacy indicators for immediate effects include thrombolysis in myocardial infarction (TIMI) blood flow grading and corrected TIMI frame count. Long-term effects will be evaluated by the comparison of cardiac radionuclide score, and patient condition such as angina readmission rate and angina scale. The safety indicators include a routine complete blood count, liver and renal function test, cardiac markers (including TnI, CK-MB, Myo), NT-proBNP, coagulation function, 12-lead electrocardiogram, and echocardiography. All adverse events during the trial will be recorded. Moreover, endothelial factors (including ET-1, NO, eNOS, iNOS), inflammatory factors (including adropin, IL-6, IL-1, IL-18, TNF-α, Lp-PLA2, hs-CRP) will be observed. Blood stasis syndrome (including platelet activation factors such as CD62 and CD63, coagulation function and blood stasis syndrome score) will be evaluated.

Trial registration: Chinese Clinical Trial Registry, ChiCTR2000035167. Registered on August 2, 2020. http://www.chictr.org.cn/showproj.aspx?proj=57349

Background

Mounting evidences have shown that obstructive coronary artery disease (CAD) is not the only cause of angina pectoris [1]. Patients with ischemia and no obstructive coronary artery (INOCA) may develop epicardial or microvascular dysfunction[2], which is characterized by normal or near normal-coronary arteries on angiography (stenosis severity < 50%)[3]. There are various diagnoses that may lead to chest pain syndromes without obstructive CAD, such as microvascular angina, gastroesophageal reflux, musculoskeletal chest pain, cardiac syndrome X, cardiac syndrome Y (coronary slow flow), coronary spasm, no reflow phenomena etc. [4].

Coronary slow flow (CSF) is a phenomenon initially described by Tambe et al in 1972[5], in which contrast medium is observed progressing through the coronary arteries slowly in the absence of stenosis on chest pain patients scheduled for selective coronary angiography[6]. It is different from X syndrome and typically affects young male smokers[7–8]. CSF is associated with severer myocardial ischemia than cardiac syndrome X[9]. They are often accompanied by recurring refractory angina or acute coronary syndrome (ACS) which would require hospitalization[10]. Moreover, life-threatening arrhythmias and

sudden cardiac death are also associated with CSF[11]. CSF has an incident rate about 1%-7% in patients who undergo coronary angiography [12], and this number is increasing annually[13].

Despite increasing awareness and research, the pathophysiology of CSF remains uncertain. It is generally considered a product of multiple factors[14], such as microvasculature functional and morphological abnormalities[15], vascular endothelial dysfunction[16], oxidative stress[17], inflammation[18], atherosclerosis[19–20], and anatomical factors of epicardial arteries are all implied. Currently, the treatments for CSF mainly include enhancement of microcirculation, protection of the vascular endothelium, anti-inflammatory treatment, and atherosclerosis inhibition. Drugs such as Statins[21], Nebivolol[22], Dipyridamole[23], Calcium channel blockers[24–25], Trimetazidine[26] and Nikodir[27] have been proven clinically effective for CSF. Coronary angiography(CAG) is the only effective way to diagnose CSF. It is mainly assessed by thrombolysis in myocardial infarction(TIMI) blood flow grading and corrected TIMI frame count(CTFC)[28–29], which are shown in Table 1 and Table 2 respectively. In addition, some studies have shown that radionuclide myocardial perfusion imaging(MPI)[30] has great significance in the diagnosis and prognosis evaluation of microangiopathy. The scores of MPI (including SSS, SRS and SDS) can evaluate coronary blood flow through assessing coronary microangiopathy[31], the detail is described in Fig. 1.Both of them can contribute to CSF diagnosis and assessment.

In traditional Chinese medicine (TCM), Shexiang Tongxin Dropping Pills(STDP) is a formula that consists of moschus, Radix rhizoma ginseng, Calculus bovis, bear gall, Venenum bufonis, borneol and Salvia miltiorrhiza. STDP is widely employed in the treatment of cardiovascular diseases in China[32]. A number of studies have shown that STDP can improve endothelial cell function[33–34], relieve microvascular spasm[35] and inflammation[36], reduce the number of white blood cells attached to vascular endothelium[33], and has anti-atherosclerosis property[37].The positive immediate effect of STDP on CSF has been confirmed in a small-sample clinical study[38]. However, the study only employed self-controlled method, it did not utilized randomization, blinding and other clinical research principles. Therefore, the objectivity of the results and the application of the study were limited, and the assessment on the long-term efficacy of STDP is still lacking.

The efficacy and safety of STDP in improving the slow blood flow of patients post- PCI operation have been systematically reviewed by our previous research[39]. But it did not standardized the dosage, method, cycle of STDP intake. It is therefore crucial to carry out more high quality and multicenter prospective and randomized controlled experiments to provide a solid ground for STDP clinical applications.

Methods

Purpose and study design

The purpose of this study is to assess the immediate effect and long-term effect of STDP on coronary artery perfusion in CSF patients. Further explore its mechanism to provide a internationally recognized clinical evidence for using STDP on improving coronary artery slow blood flow. And initiate a Chinese

medicine treatment scheme for coronary artery slow blood flow. This research is designed as a prospective, double-blinded placebo-controlled study which was conducted in China from 1 Jan.2020 to 31 Dec.2022. A flow chart of this study is shown in Fig.1. The enrollment of patients will take place from 1 July.2020 to 30 Nov.2021, with a 3 months observation period. Central ethical approval has been confirmed by the Research Ethics Committee of Dongzhimen Hospital Affiliated to Beijing University of Chinese Medicine (DZMEC-KY-2020-31). The trial was registered in the Chinese Clinical Trial Registry (ChiCTR2000035167).

Inclusion and exclusion criteria

Patients will be screened for eligibility after hospital admission as soon as possible. Patients will be considered eligible if they meet the following criteria:

1. Clearly diagnosed with CSF according to the criteria published in Circulation Journal 2012[40], which is provided in Table 3.

2. Diagnosed with blood stasis syndrome in TCM according to the diagnostic standard issued by the Professional Committee of Promoting Blood Circulation and Removing Blood Stasis of the Chinese Society of Integrated Chinese and Western Medicine in 2016[41]. (Diagnosis could be made when fulfilled one of the following three：i.Tongue is purplish dark or has ecchymosis, stasis dots; ii.Lips are bluish or dark; iii.Varicose veins of the tongue)

3. Age between 18 to 80 years old, regardless of gender;

4. Agreed to participate in the research and signed the informed consent form.

The exclusion criteria are as follow:

1. Have history of myocardial infarction or is diagnosed with acute myocardial infarction

2. Have history of percutaneous coronary intervention

3.Accompanied with heart valve diseases, cardiomyopathies, myocardial bridging, aortic dissection, acute pericarditis, heart failure

4.Accompanied with uncontrolled grade 3 hypertension (systolic blood pressure≥180mmHg and/or diastolic blood pressure≥110 mmHg), severe arrhythmias, severe liver, kidney, hematopoietic system diseases or malignant tumors, or major mental illnesses

5. Accompanied with severe liver, renal abnormalities (ALT, AST, Scr exceed the upper limit of reference range by 1.5 times.)

6. Allergic to the experimental drugs

7. Known pregnancy or lactation

8. Abnormal thyroid function tests

9. Participates in other clinical study with an investigational product or device during the last 30 days or during the study

Dropout criteria

The purpose of the suspension is to protect the rights of the participants, to ensure the quality of the study, and to avoid unnecessary economic losses. The discontinuity conditions are as follows: Firstly, a serious safety problem occurs during the trial and the investigator believes that the safety of the subject may be impaired. Secondly, there are serious deviations during the implementation and the efficacy cannot be further evaluated. Thirdly, the trial sponsor requires the suspension. Fourthly, the administrative department aborts the trial. It should be noted that all CRFs should be retained for future investigation.

Researchers must notify subjects, applicants, ethics committees, and drug regulatory authorities of the discontinuation of clinical trials and state the reasons. The applicant shall notify the researcher, the ethics committee and the State Food and Drug Administration before suspending the clinical trial and state the reasons.

Recruitment strategies

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

Randomization and blinding

The enrolled patients will be randomly assigned to the placebo controlled group or the STDP group, allocated by the central randomized management system according to a ratio of 1: 1. The randomization sequence will be generated in varying block sizes. After informed consent is obtained, the researcher will log into the central randomized management system of the network. The central randomized management system will generate a unique identification code and random number for each patient, which can be used to represent the identity of the patient and indicate the therapeutic intervention.The research team members,except for the clinical research methodology personnel,will be blinded to the treatment and the group assignment. Participants were informed about the information regarding the case group and the control group, while they were not told their group assignment, thereby allowing blinding of the participants between the treatment groups.

Intervention

After the diagnosis of CSF, patients enrolled in the STDP group will subject to an immediate sublingual intake of 4 pills of STDP, followed by a continual 3 months period of 2 pills three times daily. On the other hand, patients enrolled in the control group would be given 4 pills of placebo for immediate sublingual intake after the diagnosis, then subjected to an identrcal intake routine of the STDP group but with placebo for the following 3 months. During the trial, any Chinese medicine related treatment of CSF should not be taken orally or intravenously. Nitrates, alprostadil, nicorandil and other drugs should be stopped 12h before the angiography. In the later follow-up, patients are free to take antihypertensive or hypoglycemic agents in accordance with their health condition, this would be recorded in detail.

Outcomes

The primary outcomes include CTFC, PMI score, readmission rate and SAQ score. CAG will be performed both before and 5 minutes after the sublingual intake of STDP. LAD, LCX and RCA will be recorded according to the CTFC method. MPI data will be taken at baseline and 3 months after taking the drug. ET-1, NO, eNOS, iNOS, adpron, IL-6, IL-1, TNF-α, Lp-PLA2, hs-CRP, CD62 and CD63 will be collected for mechanism indications. Adverse events(AEs) during the period of trials will be recorded to evaluate safety. Abnormal changes in routine blood count as well as ECG, and echocardiography will also be closely monitored during the trial. Centralized, blinded reviews of angiographic data will be conducted respectively by two physicians.

Adverse events

The adverse events(AEs) are defined as any untoward medical occurrences in a patient during the trial that are not considered related to the clinical state of the patient. Information of AEs will be appropriately documented throughout the trial, including the time, severity, and duration of the AEs, the measures adopted, and the outcomes. The relationships of AEs to the research medication are assessed by an independent data monitoring committee(DMC). Serious adverse events related to the protocol will be sent to the DCM within 24 h after being received by the trial coordinator. If a correlation between the AEs and the trial drug fail to be ruled out, the event will be reported to the ethical committee and the project supervisor to determine whether the treatment should be suspended for the individual. Related adverse events that result in a participant’s withdrawal from the study or are present at the end of the study will be followed up until satisfactory resolution.

Table 1 Calendar summary

	Study period		
	Enrolment and allocation	Treatment period	
Time point	**0**	**5 minutes**	**3-month**
Enrolment			
Eligibility screen	□		
Informed consent	□		
Allocation	□		
Interventions			
STDP group	□		
Control group	□		
Assessments			
CTFC	□	□	
MPI□SAQ	□		□
Inflammatory factors	□	□	□
Endothelial function	□	□	□
Evaluation of blood stasis syndrome	□	□	□
Rehospitalization			□

Abbreviations□STDP Shexiang Tongxin Dropping Pills, CTFC corrected thrombolysis in myocardial infarction frame count, MPI myocardial perfusion imaging, SAQ Seattle angina questionnaire

Data collection and management

The data will be managed according to standard operating procedures (SOPs). The data from the paper case report form (CRF) will be entered and stored in the electronic data capture system. The CRF data will be regularly reviewed by a specialized quality inspector. Monitored results would be presented to the principal investigator, who is responsible for the accuracy, completeness, and timeliness of the data recorded. After blinded review and confirmation on the authenticity of established database, the data will be locked and no changes will be permitted.

Sample size

This project is an exploratory research. The sample size is mainly based on the number of patients that can be included during the study period and the project funding. The results of the previous investigation have found [13] that the incidence rate of CSF is about 1%-7% in coronary angiography□CAG□patients.

There are approximately 800 CAG patients in Dongzhimen Hospital Affiliated to Beijing University of Chinese Medicine each year. Based on the 4% incidence rate of CSF, 64 patients can be enrolled within a two years period, including 32 in the experimental group and 32 in the control group.

Statistical analysis methods

The statistical analysis plan will be written by statisticians and finalized before the database is locked. Statistical analysis will be performed using SPSS20.0 software (SPSS Inc., Chicago, Illinois). All hypothesis testing will use two-sided testing, and $\alpha=0.05$.

For other categorical variables, comparisons between treatment groups will be done using Fisher's exact test or the chi-square test as appropriate. Continuous variables will be compared using the *t* test or Wilcoxon rank-sum test if suitable. Chi-square or Fisher's exact tests will be used to compare the frequency of AEs between groups.

Quality management

Data management personnel should be qualified, effectively trained, and familiar with the functions of data management. Physicians and evaluators of this study will be trained in SOPs in advance. The sponsor must train all the related researchers on Good Clinical Practice(GCP)and the trial protocol before the start of the trial. Only after obtaining authorization from the principal investigator, can investigator enter the study and conduct within the authorized scope. The angiographic images should be sent to the data center for unified blinding evaluation to obtain high-quality research data. The accuracy, reliability, and abnormal judgment criteria of laboratory tests should be unified in research center.

Ethical plan

This clinical trial protocol follows the Helsinki declaration (October 2013 version:64th General Assembly of the World Medical Association, Fortaleza, Brazil) and Chinese clinical trials regulations. The protocol can be implemented only after the approval of the ethics committee. When the protocol is revised, the trial process must be approved by the ethics committee, and the informed consent needs to be signed again. Insurance will be provided for subjects participating in the study. All participants will be informed about the nature of the trial, its aims, expected advantages, and possible risks. All eligible participants, or legally authorized representative in case of patient's incapacity, will provide written informed consent. The protocol and the results of the present study will be published in peer-reviewed journals or scientific conference presentations according to the guidelines of the Standard Protocol Items:Recommendations for Interventional Trials(SPIRIT) and Consolidated Standards of Reporting Trials(CONSORT) statements.

Discussion

Chronic coronary flow (CSF) is a kind of phenomenon characterized with chest pain, but no obvious stenosis (the stenosis degree $\leq$ 40%) is observed during coronary angiography while the progression of contrast medium in distal coronary artery is delayed. Some researches suggest that CSF is associated

with a variety of cardiovascular diseases, potentially leading into myocardial ischemia, acute coronary syndrome and even acute myocardial infarction[42]. A long-term follow-up found 80% of CSF patients had recurring angina pectoris, one third of them were repeatedly hospitalized, this had seriously affected the quality of life of the patients[43]. Morever, the results of a nine-year observational study have shown that overall major adverse cardiovascular events occurred in 9.3%[44]. Although CSF was made known for many years, there is no remarkable therapeutic effect. The treatments of CSF at present, mainly include improving microcirculation, protecting vascular endothelium, anti-inflammation, inhibiting atherosclerosis etc. However, due to the lack of obvious fixed stenosis in CSF patients, routine anti-angina pectoris treatment is often unsatisfactory. Therefore, prompting an urgent clinical need for new effective drugs treatment in CSF. It has been shown that Shexiang Tongxin Dropping Pills(STDP) can reduce myocardial injury and myocardial hypoxia, increase coronary blood flow, enhance endothelial cell function to improve coronary slow blood flow, relieve microvascular spasm, and demonstrates anti-inflammation and anti-atherosclerosis property etc.. As for CSF, sublingual administration of the drug can accelerate absorption to produce immediate results[38]. Moreover, STDP have the advantages of convenient administration, small dosage, high clinical safety and tolerance. These properties exhibit a promising prospect for clinical application.

This is a randomized, double-blinded, placebo-controlled clinical study to evaluate and explore the mechanism on the immediate effect and long-term efficacy of STDP on CSF patients' coronary perfusion. We selected TIMI blood flow grading and CTFC (at baseline and 5 minutes after medication) to evaluate the velocity of coronary blood flow. Cardiac radionuclide score (both before and after 3 months of medication) will be calculated to assess the state of coronary blood perfusion. Blood sampling on before, after 5 minutes, and after 3 months of medication, including vascular endothelial function(ET-1, NO, eNOS, iNOS, adropin), inflammatory factor evaluation index （IL-6, IL-1, TNF-α, Lp-PLA2, hs-CRP）, and blood stasis syndrome (CD62, CD63, blood coagulation function and blood stasis syndrome score) will be employed for mechanism exploration. In addition, the routine complete blood count, liver and renal functions, blood lipids, heart lesions (TnI, CK-MB, Myo), NT-proBNP, routine urinalysis, routine stool analysis, 12-lead electrocardiogram and echocardiography before and after CAG and after 3 months of medication will be covered to evaluate the safety of STDP.

This study will be the first, well-designed, double-blinded randomized controlled trial with strict quality control to evaluate the efficacy and safety of STDP as well as its mechanisms. The results of this trial will provide high-quality based evidence for traditional Chinese medicine treatments and preventions of diseases while highlight on utilizing such advantages of TCM on CSF patients.

Trial Status

The study is currently in the process of recruiting participants. Recruitment of participants commenced on 1 July.2020 and will be completed by 31 Nov.2021.

Abbreviations

CAG coronary arteriography, ECG Electrocardiography, CTFC corrected thrombolysis in myocardial infarction frame count, SAQ Seattle angina questionnaire, ET-1 Endothelin-1, NO nitric oxide, eNOS endothelial NO synthase, INOS inducible NO synthase, IL-6 Interleukin-6, IL-I Interleukin-1, TNF-α Tumor Necrosis Factor-alpha, Lp-PLA2 Lipoprotein-associated phospholipase A2, hs-CRP High-sensitivity C-reactive protein, CD cluster of differentiation, MPI myocardial perfusion imaging, cTnI Cardiac troponin I, CK-MB Creatine kinase, MB Form.Myo myoglobin.NT-proBNP N-terminal prohormone brain natriuretic peptide.

Declarations

Acknowledgements

Thanks are due to Prof. Yan Liu from Key Laboratory of Chinese Internal Medicine of Ministry of Education, Dongzhimen Hospital, Beijing University of Chinese Medicine, for his advice on research design.

Authors' Contributions

BRL□YL□LYM□JL, and JGLi drew up the research design. KLH drafted the protocol. QF wrote the manuscript in English and submitted it for publication. XYZ participated in the design amendment and helped with the project coordination. YP and WZ, conducted the literature search for trial design. QG contributed to protocol ethics and trial registration. JQY revised the details and the language. YQL made the statistical plan. XZH, ML, and LJZ are the principal investigators of the whole project. All authors reviewed the manuscript content and approved the final version for submission.

Funding

This study is funded by grants from the Fundamental Research Funds for the Central Universities (NO. 2020-JYB-ZDGG-116). This funding source had no role in the design of this study and will not have any role during its execution, analyses, interpretation of the data, or decision to submit results.

Availability of data and materials

The datasets generated and/or analyzed during the current study are not publicly available, owing to the protection of privacy for patients, but they are available from the corresponding author on reasonable request.

Ethics approval and consent to participate

All procedures performed in studies involving human participants are carried out in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. The protocol and relevant documents have been approved by the Research Ethics Committee of Dongzhimen Hospital Affiliated to

Beijing University of Chinese Medicine (DZMEC-KY-2020-31). The written informed consent form will be provided to patients for signature before enrollment.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

References

1. Huang FY, Huang BT, Lv WY, et al. The prognosis of patients with nonobstructive coronary artery disease versus normal arteries determined by invasive coronary angiography or computed tomography coronary angiography: a systematic review. Med (Baltim). 2016;95(11):e3117.
2. Marinescu MA, Löffler AI, Ouellette M, et al. Coronary microvascular dysfunction, microvascular angina, and treatment strategies. JACC Cardiovasc Imaging. 2015;8(2):210–20.
3. Bairey Merz CN, Pepine CJ, Walsh MN, et al. Ischemia and no obstructive coronary artery disease (INOCA): developing evidence-based therapies and research agenda for the next decade. Circulation. 2017;135(11):1075–92.
4. Kumar S, Mehta PK, Eshtehardi P, et al. Functional coronary angiography in symptomatic patients with no obstructive coronary artery disease. Catheter Cardiovasc Interv. 2020: 1–9.
5. Tambe AA, Demany MA, Zimmerman HA, et al. Angina pectoris and slow flow velocity of dye in coronary arteries—A new angiographic finding. Am Heart J. 1972;84(1):66–71.
6. Sanati H, Kiani R, Shakerian F, et al. Coronary slow flow phenomenon clinical dindings and predictors. Res Cardiovasc Med. 2016;5(1):e30296.
7. Ghaffari S, Tajlil A, Aslanabadi N, et al. Clinical and laboratory predictors of coronary slow flow in coronary angiography. Perfusion. 2017;32(1):13–9.
8. Kaski JC. Cardiac syndrome X in women: the role of oestrogen deficiency. Heart. 2006;92(Suppl 3):iii5–9.
9. Özde C, Aktüre G, Aytekin S, et al. Assessment of the relationship between coronary flow rates and myocardial perfusion abnormality in patients with nonobstructive coronary artery disease: an observational study in cardiac syndrome X and coronary slow flow. Nucl Med Commun. 2019;40(11):1122–9.
10. Fineschi M, Gori T. Coronary slow-flow phenomenon or syndrome Y. J Am Coll Cardiol. 2010;56(3):239–40.
11. Carvalho FP, Azevedo CF. Coronary slow flow phenomenon—adding myocardial fibrosis to the equation. Arq Bras Cardiol. 2020;114(3):552–3.

12. Alvarez C, Siu H. Coronary slow-flow phenomenon as an underrecognized and treatable source of chest pain: case series and literature review. J Investig Med High Impact Case Rep. 2018;6:2324709618789194.
13. Wang S, Xue Q, Liu Y, et al. Analysis of correlative factors of chronic coronary blood flow in large [in Chinese]. Xin Zang Za Zhi. 2017;29(02):180–3.
14. Wang X, Nie SP. The coronary slow flow phenomenon: characteristics, mechanisms and implications. Cardiovasc Diagn Ther. 2011;1(1):37–43.
15. Yuksel S, Pancar Yuksel E, Yenercag M, et al. Abnormal nail fold capillaroscopic findings in patients with coronary slow flow phenomenon. Int J Clin Exp Med. 2014;7(4):1052–8.
16. Çelik O, Demirci E, Aydın M, et al. Evaluation of ghrelin levels and endothelial functions in patients with coronary slow flow phenomenon. Interv Med Appl Sci. 2017;9(3):154–9.
17. Kopetz V, Kennedy J, Heresztyn T, et al. Endothelial function, oxidative stress and inflammatory studies in chronic coronary slow flow phenomenon patients. Cardiology. 2012;121:197–203.
18. Yayla, Akboa MK, Gayretli YK, et al. A novel marker of inflammation in patients with slow coronary flow: lymphocyte-to-monocyte ratio. Biomarkers Med. 2016;10(5):485–93.
19. Camsari A, Ozcan T, Ozer C, et al. Carotid artery intima-media thickness correlates with intravascular ultrasound parameters in patients with slow coronary flow. Atherosclerosis. 2008;200(2):310–4.
20. Genc Tapar G, Elcik D, Dogan A, et al. An investigation of the relationship between arterial aortic stiffness and coronary slow flow that was detected during coronary angiography. Echocardiography. 2020;37(4):528–35.
21. Niu H, Wei Z, Zhang Y, et al. Atorvastatin improves coronary flow and endothelial function in patients with coronary slow flow. Exp Ther Med. 2018;15(1):904–8.
22. Simsek H, Yaman M, Babat N, et al. Decreased risk of ventricular arrhythmias with treatment of nebivolol in patients with coronary slow flow. Kardiol Pol. 2016;74(10):1174–9.
23. Suner A, Cetin M. Is dipyridamole useful in improving left ventricular systolic and diastolic function in patients with coronary slow flow? Echocardiography. 2016; 33(10): 1472–1478.
24. Li L, Gu Y, Liu T, et al. The effects of diltiazem sustainedrelease capsules in patients with coronary slow flow phenomenon at 6-month follow-up. PLoS One. 2012;7(6):388–91.
25. Mehta HH, Morris M, Fischman DL, et al. The spontaneous coronary slow-flow phenomenon: reversal by intracoronary nicardipine. J Invasive Cardiol. 2019;31(3):42–5.
26. Suner A, Cetin M. The effect of trimetazidine on ventricular repolarization indexes and left ventricular diastolic function in patients with coronary slow flow. Coron Artery Dis. 2016;27(5):398–404.
27. Chen Z, Chen X, Li S, et al. Nicorandil improves myocardial function by regulating plasma nitric oxide and endothelin-1 in coronary slow flow. Coron Artery Dis. 2015;26(2):114–20.
28. Gibson CM, Cannon CP, Daley WL, et al. TIMI frame count a quantitative method of assessing coronary artery flow. Circulation. 1996;93(5):879.

29. Sanghvi S, Mathur R, Baroopal A, et al. Clinical, demographic, risk factor and angiographic profile of coronary slow flow phenomenon: a single centre experience. Indian Heart J. 2018;70(Suppl 3):290–4.
30. Li Y, Zhang H, Hao YF, et al. Evaluation of hyperbaric oxygen effects on slow coronary flow patients using gated myocardial perfusion imaging tomography. Undersea Hyperb Med. 2018;45(4):403–9.
31. Liu CJ, Wu YW, Ko KY, et al. Incremental diagnostic performance of combined parameters in the detection of severe coronary artery disease using exercise gated myocardial perfusion imaging. PLoS One. 2015;10(7):e0134485.
32. Chen D, Lin S, Xu W, et al. Qualitative and quantitative analysis of the major constituents in Shexiang Tongxin Droping Pill by HPLC-Q-TOF-MS/MS and UPLC-QqQ-MS/MS. Molecules. 2015;20(10):18597–619.
33. Yang J, Zhang XW, Deng YP, et al. Effect of Shexiang Tongxin Droping Pill on the improvement of vascular endothelial function in patients with coronary heart disease [in Chinese]. Zhong Hua Zhong Yi Yao Xue Kan. 2016;34(09):2188–90.
34. Li HY, Zhang DD, Zhou Z, et al. Effect of Shexiang Tongxin Droping Pill on vascular endothelial protection [in Chinese]. Xin Dian Yu Xun Huan. 2016;35(06):415–7.
35. Zhang YD, Shi SL, Lena, et al. Effect of Shexiang Tongxin Droping Pill on microcirculation disorder in mice [in Chinese]. Zhong Xi Yi Jie He Xin Nao Xue Guan Bing Za Zhi. 2017;15(23):2969–72.
36. Chen ZY, Huang X, Zhou LH, et al. Research progress on the mechanism of action and drug target of Shexiang Tongxin Dropping Pills [in Chinese]. He Nan Zhong Yi. 2019;39(07):1117–21.
37. Niu ZC, Mao HP. A study on the stability of atherosclerotic plaque in rabbits with Shexiang Tongxin dropping pills [in Chinese]. Liao Ning Zhong Yi Yao Za Zhi. 2016;43(11):2403–6.
38. Wang S-H, Lin C, Zhao Xu, et al. Effect of Shexiang Tongxin Dropping Pills on the immediate blood flow of patients with coronary slow flow. Chinese Journal of Integrative Medicine. 2019;25(5):360–5.
39. Han SJ, Zhang XY, Zhang LJ, et al. Evaluation of clinical evidence of Shexiang Tongxin dropping pills for slow blood flow in patients after PCI [in Chinese]. Shi Jie Ke Xue Ji Shu-Zhong Yi Yao Xian Dai Hua. 2018; 20(10): 1772–1777.
40. Beltrame JF. Defining the coronary slow flow phenomenon. Circ J. 2012;76(4):818–20.
41. Chen Kj XH. L J, et al. Diagnostic criteria for practical blood stasis syndrome. [in China]. Zhong Guo Zhong Xi Yi Jie He Za Zhi. 2016;36(10):1163.
42. Kopetz VA, Penno MA, Hoffmann P, et al. Potential mechanisms of the acute coronary syndrome presentation in patients with the coronary slow flow phenomenon—insight from a plasma proteomic approach. Int J Cardiol. 2012;156(1):84–91.
43. Beltrame JF, Limaye SB, Horowitz JD. The coronary slow flow phenomenon—a new coronary microvascular disorder. Cardiology. 2002;97(4):197–202.
44. Zhu X, Shen H, Gao F, et al. Clinical profile and outcome in patients with coronary slow flow phenomenon. Cardiol Res Pract. 2019; 2019:9168153.

45. Hao XZ, Zheng XY, Wang HY, et al. Study on the effect of Tongmai Yangxin Pill on the SSS score and plasma marker miRNA-126 myocardial nuclein development in patients with coronary heart disease complicated with diabetes mellitus after operation. [in Chinese]. Lin Chuang He Shi Yan Yi Xue Za Zhi. 2018;17(01):1–4.

Figures

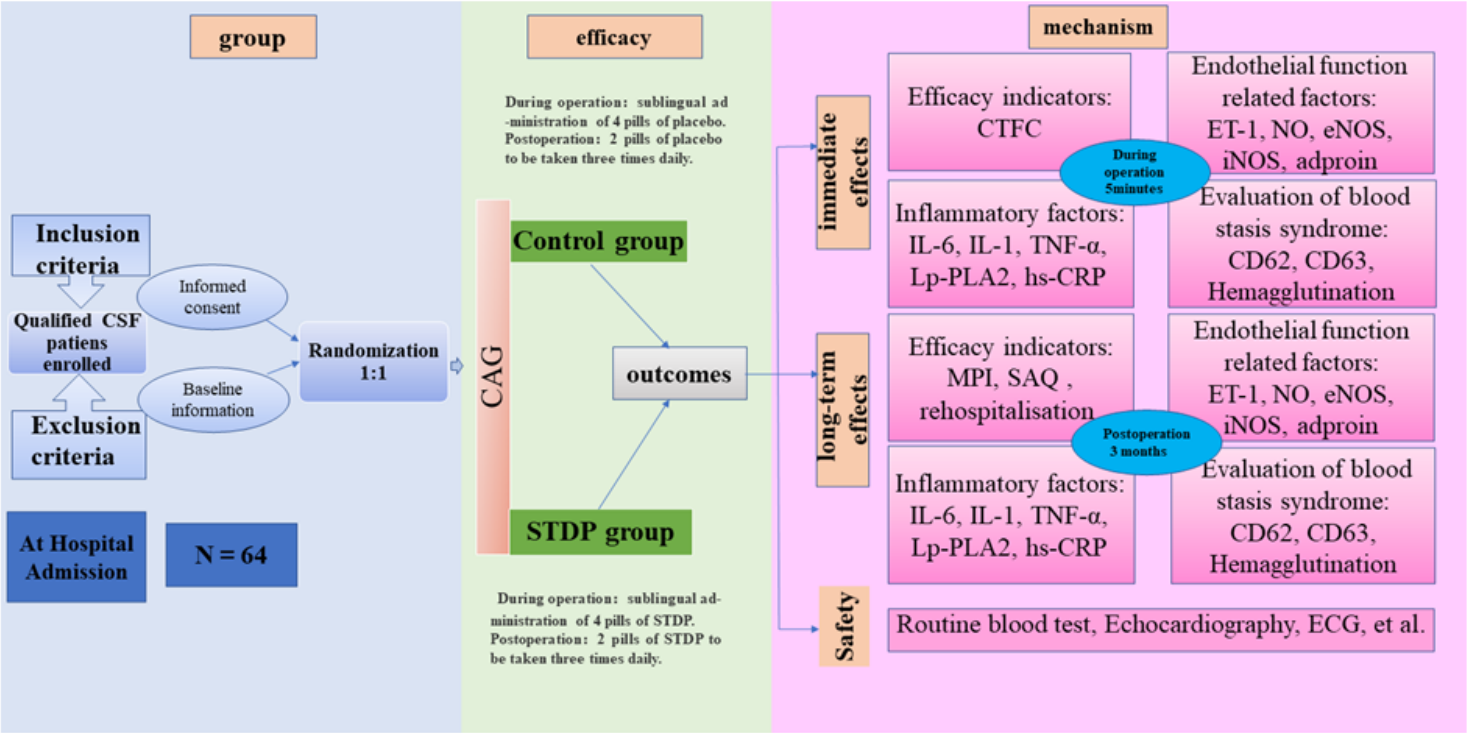

Figure 1

DIRECTION (The immediate and long-term effects of Shexiang Tongxin Dropping Pill on coronary slow flow) trial protocol diagram.

Supplementary Files

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

- SPIRITFillablechecklist.doc
- SupplementaryMaterial.docx