Randomized controlled clinical study on Yiqi Liangxue Shengji prescription for intervention cardiac function of acute myocardial infarction with ischemia-reperfusion injury

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Abstract
Introduction: The morbidity and mortality of acute myocardial infarction (AMI) patients still remains high after percutaneous coronary intervention (PCI). Myocardial ischemia-reperfusion (MIR) injury is one of the important reasons. Although the phenomenon of MIR injury can paradoxically reduce the beneficial effects of myocardial reperfusion, there currently remains no effective therapeutic agent for preventing MIR. Previous studies have shown that Yiqi Liangxue Shengji prescription (YLS) is effective in improving clinical symptoms and ameliorating the major adverse cardiovascular events of coronary heart disease patients undergoing PCI. This study aims to evaluate the effectiveness and safety of YLS in patients with acute myocardial infarction (AMI) after PCI.

Methods: This study is a randomized, double-blinded, placebo-controlled, single-central clinical trial. A total of 140 participants are randomly allocated to 2 groups: the intervention group and the placebo group. Based on routine medications, the intervention group will be treated with YLS and the placebo group will be treated with YLS placebo. All participants will receive a 8-week treatment and then be followed up for another 12 months. The primary outcome measures are N terminal pro B type natriuretic peptide (NT-proBNP) and left ventricular ejection fraction. Secondary outcomes are plasma levels of microRNA-145, plasma cardiac enzyme, and Troponin I levels in blood samples, changes in ST-segment in ECG, Seattle Angina Questionnaire, the efficacy of angina symptoms, and occurrence of major adverse cardiac events. All the data will be recorded in case report forms and analyzed by SPSS V.17.0.

Discussion: The trial will investigate whether the postoperative administration of YLS in patients with AMI after PCI will improve cardiac function. And it explores microRNAs (miRNA)-145 as detection of blood-based biomarkers for AMI by evaluating the relation between miRNAs in plasma and cardiac function.

Trial registration: Chinese Clinical Trials Registry identifier ChiCTR2000038816. Registered on October 10, 2020.

Abbreviations: AEs = adverse events, AMI = acute myocardial infarction, CHD = coronary heart disease, CHM = Chinese herbal medicine, CRFs = case report forms, H/R = hypoxia/reoxygenation, I/R = ischemia/reperfusion, MACE = major adverse cardiovascular events, MIR = myocardial ischemia-reperfusion, PCI = percutaneous coronary intervention, PPCI = primary percutaneous coronary intervention, TCM = Traditional Chinese Medicine, YLS = Yiqi Liangxue Shengji prescription.

Keywords: acute myocardial infarction, myocardial ischemia-reperfusion injury, percutaneous coronary intervention, randomized controlled trial, Yiqi Liangxue Shengji prescription

The study is in compliance with the Declaration of Helsinki (Edinburgh 2000 version). The study protocol was reviewed and approved by IRB of Dongfang Hospital Affiliated to Beijing University of Chinese Medicine (JDF-IRB-2020031102). Only clinicians holding the necessary qualifications are acting as principal investigators. Written informed consent will be obtained from each participant prior to enrollment.

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The authors have no conflicts of interest to disclose.

The datasets generated during and/or analyzed during the current study are publicly available.

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1. Introduction

Despite recent progress in the diagnosis and treatment of cardiovascular diseases, coronary heart disease (CHD) represents the leading cause of death and disability worldwide. According to the WHO, CHD had caused 7,254,000 deaths worldwide (12.8% of all deaths) in 2008. After an acute myocardial infarction (AMI), timely and successful myocardial reperfusion with the use of thrombolytic therapy or percutaneous coronary intervention (PCI) is the most effective strategy for reducing the size of a myocardial infarct and improving the clinical outcome. However, according to report, timely reperfusion by primary percutaneous coronary intervention (PPCI) and secondary preventative therapies still bring significant morbidity and mortality, with 7% death and 22% heart failure at 1 year. The process of restoring blood flow to the ischaemic myocardium, however, can induce injury. The phenomenon of myocardial ischaemia-reperfusion (MIR) injury can paradoxically reduce the beneficial effects of myocardial reperfusion. MIR often causes further myocardial injury and cardiomyocyte death, which occurs in up to 50% of reperfused ST-segment elevation myocardial infarction patients, and its presence portends a worse prognosis. And growing evidence from experimental studies suggests that MIR can paradoxically reduce the beneficial effects of myocardial reperfusion.

2. Methods and design

2.1. Patient and Public Involvement

Patients and/or public were not involved in the different stages of the study (including the design and the recruitment phase). However, we intend to disseminate the main results to trial participants and will seek patient and public involvement in the development of an appropriate method of dissemination.

2.2. Study design

This is a single-centre, randomized, double-blinded, placebo-controlled, parallel-group clinical trial. The study was registered at the Chinese Clinical Trial Registry on 10 October 2020 (ChiCTR2000038816). This study will be conducted in accordance with the principles of the Declaration of Helsinki and Good Clinical Practice guidelines. We will rigorously follow the latest Consolidated Standards of Reporting Trials (CONSORT 2017) for CHM recommendations, Standard Protocol Items: Recommendations for Interventional Trials and 2013 statement for herbal interventions. The study will recruit 140 AMI patients treated with PCI from inpatients and outpatients at the Dongfang Hospital, and has been approved by IRB of Dongfang Hospital Affiliated to Beijing University of Chinese Medicine (JDF-IRB-2020031102). All patients will provide written informed consent. The patient recruitment pathway is shown in Figure 1.

2.3. Overall objective

The trial will investigate whether the postoperative administration of YLS in AMI patients treated with PCI will improve cardiac function and mortality, with 7% death and 22% heart failure at 1 year.
function. And it explores microRNAs (miRNA)-145 as detection of blood-based biomarkers for AMI by evaluating the relation between miRNAs in plasma and cardiac function.

2.4. Patient inclusion and exclusion criteria

On arrival at the hospital, patients presenting AMI and treat with PCI will be screened for study eligibility and written informed consent will be obtained.16,18,19 Patients received standard secondary prevention treatment for coronary heart disease and Oral loading with 300 mg of Aspirin and clopidogrel hydrogen sulphate tablets (or 180 mg of ticagrelor) will be performed before surgery. Patient inclusion and exclusion criteria are listed in Table 2.

2.5. Removal, dropout, and termination criteria

Participants can voluntarily drop out at any time during the trial. Eligible subjects failing to complete the observation period presented in the trial will be considered as dropout cases regardless of the time and reason. Reasons for dropout will be recorded, and the last data recorded for these participants will be included in the data analysis. The trial will be suspended in a specific participant if serious adverse events (AEs) relevant to the YLS occur; the participant decides to join in another clinical research project in terms of cardiovascular diseases; the participant demonstrates hypersensitivity toward YLS, such as abnormal thirsty, stomach ache, and diarrhoea; the participant suffers from acute life-threatening disease. The whole research would be terminated in the following circumstances: masking of the randomization fails; unblinding rate exceeds 20% of the sample size; assessments of all follow-up are completed.

2.6. Randomization and masking

Consented patients will be randomized to receive either CHM or placebo using concealed random allocation from a computer-generated random numbers table through the Dongfang hospital Clinical Research Institute. Once randomized, the patient will receive postoperative administration of either YLS or placebo after reperfusion of the culprit artery, as soon as possible. The treatment allocation will be concealed from the patient, the interventional cardiologist, the blinded research staff collecting the data and clinical endpoints, and other staff analyzing the outcome data.

### Table 1
Components and dose of Yiqi Liangxue Shengji prescription.

| Chinese name | English name | Pharmacological effects | Main active components | Weight (g/bag) | Reference |
|--------------|--------------|-------------------------|------------------------|---------------|-----------|
| Huang Qi     | Astragalus membranaceus | Anti-oxidation, regulation of mitophagy, anti-inflammation, immunomodulatory effects, anti-neurodegeneration, | Triterpene saponins (Astragalosides, Acetylastragaloside, Acetylastragaloside isostraflagaksides, Astramembranarin etc); Flavonoids (Islavonones, Isloflavans, Isoflavans, Pericarpins etc); Polysaccharides (Glucans, Heteropolysaccharides) | 30 | (Shan et al, 2019) (Liu et al, 2017) |
| Dan Shen     | Salvia miltiorrhiza | Endothelial protective effects, proliferation and migration of VSMCs, improve microcirculatory, anticoagulant, anti-thrombotic, anti-inflammatory, | Diterpene chineone (tanshinone I-VI, cryptotanshinone, isothanone I-II, Danshenol A etc); phenolic acid (Danshensu, salvianolic acid A, salvianolic acid B, protocatechuic aldehyde, etc) | 15 | (Li et al, 2018) |
| Mudan Pi     | Cortex Moutan | Anti-oxidative, anti-inflammatory, anti-tumour, vasodilatatory effects, improving blood circulation, inhibiting inflammation | paenonol, paenoflavin, paenoside, apo-paucoside, oxy-paucoside, galloylpaeonol, galloyloxypaeonol, benzoyloxypaeonol, benzoylpaeonol and gallic acid, etc | 10 | (Wang et al, 2017) |
| Jinjin Hua   | Lonicerae japonicae flos | Anti-inflammatory, bacteriostatic activity, antiviral activity, liver protective activity, anti-inflammatory, | Chorioxic acids (Chorioxic acid, Neochlorogenic acid, Isochroxic acid A, B, C, etc); Cinnamic acids (Caffeic acid, 3-O-Benzoylbenzoic acid, etc); Benzoic acids (2,5-Dihydroxybenzoic acid-5-O-b-d-glucopyranoside) | 10 | (Li et al, 2019) |

Li Y, Li W, Fu C, Song Y, and Fu Q (2019). Lonicerae japonicae flos and Lonicerae flos: a systematic review of ethnopharmacology, phytochemistry, and pharmacology. Phytochem Rev, 1–61. doi: 10.1007/s11101-019-09655-7.

Li ZM, Xu SW, and Liu PQ (2018). Salvia miltiorrhiza (Danshen): a golden herbal medicine in cardiovascular therapeutics. Acta Pharmacol Sin 39, 802–824.

Liu P, Zhao H, and Luo Y (2017). Anti-aging implications of Astragalus Membranaceus (Huangqi): a well-known Chinese tonic. Aging Dis 8, 868–896.

Shan H, Zheng X, and Li M (2019). The effects of Astragalus Membranaceus active extracts on autophagy-related diseases. Int J Mol Sci 20(8). doi: 10.3390/ijms20081904.

Wang Z, He C, Peng Y, Chen F, and Xiao P (2017). Origins, phytochemistry, pharmacology, analytical methods, and safety of Cortex Moutan (Paeonia suffruticosa Andrew): a systematic review. Molecules (Basel, Switzerland) 22, 846.
The eligible consented patient will then be randomized to receive either:

1. **CHM treatment**: YLS will be administered as a granule (1 bag at a time, 2 times per day, 8 weeks). This dosing regimen is identical to that used in the other trials.[20] Furthermore, this dose was also found to be cardioprotective in a preclinical model using animal.[21]

2. **Placebo control**: Both YLS and placebo have the same outer packaging, color, shape, and flavor, so that neither the participant nor the investigator could recognize which group of intervention the participants are receiving before unblinding. After the treatment, the packaging will be returned to the investigators.

All patients will be transferred to the coronary care unit after the primary angiographic procedure. Intravenous glycoprotein IIb/IIIa inhibitor will be maintained for 18 to 36 hours after PCI. A loading dose of aspirin and P2Y12 inhibitors will be given before the procedure. An intravenous bolus of unfractionated heparin (100 U/kg) will be administrated right before the procedure to achieve therapeutic activated clotting time. Dual-anti-platelet therapy will be maintained during the deferred period and for at least 1 year after PCI. The peri-procedural treatment is in accordance with the Chinese guidelines for the management of AMI.[22]

### 2.7. Sample size calculation

The formula used to calculate the sample size is as follows, which is based on superiority clinical trial hypothesis test sample size estimation.[23] The sample size was calculated on the basis of expected reduction in NT-proBNP. One previous study suggested

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**Figure 1.** Study flowchart.
that the reducing value for NT-proBNP level in AMI patient treatment with PCI is 32%. Therefore, we assume the reduction in NT-proBNP level as 58% in this study. Given a type I error rate of $\alpha = 0.05$, type II error rate of $\beta = 0.2$, $U_0(0.05)=1.65$, $U_\beta (0.2)=1.28$. The sample size for 1 arm needs to be 63, resulting in $n = 2 \times 63 = 126$ patients. Considering a dropout rate of 10%, a total of 138 patients need to be allocated to reach the required number of patients for the efficacy analysis. For convenience of randomization, we decided to recruit 140 patients. The formula used to calculate the sample size is as follows:

$$n_1 = \left( \frac{U_0 + U_\beta}{\beta} \right)^2 \times 2P \times \left( 1 - P \right) \left( P_1 - P_2 \right)^2 = n_2$$

### 2.8. Outcome measures

#### 2.8.1. Background information

Background information includes demographic data and general clinical data. Demographic data consists of gender, age, height, weight, and so on. General clinical data consists of medical history, course of disease, treatment history, combined diseases, concomitant medications, and so on. The participants’ information and privacy will be strictly protected and forbidden to the public.

#### 2.8.2. Safety outcomes

Safety is assessed by vital signs, laboratory examinations, and AEs. Vital signs include body temperature, breathing, blood pressure, and heart rate. Laboratory examinations include blood, urine, stool, liver, and kidney function. AEs will be recorded all the time during the treatment. The development of AEs will also be observed until the adverse reactions disappear.

#### 2.8.3. Primary and secondary outcomes

The primary outcome measures of the study are NT-proBNP and left ventricular ejection fraction, which will be measured at baseline and 8 weeks after randomization. Secondary outcomes include plasma levels of microRNA-145, plasma creatine kinase-MB, and Cardiac Troponin I levels in blood samples. At the same time, the trial also observes the occurrence of MACEs defined as the composites of deaths from any cardiac causes, myocardial infarction, and revascularization (PCI or CABG) at 8 weeks after randomization. The efficacy of angina symptoms, Seattle Angina Questionnaire, will be recorded at baseline and 8 weeks after randomization and TCM syndrome efficacy.[24] Items to be measured and the time window of data collection are shown in Table 3.

### 2.9. Adverse events

AEs are defined as negative or unintended clinical manifestations following the treatment. Patients will be asked to report to the investigators any abnormal reactions occurring at any time during the trial. In addition, investigators will collect information about abnormal reactions monthly. All details of related and unexpected AEs, such as time of occurrence, degree and duration of AEs, suspected causes, and the effective measures and outcomes will be recorded on electronic case report form. Any AEs, such as subjective discomfort and laboratory abnormalities, should be taken seriously. Careful analysis and immediate measures are taken to protect the safety of the subjects until the adverse events disappeared.

### 2.10. Quality control of data

Patients’ baseline characteristics are collected with case report forms (CRFs) during hospitalization at least 24 hours after PCI by investigators of each center. Angiographic data are recorded in the PCI procedure. According to the follow-up plan, patients are required to undergo recording of history and echocardiogram in each center at 1- and 12-month follow-up.

Data usage adheres to local laws and regulations of participating centers. Patient privacy is protected by restricting the access to dataset to relevant individuals—investigators.

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**Table 2**

**Patient inclusion and exclusion criteria for the trial.**

### Inclusion criteria

1. 18 yr old $\leq$ age $\leq$ 80 yr old.
2. Provision of written informed consent by participants or surrogates voluntarily.
3. Clinical diagnosis of acute myocardial infarction (AMI) occurred within 12 h,[22] and all participants must have been treated with PCI.
4. Patients are diagnosed as having a syndrome of deficiency of Qi and blood stasis according to TCM standards.[23]

### Exclusion criteria

1. Severe valvular heart disease (aortic stenosis), severe psychoneurosis, climacteric syndrome, hyperthyroidism, cervical spondylosis, gallbladder heart syndrome, gastro-oesophageal reflux disease.
2. Uncontrolled hypertension with systolic blood pressure $\geq$180 mm Hg or diastolic blood pressure $\geq$110 mm Hg, severe cardiac insufficiency with Ejection Fraction $< 35\%$, severe arrhythmia (fast atrial fibrillation, atrial flutter, paroxysmal ventricular tachycardia, atrioventricular block higher than second degree subtype II, complete bundle branch block).
3. Patients with severe primary diseases like heart, brain, liver, kidney, hemopoietic system-related diseases, and patients whose Alanine Aminotransferase or Aspartate Transaminase is higher than 1.5 times of the upper limit, patients with renal insufficiency (serum creatinine $> 194.5$ μmol/L) or insulin-dependent diabetes mellitus.
4. Patients with depression or anxiety.
5. Stroke or resuscitated sudden death in the past 6 mo.
6. Patients with malignant tumor.
7. Pregnant women or breast feeding women.
8. Hyperthyroidism with TSH levels more than 1.5 times upper limit of normal.
9. Increased bleeding risk (gastrointestinal bleeding, traumatic head injury, and bleeding diathesis).
10. Patients with allergic constitution or are allergic to many kinds of TCM herbs and ingredients of the study drug.
11. Participation in other clinical trials in last 1 mo.
12. Patients unable or unwilling to sign the informed consent form.

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PCI = percutaneous coronary intervention, TCM = Traditional Chinese Medicine.
analyses. After randomization will be excluded from per-protocol statistical to participate or not treated according to the allocated procedure set, patients who undergo randomization but withdraw consent contact, at which point they will be censored. In the per-protocol lost to follow-up will be considered at risk until the date of last collected for the entire follow-up period for all patients. Patients protocol set. Primary and secondary endpoint data will be conducted in both the intention-to-treat set and the per-

2.11. Statistical analyses

The statistical analyses of primary and secondary outcomes will be conducted in both the intention-to-treat set and the per-protocol set. Primary and secondary endpoint data will be collected for the entire follow-up period for all patients. Patients lost to follow-up will be considered at risk until the date of last contact, at which point they will be censored. In the per-protocol set, patients who undergo randomization but withdraw consent to participate or not treated according to the allocated procedure after randomization will be excluded from per-protocol statistical analyses.

IBM SPSS V17.0 software pack was used for data analysis. The normal distribution of the data was tested with Pearson test. Independent sample t test was used for the comparison of data with normal distribution, while Spearman test was used for the comparison of data without normal distribution. Data with normal distribution were expressed as arithmetic mean ± standard deviation, while data without normal distribution were expressed as median value (minimum–maximum). A P value between .1 and .05 was considered marginally significant, a P value between .01 and .05 was considered significant, .001 and .01 highly significant, and < .001 very highly significant.

2.12. Ethics and dissemination

This trial has been registered at Chinese Clinical Trial Registry http://www.chictr.org.cn/showproj.aspx?proj=61713. The data of this trial will be managed by ResMan at http://www.medresman.org/ and posted on Chinese Clinical Trial Registry. The results of this study will be disseminated to the public through academic conferences and peer-reviewed journals.

3. Discussion

Several cardioprotective therapies, which have been conferred robust cardioprotection in experimental animal models of acute ischemia and reperfusion injury, have failed in the clinical setting of AMI for patient benefit.[25] Although the cardioprotective strategies act through common end-effectors, multiple mechanisms affect cardiomyocyte death. The treatments emerging from experimental studies may be suboptimal in patients with comprehensive comorbidities.[26,27] Therefore, additive or synergistic cardioprotective effects of multiple cardioprotective agents might be better cardioprotective strategies to reduce myocardial infarction.[28] As a supplementary and complementary medicine, the characteristics of CHM that is multiple treatment target are attracting more attention. As the principal active components, pharmacological studies have shown that Astragalus membranaceus could perform the function of anti-oxidation, regulation of mitophagy, anti-inflammation, immunomodulatory effects, anti-neurodegeneration.[29,30] Salvia miltiorrhiza is reported to protect vascular endothelial cells against hypoxia, regulate proliferation and migration of VSMCs, improve microcirculatory, and have function of anticoagulant, anti thrombotic, anti-inflammatory, [31] Previous studies have shown that Cortex Moutan and Lonicerae japonicae flos both have cardioprotective function[32,33] (Table 1). However, whether the postoperative administration of YLS in AMI patients treated with PPCI will improve cardiac function still requires confirmation by randomized, double-blinded, placebo-controlled, parallel-group clinical trial with the objective of determining the effectiveness and safety of YLS.

This trial tried to incorporate miRNA-145 as one of surrogates for hard clinical endpoints. miRNAs are single-stranded RNA
molecules 20 to 25 nucleotides in length coded by genes transcribed by DNA, which are known as “noncoding RNA.” While miRNAs are not converted to protein products, they act to gene expression, primarily through translation repression or RNA degradation. Several investigations have demonstrated that miRNAs may play a major role in regulating most of the human genome, including gene alterations associated with various aspects of heart disease, such as ischemic MIR. Genetic or pharmacological manipulation of miRNAs has been indicated to modulate the sensitivity of the myocardium to MIR, protective noncoding RNAs may have a role in the setting of anticipated ischemia. Because of their significant role in all stages of MIR, regulating miRNAs is a promising therapeutic strategy. The miRNAs in plasma and serum are reported to be present in a remarkably stable form and can be detected in the peripheral circulation. Therefore, the miRNAs can be considered as promising novel biomarkers for the diagnosis and prognosis of cardiovascular diseases. Previous studies reported that the expression of miR-145 is associated with MIR. In animal model of ischemia/reperfusion injury and myocardial hypoxia/reoxygenation-induced cell model, miRNA-145 were significantly reduced, which indicated that the abnormal expression of miR-145 may be the good candidate for MIR. A potential limitation of our study is that the trial will be undertaken in China, it is uncertain whether the similar effects are available to other ethnic groups and regions. To conclude, the aim of this trial is to demonstrate that YLS will protect the myocardial function in patients with AMI after successful PCI and subsequently yield long-term benefit.

Author contributions

DL and QL are the principal investigator of this study. CC and JYX conceptualized the study design and wrote the manuscript. JW and KZ modified the manuscript. CC, RLF and JYX participated in the establishment of the eCRF. CC, RLF and JYX participated in the recruitment of patients. CC and JYX designed the method for statistic analysis. CC, RLF and JYX will participate in the data collection and analysis. All authors read and approved the final manuscript.

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Writing – review & editing: Qian Lin.

Correction

The corresponding author originally appeared incorrectly as Cong Chen and has since been corrected to Dong Li.

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