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ORIGINAL ARTICLE

Assessment of Complementary Treatment with *Yiqi Fumai* Lyophilized Injection on Acute Decompensated Ischemic Heart Failure (ACT-ADIHF): Rationale and Design of a Multicenter, Randomized, Controlled Trial

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Abstract

Background Heart failure (HF) is the end stage of many heart diseases, and ischemic heart disease (IHD) is the primary cause. *Yiqi Fumai* lyophilized injection, a contemporary Chinese medicine preparation, widely used in the treatment of IHF patients, shows clinical efficacy on improving symptoms and cardiac function, but the quality of the current literature does not address multiple important issues. This article describes a protocol for assessment of complementary treatment with *Yiqi Fumai* lyophilized injection in acute decompensated IHD.

Methods The protocol is designed as a multicenter randomized controlled trial to assess the efficacy and safety of complementary treatment with *Yiqi Fumai* lyophilized injection on acute decompensated IHD. This trial will be carried out in 37 hospitals in China and expected to enroll 666 inpatients with acute decompensated IHF due to coronary heart disease. On the basis of standardized western medications, patients are randomized to either the treatment group (250 ml 5% glucose / sodium injection + 5.2 g *Yiqi Fumai* lyophilized injection) or the control group for 7 days and follow-up for 30 ± 3 and 60 ± 3 days. The primary outcome is change in brain natriuretic peptide (BNP) concentrations. The secondary outcomes are composite endpoint, left ventricular ejection fraction, blood troponin T/I, cardiothoracic ratio, life quality scale, scores of the four traditional Chinese medicine (TCM) diagnostic methods.

Discussion Standardized western medications together with TCM have been extensively used in China and have developed into a comprehensive treatment model. The trial will provide clinical research evidence for application of complementary treatment with intravenous *Yiqi Fumai* lyophilized injection on decompensated IHF.

Trial Registration This study protocol has been listed in the Chinese Clinical Trial Registry (registration number: ChiCTR-IPR-15007396, http://www.chictr.org.cn/showproj.aspx?proj=12370) on November 6, 2015.

Keywords Traditional Chinese medicine · *Yiqi Fumai* lyophilized injection · Acute decompensated ischemic heart failure Brain natriuretic peptide

Introduction

Heart failure (HF) is the end stage of many heart diseases. The high hospital admission rate and low 5-year survival rate in HF are comparable to malignant tumor and have seriously threatened the health of people. Studies have shown that ischemic heart disease (IHD) is the primary cause of heart failure [1]. HF guidelines have constantly been updated, so the treatment for ischemic HF patients is now more standardized. Thus, the clinical prognosis has been improved. Even so, the readmission rate of HF patient remains high and the heart function continues to deteriorate [2].

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Standardized western medications together with traditional Chinese medicine (TCM) have been extensively used in China and have developed into a comprehensive treatment model. Intravenous *Yiqi Fumai* lyophilized injection, a contemporary Chinese medicine preparation, has often been used on ischemic HF patients. Small sample size clinical studies have suggested that intravenous *Yiqi Fumai* lyophilized injection used along with standardized western medications can further improve clinical efficacy by improving symptoms and cardiac function of patients [3]. However, the quality of the current literatures has limitations. This study aims to evaluate the efficacy and safety of using intravenous *Yiqi Fumai* lyophilized injection to treat acute exacerbation ischemic HF through central randomization and parallel controlled trial design.

Methods/Design

Study Objectives

To prove complementary treatment with intravenous *Yiqi Fumai* lyophilized injection based on standardized western treatment can reduce brain natriuretic peptide (BNP) concentratrions, and the incidence of 2-month cardiovascular events in acute decompensated ischemic HF patients.

Design Overview

The study is designed as a multicenter randomized controlled trial. To avoid regional differences, 37 hospitals from different regions of China will be participating in this trial. A research assistant at each participating unit will be responsible for data collection. Data management and statistical analysis will be performed by the statistical department in First Teaching Hospital of Tianjin University of Traditional Chinese Medicine. This study is conducted in accordance with the Declaration of Helsinki and has been approved by the ethics committee in First Teaching Hospital of Tianjin University of Traditional Chinese Medicine (Ethics approval number: TYLL2015[K] No.004). The study has also been registered with the Chinese Clinical Trial Registry (ChiCTR-IPR-15007396). All study subjects have to sign informed consent prior to randomization.

Patient Selection Criteria

Six hundred sixty-six subjects from 37 participating level-A hospitals who satisfy both the inclusion and exclusion criteria will be recruited into the study (inclusion and exclusion criteria in Table 1). Basic information of the subjects will be collected (including sex, age, medical history, medication), severity of disease (including classification of cardiac function, scores from the four TCM diagnostic methods and life quality scale), and physical and chemical examinations (left ventricular ejection fraction, cardiothoracic ratio, blood troponin T/I, etc.).

Randomization Process

Interactive Web Response System (IWRS), a central randomization management system, will be employed for randomized

Table 1 Inclusion and exclusion criteria

Inclusion criteria	Exclusion criteria
1. Age 40–79 y	1. First diagnosis of acute HF
2. Diagnosed with coronary heart disease	2. Has one of the following conditions: (a) acute coronary syndrome, (b) hypotension (systolic <90 mmHg), (c) cardiogenic shock, (d) resistant hypertension (systolic ≥ 180 mmHg and/or diastolic ≥ 110 mmHg), (e) second degree and above sinoatrial or atrioventricular block without pacemaker, uncontrolled malignant arrhythmia, (f) severe heart valve diseases, (g) dilated cardiomyopathy, (h) hypertrophic obstructive cardiomyopathy, (i) myocarditis, (j) pulmonary embolism, (k) pulmonary heart disease, (l) stroke within 6 months, etc.
3. Satisfy the diagnostic criteria of acute exacerbation of chronic HF	3. Scheduled revascularization treatment or cardiac resynchronization therapy (CRT) within 2 months
4. NYHA classification III~IV	4. Liver function alanine aminotransferase (ALT) more than three times the upper limit of normal (ULN)
5. BNP > 200 pg/ml	5. Serum creatinine more than two times the ULN
6. Signed informed consent	6. Severe endocrine disease such as hyperthyroidism
	7. Hemoglobin ≤ 9 g/dl
	8. Mental disorders
	9. Malignant tumor
	10. Pregnant or planned pregnancy, breastfeeding mothers
	11. Suspected or diagnosed with allergy to intervention drug
	12. Participated in other research within 2 months

group allocation. Through a dynamic randomization process, the patients are either allocated to the treatment group (YQFM group) or the control group in the ratio of 1:1. When a patient satisfies the inclusion and exclusion criteria, the research assistant will enter the IWRS, input the required information as prompted by the system and a study subject identification number (SSID) will be produced. According to the SSID, there will be a selection performed based on stratification factors such as classification of the cardiac function, age, and sex. Then, the randomization system will generate the randomization code and the information of the study group allocated to the study subject.

Interventions

This study has two phases, the intervention phase and follow-up phase. With reference to the China HF diagnosis and treatment guidelines 2014 [4], patients recruited into the study will be provided standardized western medications (V0 phase). If there are no contraindications, western medicine such as antiplatelets, statins, diuretics, angiotensin-converting-enzyme inhibitors (ACEI) or angiotensin II receptor blockers (ARB), β-blockers, spironolactone and digitalis should be used. Study subjects in the control groups will only receive standardized western medications, while the patients in the treatment group will receive eight bottles of intravenous *Yiqi Fumai* lyophilized injection (0.65 g/bottle) in addition to standardized western medications. Each bottle of *Yiqi Fumai* will be added into 250 ml of 5% glucose/sodium chloride intravenous infusion and administered at a rate of 60 ml/h (infusion pump recommended) once daily. The patients will receive the intervention for 7 days and other Chinese medicine is to be avoided. After the 7-day intervention, the patients will enter a 2-month follow-up phase. Patients are to follow-up on 8 days (V1), 30 ± 3 days (V2), and 60 ± 3 days (V3) after allocated into the study groups (see Table 2 for details).

Intervention should be administered for 7 days unless the occurrence of certain adverse events that has contraindications. In the presence of comorbidities and complications, western medicine can be given with reference to the relevant guidelines. Researchers are to document all the latest drugs that the patients are taking. When necessary, patients should seek emergency medical help.

Outcomes

The primary outcome is BNP level. The secondary outcomes are composite endpoint (all-cause death, HF emergency/

Table 2 Research flowchart

Item	Research phase			
	Screening/enrolment	Follow-up		
Time	Before enrolment	8 days after enrolment	30 ± 3 days after enrolment	60 ± 3days after enrolment
	V0	V1	V2	V3
Confirm inclusion and exclusion criteria	√			
Signed informed consent	√			
Basic information	√			
Medical history, treatment history, and allergies	√			
Current medications	√	√		√
Retrieve central randomization code	√			
Assign study medications	√			
Efficacy evaluation				
BNP	√	√		√
Troponin T/I	√	√		√
Echocardiogram	√	√		√
Cardiothoracic ratio	√	√		√
NYHA classification	√	√		√
Scores of the four TCM diagnostic methods	√	√		√
Life quality scale	√			√
Endpoints and proof		√	√	√
Safety				
Adverse events records		√	√	√
Blood pressure, heart rate, etc.	√	√	√	√
Blood and urine routine	√	√		√
Liver and kidney profiles	√	√		√
Electrolytes	√	√		√
12-lead electrocardiogram	√	√		√
Appointment for next follow-up		√	√	
Study completion status				√
CRF examination				√

readmission, acute coronary syndrome, revascularization, malignant arrhythmia, cardiogenic shock, stroke, and pulmonary embolism), left ventricular ejection fraction (LVEF), blood troponin T/I (TNT/TNI), cardiothoracic ratio, life quality scale, scores of the four TCM diagnostic methods, etc.

Follow-up Protocol

All recruited patients will be scheduled for follow-up visits (V1, V2, and V3) after allocation. Acquisition of BNP, echocardiogram, TNT/TNI, cardiothoracic ratio, and scores of the four TCM diagnostic methods will be evaluated before allocation of group, and V1 and V3. Life quality scale will only be evaluated before group allocation and V3 after group allocation.

Sample Size Estimation

Sample size was calculated based on 30% decrease in BNP after treatment. It was hypothesized that the decrease in BNP > 30% in 60% of those given standard western medicine treatment and 70% of those given both Chinese medicine and western medicine. The subjects were arranged in the ratio of 1:1 into the treatment group or control group. There should be 333 patients in each group based on one-tailed difference test formula (significance level α is 0.05 and power (1-β) is 0.80 in one-sided test) and less than 20% of the incomplete rate.

Statistical Approach

Statistical analysis will be performed using SAS 9.1 software. Confidence interval was used to analyze if the main outcome measure has superior efficacy in one group over the other. Other outcome measures were analyzed using two-tailed test, with significance level $\alpha = 0.05$ (otherwise stated). Numerical data are described by mean, standard deviation, maximum value, and minimum value. Categorical data are described by frequency, percentage, and composition ratio.

Safety Assessment

Safety assessment was based on vital signs, laboratory examinations, and adverse events. Vital signs documented before and after treatment will include blood pressure, heart rate, etc. Laboratory examinations to be performed include blood and urine routines, electrolytes, liver and kidney profile, and electrocardiogram (detailed monitoring schedule in Table 2). Adverse events, especially the severe adverse events, are to be reported to the research group committee within 24 h. The study design refers to Fig. 1.

Discussion

Intravenous *Yiqi Fumai* lyophilized injection originates from the ancient formula *shengmai* powder and is widely used in the treatment of acute decompensated ischemic HF in China. The raw materials of the injection are red ginseng, liriope, schisandra, and chinensis; excipients are meglumine and mannitolm, are manufactured using modern technology, and contain ginsenosides, ophiopogon polysaccharide, and other active ingredients [5, 6]. Modern pharmacological research shows that ginseng can excite the cerebral cortex and vascular motorium, improve the ability of adrenal cortex secretion, and inhibit the activity of Na^+-K^+-ATP enzyme to promote calcium influx, strengthen myocardial contraction, and improve heart function [7]; *Ophiopogon japonicus* polysaccharides can protect myocardial cells, improve blood flow, and have the function of increasing free radicals and scavenging oxygen free radicals caused by inhibition of myocardial ischemia to dilate coronary artery and increase coronary blood flow [8]; Schisandra chinensis can significantly improve the common hypoxia tolerance of animals and has a strong protective effect on animals' acute myocardial ischemia [9].

A systematic review [3] included a total of 18 articles and 1939 patients, which used Intravenous *Yiqi Fumai* lyophilized injection along with conventional western medications in the assessment of the curative effect and safety on HF, shows that Intravenous *Yiqi Fumai* lyophilized injection along with conventional western medications may further improve symptoms and cardiac function, and improve clinical effects, which make a fundamental contribution for further evaluation of the clinical efficacy of intravenous *Yiqi Fumai* lyophilized injection in the treatment of HF. In order to objectively evaluate the efficacy of intravenous *Yiqi Fumai* lyophilized injection on HF, a proper outcome is essential. BNP is one kind of heart peptide hormones, mainly secreted by the brain and ventricles, and has the function of promoting diuresis, vasodilating, inhibiting the release of catecholamine by sympathetic nervous system, and reducing the vasoconstriction, as well as raised blood pressure caused by angiotensin-aldosterone [10]. During acute exacerbated phase of HF, ventricular pressure overload and blood volume increases, thus stimulates the myocardial cells to synthesize BNP and releases it into the blood. BNP level is a sensitive indicator of HF damage in its early stage and it is used clinically to assess the severity of the condition and effectiveness of the treatment [11, 12]. Studies have also shown that decrease in BNP level in HF patients would indicate that the risk of readmission and death is reduced [13–15]. Thus, BNP is a suitable primary outcome measure for our research.

In recent years, guidelines for the diagnosis and treatment of HF have been updated continuously, and the overall treatment level has been improving. However, further reduction of death

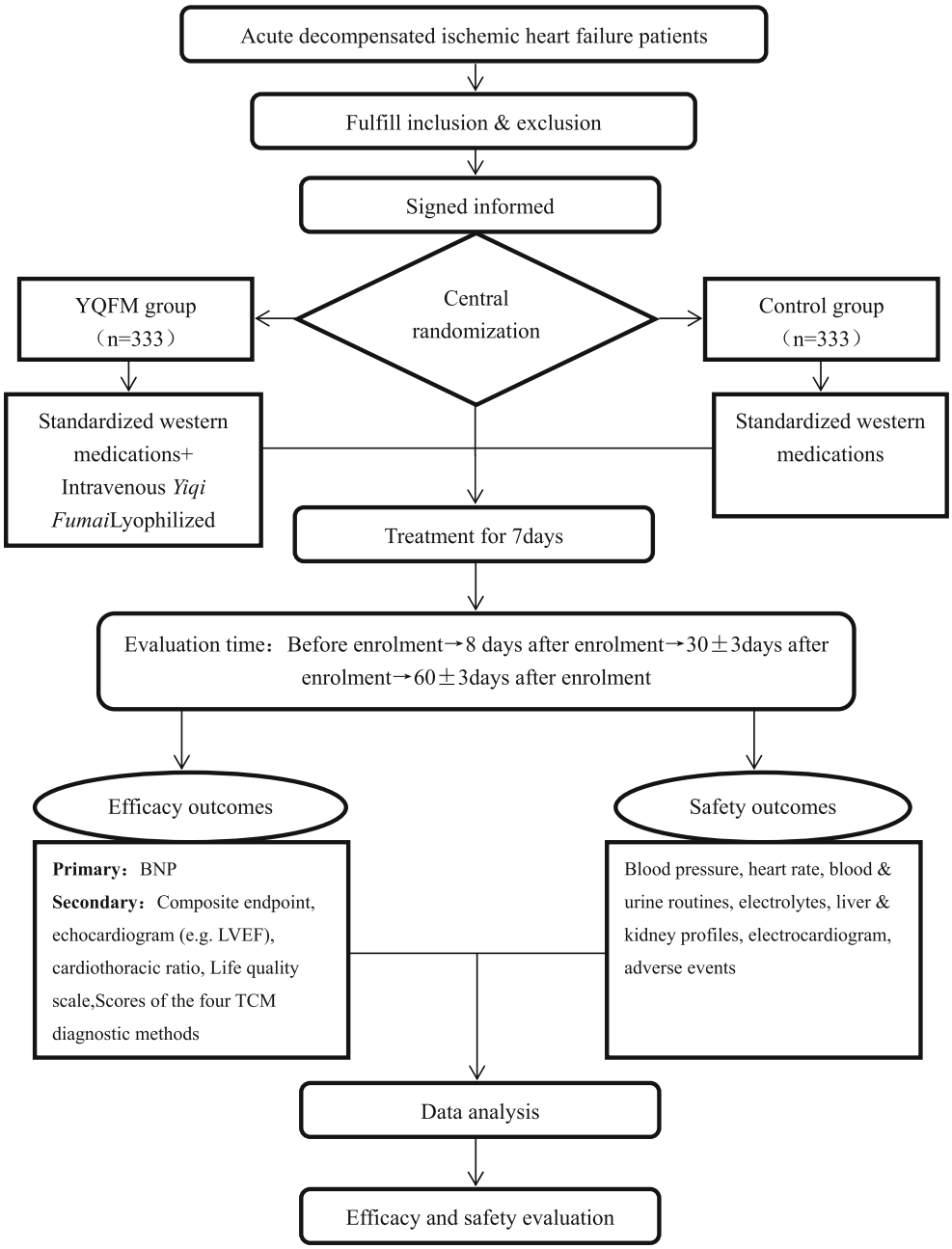

Fig. 1 Study design of the ACT-ADIHF trial

and rehospitalization, improvement of clinical symptoms, exercise tolerance, quality of life, and reduction of financial burden remain the constantly goal in clinical treatment.

Conclusions

The aim of ACT-ADIHF is to bring patients long-term benefits by showing complementary treatment with intravenous *Yiqi Fumai* lyophilized injection may reduce BNP level, the incidence of 2-month cardiovascular events, and improve cardiac function and quality of life in acute decompensated ischemic HF patients.

Trial Status

Since 23 October 2015, this study has recruited 560 patients, and 450 patients have completed 2 months of follow-up.

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Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

Ethical Approval This study is conducted in accordance with the Declaration of Helsinki and has been approved by the ethics committee in First Teaching Hospital of Tianjin University of Traditional Chinese Medicine (Ethics approval number: TYLL2015[K] No.004).

Informed Consent Written informed consent was obtained from all patients or their legally authorized representatives before randomization.

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