Efficacy and Safety of Huxin Formula in Patients after CABG: A Multicenter, Double-Blind, Randomized Clinical Trial

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Keywords

Huxin Formula · Coronary artery bypass grafting · Efficacy · Randomized clinical trial

Summary

Background: Coronary artery bypass grafting (CABG) is widely used in the treatment of coronary artery disease. A multicenter, double-blind, randomized, controlled clinical trial was designed to evaluate the efficacy and safety of Huxin Formula post CABG. **Patients and Methods:** 270 inpatients with coronary heart disease participated in this study. CABG patients in the control group were treated with placebo, while patients in the experimental group were treated with Huxin Formula 1 week after the surgery. All patients were treated for 6 months and followed up for another 6 months. The main outcomes (death, nonfatal myocardial infarction, repeat revascularization, and readmission) were assessed 360 days after treatment, and secondary outcomes (frequency and scores of angina pectoris, etc.) were assessed 0, 90, 180, 270, and 360 days after treatment. **Results:** Our results showed no significant difference between the 2 groups for the primary endpoints. In patients with cardiac function class II (New York Heart Association), the score of angina pectoris was significantly lower (3.88 ± 3.86 vs. 5.45 ± 3.59) and the frequency of angina pectoris attacks was less (0.96 ± 1.01 vs. 1.36 ± 0.94) after 90 days of treatment with Huxin Formula compared to placebo ($p < 0.05$). In patients with 3 coronary vessel lesions, the cardiac function class (1.14 ± 0.35 vs. 1.05 ± 0.21) after 360 days was significantly higher in the control group compared to the treatment group ($p < 0.05$). There were no obvious adverse reactions. **Conclusion:** Huxin Formula may improve cardiac function of patients with 3 coronary vessel lesions and relieve symptoms of patients with cardiac function class II but failed to show superiority in primary outcomes.

Schlüsselwörter

Huxin-Formel · Koronararterien-Bypass-Chirurgie · Wirksamkeit · Randomisierte klinische Studie

Zusammenfassung

Hintergrund: Die Koronararterien-Bypass-Chirurgie (CABG) ist eine weit verbreitete Maßnahme in der Behandlung koronarer Herzerkrankungen. Eine multizentrische, doppelblinde, randomisierte kontrollierte klinische Studie wurde durchgeführt, um die Wirksamkeit und Sicherheit der Huxin-Formel nach einem chirurgischen Eingriff zu evaluieren. **Patienten und Methoden:** 270 stationäre Patienten mit koronarer Herzerkrankung nahmen an der Studie teil. CABG-Patienten der Kontrollgruppe wurden mit Placebo behandelt, während Patienten in der Experimentgruppe eine Woche nach dem chirurgischen Eingriff mit der Huxin-Formel behandelt wurden. Alle Patienten wurden 6 Monate lang behandelt, mit anschließendem Follow-up für ebenfalls 6 Monate. Die Hauptparameter (Tod, Herzinfarkt, wiederholte Revaskularisierung und erneute stationäre Aufnahme) wurden 360 Tage nach der Behandlung erfasst. Die Sekundärparameter (Frequenz und Scores der Angina Pectoris, etc.) wurden 0, 90, 180, 270, und 360 Tage nach Behandlung erfasst. **Ergebnisse:** Unsere Ergebnisse zeigten für die Hauptparameter keine signifikanten Unterschiede zwischen den 2 Gruppen. Bei Patienten mit Herzfunktion der Klasse II (New York Heart Association) war der Angina-Pectoris-Score signifikant niedriger ($3,88 \pm 3,86$ vs. $5,45 \pm 3,59$); gleiches galt für die Häufigkeit von Angina-Pectoris-Anfällen ($0,96 \pm 1,01$ vs. $1,36 \pm 0,94$) nach 90 Behandlungstagen mit der Huxin-Formel, im Vergleich zur Placebobe-handlung ($p < 0,05$). Bei Patienten mit 3 Herzkranzgefäßläsionen stieg die Herzfunktionsklasse ($1,14 \pm 0,35$ vs. $1,05 \pm 0,21$) in der Kontrollgruppe nach 360 Tagen im Vergleich zur Placebogruppe signifikant ($p < 0,05$). Klare unerwünschte Reaktionen gab es nicht. **Schlussfolgerung:** Die Huxin-Formel könnte die Herzfunktion von Patienten mit 3 Herzkranzgefäßläsionen verbessern und Symptome von Patienten der Herzfunktionsklasse II lindern. Jedoch konnte eine Überlegenheit bezüglich der Hauptparameter nicht gezeigt werden.

Introduction

Coronary artery bypass grafting (CABG) surgery has been a well-accepted treatment for patients with severe angina since the 1970s [1]. It has been shown to be highly effective for relieving chest pain, preventing heart attacks, and prolonging life in subsets of patients [2, 3], especially those with left main and triple vessel coronary artery disease, diffuse disease, or left ventricular dysfunction. However, CABG is not only an invasive treatment but also has a negative influence on many patients mentally [3]. Therefore, a comprehensive (both physical and mental) recovery is necessary during CABG treatment.

Huxin Formula is a modified version of a Chinese medicine formula created by Prof. Deng Tie-tao, a well-known traditional Chinese medicine practitioner, and has been widely used for over 30 years in clinical practice because of its marked effects on coronary heart disease [4].

Huxin Formula mainly consists of ginseng, *Panax pseudoginseng*, *Pinellia ternate*, and *Citri reticulatae pericarpium*. The pharmacological effects of these herbs on cardiovascular diseases have been reported in vitro and in animal studies. It has been reported that ginseng has antithrombotic and antiplatelet effects in rats and in vitro [5, 6]. Ginseng increased coronary perfusion flow, attenuated myocardial ischemic injury, and protected cardiac myocytes against ischemic injury in vitro and in vivo [7, 8]. *P. pseudoginseng* prevents atherosclerosis by lowering serum lipid levels and regulating vascular CD40 and MMP-9 expression [9]. *P. pseudoginseng* also protects myocardial cells from apoptosis induced by ischemia both in vitro and in vivo [10]. *P. ternate* is widely used in clinical treatment as an expectorant and in the treatment of coronary heart disease. It has been reported that *P. ternate* has other pharmacological properties such as lipid-reducing, anti-spasm, anti-emetic, anti-tumor, and antifertility effects [11]. *C. reticulatae pericarpium* improves abnormal hemorheology

and inhibits platelet aggregation in rats with blood stasis [12]. Diets containing 1% polymethoxylated flavones (an effective constituent of *C. reticulatae pericarpium*) significantly reduced serum total and very low-density lipoprotein (VLDL) + LDL cholesterol [13]. Hesperidin, another effective constituent of *C. reticulatae pericarpium*, has been shown to play an antioxidant role in atherosclerotic rabbits [14]. Therefore, we expect Huxin Formula, which is a combination of the above cardioprotective herbs, to have beneficial effects in patients having undergone CABG.

Our earlier clinical study of Huxin Formula in 55 patients after CABG showed that Huxin Formula improves the recovery process of patients after CABG, significantly relieves symptoms, and improves heart function and quality of life [15]. However, we were not fully satisfied with the results because of the small sample size and poor study design. Therefore, a multicenter, double-blind, randomized, placebo-controlled clinical trial was designed to evaluate the efficacy and safety of Huxin Formula in patients after undergoing CABG.

Patients and Methods

Subjects

Participants were screened by investigators from 10 first-rate domestic hospitals in China, including Guangdong Provincial Hospital of Chinese Medicine, Guangdong General Hospital, Xinjiang Hospital of Chinese Medicine, Fujian Provincial Hospital, Xinjiang Provincial Hospital, The Fifth Affiliated Hospital of Xinjiang University of Medical Science, Shanxi Provincial People's Hospital, Gansu Provincial Hospital, Hainan Provincial Hospital, and Sun Yat-sen Hospital for Cardiovascular Disease in Shenzhen. The study was conducted between April 2008 and December 2010. Patients were assessed according to ESC 2006 Guidelines for Management of Patients with Stable Angina and ACC/AHA 2005 Guidelines for Management of Patients with Unstable Angina/Non-ST-Elevation Myocardial Infarction. The inclusion and exclusion criteria are shown in table 1. Patients were free to withdraw from the study at any time. Potential participants who were interested in the study received a comprehensive explanation of the protocol and signed a consent form.

Table 1. Inclusion and exclusion criteria

Inclusion criteria

- (1) Age 40–75 years without gender limitation.
- (2) Patients who met the diagnostic criteria of angina or myocardial infarction.
- (3) Patients who were diagnosed as ‘deficiency of heart-QI and phlegm stasis-bizu’ according to traditional Chinese medicine.
- (4) Patients who underwent coronary artery bypass grafting (CABG) and drainage tubes were drawn 1 week after the surgery.

Exclusion criteria

- (1) Patients with acute myocardial infarction or severe heart failure (cardiac function class IV according to the cardiac function standard of the New York Heart Association and the left ventricular ejection fraction $\leq 30\%$ by heart color Doppler).
- (2) Patients with acute myocardial infarction combined with ventricular aneurysm within 2 weeks.
- (3) Patients with severe liver and kidney dysfunction (serum alanine aminotransferase > 3 times the normal cap and/or plasma creatinine ≥ 442 $\mu\text{mol/l}$).
- (4) Patients with cancer or active gastrointestinal bleeding.
- (5) Patients also scheduled for valve surgery or transmyocardial laser revascularization.
- (6) Patients with mental illness.
- (7) Patients who were pregnant or breast-feeding.

Symptom	All the time	Most of the time	Some times	rarely	never
1. Chest pain	1	2	3	4	5
2. Chest tightness	1	2	3	4	5
3. Shortness of breath	1	2	3	4	5
4. Palpitation	1	2	3	4	5
5. Tired	1	2	3	4	5
6. Vertigo	1	2	3	4	5
7. Eating less	1	2	3	4	5
8. Insomnia	1	2	3	4	5
Activity restriction caused by CHD and angina during the pass four weeks	Seriously restricted	Largely restricted	Moderately restricted	Rarely restricted	unrestricted
9. heavy physical activity (running, lifting heavy weight, strenuous exercise, swimming or tennis)	1	2	3	4	5
10. walking up one stair	1	2	3	4	5
11. jogging	1	2	3	4	5
12. Moderate activity	1	2	3	4	5
13. sex life	1	2	3	4	5
Mental health during the pass four weeks	All the time	Most of the time	Some times	rarely	never
14. I'm nervous	1	2	3	4	5
15. I'm energetic	5	4	3	2	1
16. I'm down in spirits	1	2	3	4	5
17. I'm worried about my illness	1	2	3	4	5
18. I'm afraid about angina attack and death	1	2	3	4	5
Family and Social support	Seriously influenced	Largely influenced	Moderately influenced	Rarely influenced	Not influenced
19. Have influence in the normal social activity with family members, friends, neighbours or colleague	1	2	3	4	5
20. Have influence in my position and function in family and organization	1	2	3	4	5
21. Have influence in my communication with other patients about the experience, knowledge and problem of CHD	1	2	3	4	5

Fig. 1. Scale of Life Quality in Integrative Medicine for CAD (final score = sums of each score / total score (105) × 100%).

Ethical approval for the study was granted by the Ethics Committee of Guangzhou University of Chinese Medicine.

Design, Randomization, and Allocation

A double-blind, randomized, controlled clinical trial was conducted using stratified randomization. Eligible participants after CABG were randomly assigned to 2 groups: a treatment group in which participants received conventional treatment and Huxin Formula, and a control group in which participants received conventional treatment and placebo. Randomized codes were generated with SAS 6.12 (SAS Institute, Cary, NC, USA). Eligible patients at each center were assigned randomization numbers from the Institute of Basic Medical and Clinical Sciences of the China Academy of Chinese Medical Sciences which was responsible for the randomization of this research and was external to the trial. Participants and investigators were masked to group assignments. The prepared drugs were dispensed in similar-looking bags, and the nature of

the drug was concealed by the providers. The random allocation sequence was concealed until data collection for the entire study was completed.

Treatment Protocols

Patients in both groups accepted standard Western medicine treatment according to 2005 AHA guideline for CABG. Patients in the treatment group were provided with Huxin Formula which was prepared by Jiangyin Pharmaceutical Co., Ltd. (Jiangsu, China) using the aforementioned herbs. Patients in the control group were given placebo granules prepared by the same supplier, which taste, smell, and look similar to Huxin Formula; ingredients included amylum, bitter principle, and excipient amongst others. 10 g of Huxin Formula or placebo was dissolved in 300 ml of boiled water, cooled to 70 °C, and given once a day. Treatment started 1 week after CABG and lasted for 6 months (180 days). Patients were followed up for another 6 months (180 days).

Fig. 2. Flow chart of participants.

Outcomes

Baseline data, including sex, age, personal history, medical history, family history of cardiovascular disease, classification of cardiac function, and clinical classification of coronary heart disease were assessed. Main cardiovascular events (death, nonfatal myocardial infarction, repeat revascularization, and readmission) were also observed and recorded as main outcomes. We assessed secondary outcomes using 2 scales: i) Seattle Angina Questionnaire (SAQ), and ii) Scale of Life Quality in Integrative Medicine for Coronary Artery Disease. SAQ is the most commonly used instrument to capture comprehensive and sensitive changes in quality of life of cardiac patients [16]. The Scale of Life Quality in Integrative Medicine for Coronary Artery Disease, which was established for the first time, is scored by the sum of each score / total score(105) $\times$ 100% (fig. 1). The main outcomes were assessed 360 days after treatment, and secondary outcomes were assessed at 0, 90, 180, 270, and 360 days after treatment.

Safety Monitoring

To assess the safety of the 6-month treatment, routine blood tests, liver function tests and renal function tests were conducted before randomization, 90 days and 180 days after treatment. During the trial, adverse events were observed and recorded using case report forms. The date (beginning and end), severity (mild, moderate, severe, life-threatening), probability of adverse events associated with the drug (certain, probable, doubtful, impossible), drug administration modifications due to adverse events (continuation, dose reduction, permanent withdrawal, temporary discontinuation), and outcome (disappearance of symptoms, symptom relief, symptoms unchanged, symptoms worsening and causing death) were recorded in detail.

Statistical Analysis

A sample size calculation based on the standard deviation (SD) value of 12.06 from previous studies determined that 222 patients were needed to establish a mean difference in SAQ score of 4.86 between both groups (power 0.85, significance level 0.05). With an estimated 15% dropout rate, we set the total sample size at 260.

Statistical analysis sets included intention-to-treat (ITT), per-protocol (PP), and safety analysis sets. Descriptive analysis and inferential analysis of clinical features before and after treatment comprised the following:

For measurement data, functional indices are presented as mean $\pm$ SD. Paired t tests and Student t tests were used to compare small sample data (including 95% confidence interval) for each group before and after treatment. A rank-sum test (Wilcoxon test) was used for non-normal distribution or heterogeneity of variance. Analysis of covariance or stratified analysis was used when the baseline was not neat.

For enumeration data, the constituent ratio and rate of each index were calculated. Two-group comparisons were performed using the four-fold table test (or accurate probability method) for the total effective rate and the 2 $\times$ c table test for the constituent ratio.

For ranked data, two-group comparisons were performed using Mann-Whitney test.

For life quality analysis, the general descriptive analyses are presented as mean $\pm$ SD, maximum, minimum, and median.

For center effect analysis, two-group comparisons were performed using covariance analysis for measurement data and Cochran-Mantel-Haenszel test for enumeration data.

Logistic regression analysis was used to analyze factors that may affect the assessment of curative effect, including age, duration, classification of coronary heart disease, survival quality assessment scale of integrated traditional Chinese and Western medicine, CABG performer, and center.

The Kaplan-Meier method was used to compare cardiovascular event rates and median time. Factors influencing cardiovascular events were analyzed using Cox regression analysis.

The baseline comparison test level was $\alpha = 0.10$, the two-group effects comparison test level was $\alpha = 0.05$.

Safety Analysis

Safety analysis of each case was mainly performed as descriptive statistics, including incidence and description of adverse events (such as gas-

Table 2. Baseline clinical data

	Control group (n = 121)	Treatment group (n = 128)	p
Age ($\bar{x} \pm s$), years	60.79 $\pm$ 7.23	60.41 $\pm$ 8.04	0.70
Sex			0.87
Male	103 (85.1)	108 (84.4)	
Female	18 (14.9)	20 (15.6)	
Height ($\bar{x} \pm s$), cm	166.58 $\pm$ 6.93	165.68 $\pm$ 7.22	0.32
Weight ($\bar{x} \pm s$), kg	67.19 $\pm$ 11.41	66.03 $\pm$ 10.91	0.41
Respiratory rate ($\bar{x} \pm s$), breaths/min	19.75 $\pm$ 1.02	19.56 $\pm$ 1.42	0.23
Heart rate ($\bar{x} \pm s$), bpm	75.99 $\pm$ 11.39	76.75 $\pm$ 8.99	0.56
SBP ($\bar{x} \pm s$), mm Hg	130.18 $\pm$ 17.55	129.91 $\pm$ 18.10	0.91
DBP ($\bar{x} \pm s$), mm Hg	77.36 $\pm$ 10.40	77.60 $\pm$ 10.10	0.56
Comorbidities, n (%)			
Dyslipidemia	30 (24.8)	33 (25.8)	0.86
Hypertension	76 (62.8)	66 (51.6)	0.07
Diabetes	33 (27.3)	32 (25.0)	0.68
Stroke	7 (5.8)	8 (6.3)	0.88
Heart failure	14 (11.6)	6 (4.7)	0.05
Gastrointestinal disorder	17 (14.0)	7 (5.5)	0.02
Arrhythmia	5 (4.1)	5 (3.9)	0.93
Medical history, n (%)			
Smoking	58 (47.9)	69 (53.9)	0.35
Drinking	23 (19.0)	29 (22.7)	0.48
Family history of CVD	15 (12.4)	21 (16.4)	0.37
Allergy	10 (8.3)	7 (5.5)	0.38
Clinical classification of CHD, n (%)			0.62
Stable angina	46 (38.0)	42 (32.8)	
Unstable angina	59 (48.8)	65 (50.8)	
Myocardial infarction	16 (13.2)	21 (16.4)	
Cardiac function class, n (%)			0.11
I	24 (19.8)	32 (25.0)	
II	47 (38.8)	51 (39.8)	
III	50 (41.3)	41 (32.0)	
IV	0 (0.0)	4 (3.1)	

SBP = Systolic blood pressure; DBP = diastolic blood pressure; CVD = cardiovascular disease; CHD = coronary heart disease.

gastrointestinal reaction, urticaria, eczema, and dizziness), changes in laboratory testing results before and after the test, and relationships between abnormal changes and investigational drugs.

Results

A total of 270 patients treated with CABG were included in this study. 21 patients were eliminated, and 25 patients were excluded after 360 days. The flow of participants in the study is summarized in figure 2.

General characteristics of the patients are shown in table 2. Comparisons of baseline data between the 2 groups were performed using chi-square tests for demographic data (sex, ethnicity, and culture), general health (height, pulse, respiration, heart rate, and systolic and diastolic blood pressure), personal history (history of smoking, drinking, allergies, and family history of cardiovascular disease), medical history (dyslipidemia,

high blood pressure, diabetes, stroke, heart failure, and arrhythmia), classification of cardiac function, and clinical classification of coronary heart disease (unstable angina, myocardial infarction). There were no significant deviations ($p > 0.05$) between the 2 groups except for heart failure (14 vs. 6) and gastrointestinal disorder (17 vs. 7).

There were no significant differences ($p > 0.05$) between the control group and the treatment group on major end-points 360 days after treatment (table 3) for mortality, number of patients with nonfatal myocardial infarction, proportion of further revascularization, and re-hospitalization caused by cardiovascular events.

There were no significant differences ($p > 0.05$) between the control group and the treatment group on secondary outcomes at all time points after CABG for angina scale (attack frequency, time duration, pain intensity, nitroglycerin dose), SAQ (dimension of physical activity limitation, angina pecto-

Table 3. Major end points at 360 days

Events		Control group (n = 109)	Treatment group (n = 115)	Chi ²	p
Death, n (%)	yes	0 (0.0)	0 (0.0)	–	–
	no	109 (100.0)	115 (100.0)		
Nonfatal myocardial infarction, n (%)	yes	0 (0.0)	0 (0.0)	–	–
	no	109 (100.0)	115 (100.0)		
Repeat revascularization, n (%)	yes	0 (0.0)	0 (0.0)	–	–
	no	109 (100.0)	115 (100.0)		
Readmission, n (%)	yes	0 (0.0)	0 (0.0)	–	–
	no	109 (100.0)	115 (100.0)		

Table 4. Frequency of angina pectoris attacks in patients with cardiac function class II (PP analysis)

Time	Group	Patients, n	$\chi \pm s$	M	P ₂₅ –P ₇₅	Z	p
0 days	control group	47	2.64 ± 1.67	2.00	2.00, 4.00	–1.07	0.286
	treatment group	51	2.25 ± 1.63	2.00	2.00, 4.00		
90 days	control group	47	1.36 ± 0.94	2.00	0.00, 2.00	–1.95	0.050 ^a
	treatment group	51	0.96 ± 1.01	0.00	0.00, 2.00		
180 days	control group	47	0.68 ± 0.96	0.00	0.00, 2.00	–0.54	0.59
	treatment group	51	0.79 ± 0.99	0.00	0.00, 2.00		
270 days	control group	47	0.05 ± 0.30	0.00	0.00, 0.00	–1.04	0.30
	treatment group	51	0.00	0.00	0.00, 0.00		
360 days	control group	47	0.05 ± 0.30	0.00	0.00, 0.00	–1.04	0.30
	treatment group	51	0.00	0.00	0.00, 0.00		

^aSignificantly different versus control group (p < 0.05).**Table 5.** Scores of angina pectoris in patients with cardiac function class II (PP analysis)

Time	Group	Patients, n	$\chi \pm s$	M	P ₂₅ –P ₇₅	Z	p
0 days	control group	47	9.45 ± 4.63	9.00	6.00, 12.00	–0.39	0.70
	treatment group	51	9.17 ± 5.71	9.00	6.00, 12.00		
90 days	control group	47	5.45 ± 3.59	8.00	0.00, 8.00	–2.00	0.045 ^a
	treatment group	51	3.88 ± 3.86	4.00	0.00, 8.00		
180 days	control group	47	2.86 ± 3.72	0.00	0.00, 8.00	–0.29	0.77
	treatment group	51	3.13 ± 3.78	0.00	0.00, 8.00		
270 days	control group	47	0.18 ± 1.21	0.00	0.00, 0.00	–0.90	0.37
	treatment group	51	0.21 ± 0.85	0.00	0.00, 0.00		
360 days	control group	47	0.18 ± 1.21	0.00	0.00, 0.00	–1.23	0.22
	treatment group	51	0.33 ± 1.12	0.00	0.00, 0.00		

^aSignificantly different versus control group (p < 0.05).**Table 6.** Classification of cardiac function in patients with 3 coronary vessel lesions (PP analysis)

Time	Group	Patients, n	$\chi \pm s$	M	P ₂₅ –P ₇₅	Z	p
0 days	control group	83	2.19 ± 0.76	2.00	2.00, 3.00	–1.36	0.17
	treatment group	89	2.02 ± 0.76	2.00	1.00, 3.00		
90 days	control group	83	1.31 ± 0.54	1.00	1.00, 2.00	–1.58	0.12
	treatment group	89	1.19 ± 0.39	1.00	1.00, 1.00		
180 days	control group	83	1.22 ± 0.44	1.00	1.00, 1.00	–1.65	0.10
	treatment group	89	1.11 ± 0.31	1.00	1.00, 1.00		
270 days	control group	83	1.17 ± 0.41	1.00	1.00, 1.00	–1.85	0.07
	treatment group	89	1.07 ± 0.26	1.00	1.00, 1.00		
360 days	control group	83	1.14 ± 0.35	1.00	1.00, 1.00	–2.15	0.03 ^a
	treatment group	89	1.05 ± 0.21	1.00	1.00, 1.00		

^aSignificantly different versus control group (p < 0.05).

ris stable state, heart attacks, disease knowledge, and treatment satisfaction) and the quality of life scale of integrative medicine.

As shown in tables 4 and 5, according to the CABG PP population and stratified analysis of cardiac function before treatment, patients with cardiac function class II (according to the New York Heart Association (NYHA) Functional Classification) in the treatment group had a lower frequency of angina pectoris attacks (0.96 ± 1.01 vs. 1.36 ± 0.94) and a significantly lower angina pectoris score (3.88 ± 3.86 vs. 5.45 ± 3.59) after 90 days than the control group ($p = 0.05$ and $p < 0.05$, respectively). There were no significant deviations ($p > 0.05$) between the 2 groups at the other 4 time points.

As shown in table 6, according to the CABG PP population and stratified analysis of the number of pathological coronary vessels before treatment, patients in the control group with 3 coronary vessel lesions had a significantly higher cardiac function grade (1.14 ± 0.35 vs. 1.05 ± 0.21) after 360 days than patients in the treatment group ($p < 0.05$). There were no significant deviations ($p > 0.05$) between the 2 groups at the other 4 time points.

The incidence of adverse events and specific events, such as gastrointestinal reactions, urticaria, eczema and dizziness, in the treatment group was similar to the control group. No obvious adverse reactions were found with the use of Huxin Formula.

Discussion

Coronary heart disease is one of the leading causes of death around the world. Currently, main treatments of coronary heart disease include: i) conventional medicine including nitrates, beta blockers, calcium channel blockers, and antiplatelet/anticoagulant therapy; ii) interventions such as percutaneous coronary artery lumen balloon angioplasty or coronary artery stent placement; and iii) surgery such as CABG.

For a large number of patients with coronary heart disease, CABG remains the preferred strategy for coronary revascularization [17–19]. However, over the last 10 years, the number of high-risk patients undergoing CABG surgery has increased significantly, resulting in worse clinical outcomes, which appears to be related to the ageing population, increased complications (such as diabetes, obesity, hypertension, stroke), and accompanying valve diseases [20]. Developmental advancements of percutaneous coronary intervention are also responsible for more complicated coronary artery diseases in patients undergoing CABG. Moreover, CABG itself causes physical trauma in patients and entails a lengthy recovery, and some patients do not survive the surgery. Extracorporeal circulation during the surgery may also cause many side effects and complications. In an early study, 33% of CABG patients were re-hospitalized within the first 2 years after surgery, with the most common reasons for re-admission being acute myocardial infarction, arrhythmia, and angina [21]. Restenosis and myocar-

dial infarction after CABG not only increase medical costs but also affect long-term survival [22].

In addition, studies have shown that a significant proportion of CABG patients experience psychological difficulties post-surgery, which is seen especially in elderly patients [23, 24]. Undergoing CABG surgery appears to place physiological, psychological, and social strain on these patients, and may ultimately influence their quality of life.

According to the 2011 ACCF/AHA guidelines for CABG [25], postoperative antiplatelet therapy using Aspirin or clopidogrel is recommended. The treatment can reduce cardiovascular events (death, myocardial infarction, stroke, renal failure, and bowel infarction, etc.) [26] but does not significantly relieve symptoms and improve quality of life.

Huxin Formula is a modified version of a Chinese medicine formula created by Prof. Deng Tie-tao, a well-known traditional Chinese medicine practitioner, and has been widely used in clinical practice because of its marked effects on coronary heart disease. Huxin Formula mainly consists of ginseng, *P. pseudoginseng*, *P. ternate*, *Citri reticulatae pericarpium*. The pharmacological effects of these agents on cardiovascular diseases have been reported in a growing number of studies, especially for active ingredients such as ginsenosides [27, 28] and notoginsenosides [29–31].

Our earlier clinical study of Huxin Formula in 55 patients after CABG showed that Huxin Formula improves the recovery process of patients after CABG, significantly relieves symptoms, and improves heart function and quality of life [15]. However, we were not fully satisfied with the results because of limitations such as the small sample size and use of a single center. Therefore, the present study was designed to overcome these deficiencies. The results of this study showed that Huxin Formula may relieve symptom of patients with cardiac function class II, but no advantage was seen for primary outcomes compared to placebo.

Improved heart function is a major goal for most patients undergoing CABG. Angina and dyspnea symptom relief, level of physical activity, and complications after surgery were investigated when assessing physical functioning [32, 33]. The 3 main complications after CABG are myocardial infarction, heart failure, and atrial fibrillation [34]. In general, patients with more serious vascular lesions are more susceptible to cardiac dysfunction. Therefore, improving cardiac function as soon as possible after CABG is crucial to the prognosis of patients. In the present research, we found that in patients with 3 coronary vessel lesions, classification of cardiac function after 360 days was significantly higher in the control group compared to the treatment group ($p < 0.05$). The results showed that Huxin Formula may ameliorate cardiac function in patients after CABG, especially in those with more serious vascular lesions.

There are 2 limitations to this study, which may have caused the negative results for primary and secondary outcomes: i) The short intervention period: patients were treated with Huxin Formula for 180 days after CABG, but since coro-

nary heart disease is a chronic disease which takes a relatively long time to treat, 180 days may not be long enough; ii) The short follow-up period: patients were followed up for 360 days after treatment with Huxin Formula, which may not have been long enough to see the overall effect on major endpoints such as mortality, number of patients with nonfatal myocardial infarction, proportion of further revascularization, and re-hospitalization caused by cardiovascular events.

Conclusion

The results of this study show that Huxin Formula is safe for use in the clinical treatment of patients having undergone CABG. It may improve the cardiac function of patients with 3 coronary vessel lesions and relieve symptoms of patients with cardiac function class II but failed to show superiority in primary outcomes. The relatively short intervention period and follow-up duration limits the generalizability of the results.

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Acknowledgement

This work was supported by the National Key Technology Research and Development Program of China (No. 2006BAI04A01). Trial Registration: ClinicalTrials.gov Identifier: NCT00965471.

The authors thank Dr. Ruobing Wu of Guangdong General Hospital, Dr. Wei Gao of Xinjiang Hospital of Chinese Medicine, Dr. Tao Han of Fujian Provincial Hospital, Dr. Jinshan Ma of Xinjiang Uygur Autonomous Region People's Hospital, Dr. Zhanshe Hao of Shanxi Provincial People's Hospital, Dr. Tao You of Gansu Provincial Hospital, Dr. Chaoguang Wu of Hainan Provincial Hospital, and Dr. Jian'an Yang of Sun Yat-sen Hospital for Cardiovascular Disease, Shenzhen for participating in this trial.

Disclosure Statement

The authors declare no conflict of interest.

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