

## **Curative effect of Yiqi Huoxue Tongmai decoction on in-stent restenosis after percutaneous coronary intervention in coronary heart disease.**

Guofang Dai<sup>1</sup>, Jinying Zhang<sup>2\*</sup>

<sup>1</sup>Department of Cardiology, the First Hospital of Traditional Chinese Medicine of Luoyang, Luoyang, PR China

<sup>2</sup>Department of Cardiology, the First Affiliated Hospital of Zhengzhou University, Zhengzhou, PR China

### **Abstract**

**This study aimed to investigate the curative effect of Yiqi Huoxue Tongmai decoction on In-Stent Restenosis (ISR) after Percutaneous Coronary Intervention (PCI) in Coronary Heart Disease (CHD). 95 cases of patients with ISR after PCI due to CHD were randomly divided into control group (46 cases) and Traditional Chinese Medicine (TCM) group (49 cases) who received conventional Western medicine therapy and therapy with Yiqi Huoxue Tongmai decoction based on conventional Western medicine therapy, respectively. After 12 months of treatment, the clinical efficacy, symptom scores, Electrocardiogram (ECG), coronary angiography, biochemical indexes in two groups were observed. Results showed that, the total clinical effective rate and total effective rate by ECG in TCM group were significantly higher than control group ( $P<0.05$ ). After treatment, the scores of chest pain, chest tightness, fatigue and dry mouth in TCM group were significantly lower than control group, respectively ( $P<0.05$ ); the ISR rate in TCM group was significantly lower than control group ( $P<0.05$ ); the blood lipid levels in TCM group were also significantly lower than those in control group ( $P<0.05$ ). Yiqi Huoxue Tongmai decoction has obvious curative effect on ISR after PCI in CHD patients, with no obvious adverse side effect.**

**Keywords:** Yiqi Huoxue Tongmai decoction, Coronary heart disease, Percutaneous coronary intervention, Restenosis.

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### **Introduction**

Coronary Heart Disease (CHD) is an important disease threatening human health. In addition to drug therapy and coronary artery bypass surgery, Percutaneous Coronary Intervention (PCI) is important tool for the treatment of this disease [1]. With the application of a large number of stents, the In-Stent Restenosis (ISR) has caused more and more attention [2]. With the development of medical science and clinical practice of continuous improvement, new methods and means can be discovered to further reduce the ISR for the treatment of CHD [3,4]. Traditional Chinese Medicine (TCM) believes that, the ISR after PCI belongs to stasis syndrome category, and the coronary interventional therapy is an exogenous trauma from a medical view [5]. The patients with ISR after PCI have clinical manifestations with common signs of blood stasis such as recurrent angina, dark or puckery tongue and stuffy pain with increased integral values of blood stasis [6,7]. Whether the appropriate interventions by TCM can reduce the rate of ISR after PCI, as well as improve the quality of life of CHD patients is a hotspot in present researches. This study investigated the curative effect of TCM Yiqi Huoxue Tongmai decoction on the ISR after PCI in CHD patients. The objective was to provide a basis for further application of this TCM decoction to treatment of CHD.

### **Materials and Methods**

#### ***Subjects***

Ninety-five patients with ISR after PCI due to CHD in Department of Cardiology, the First Hospital of Traditional Chinese Medicine of Luoyang (Luoyang, China) from July 2011 to June 2015 were enrolled in this study. They were divided into TCM group (49 cases) and control group (46 cases), which received ISR treatment using TCM and Western medicine, respectively. This study was conducted with approval from the Ethics Committee of the First Hospital of Traditional Chinese Medicine of Luoyang. Written informed consent was obtained from all participants.

#### ***Diagnostic criteria***

Western diagnosis was performed in accordance with the nomenclature and diagnostic criteria of the ischemic heart disease from the union group of International Society of Cardiology and the Society and the World Health Organization, as well as the revised CHD diagnostic reference standard of National Integrative prevention of angina pectoris and cardiac arrhythmia research symposium in 1979. TCM standard was based on the TCM diagnostic standards of CHD reference

developed by China Association of Integrative Medicine Cardiovascular Society in October, 1990. The blood stasis due to Qi deficiency syndrome had manifestations such as worsened when tired, shortness of breath, fatigue, spontaneous sweating, palpitations, chest pain, pain in specific place, big fat tongue, teeth marks, petechiae or ecchymosis and weak wiry pulse.

### ***Inclusion criteria***

Patients with blood stasis due to Qi deficiency were diagnosed by coronary angiography for coronary artery disease underwent PCI; the age was 45-75 years old.

### ***Exclusion criteria***

Patients were combined with severe primary disease such as severe cardiopulmonary dysfunction, severe arrhythmia and liver and kidney systems; patients were combined with other serious diseases impacting quality of life or seriously affect the survey for quality of life, such as rheumatoid arthritis, stroke, Alzheimer's disease and mentally illness, pregnant or lactating women; patients were with the efficacy or safety judgments affected by not meet the inclusion criteria, without performing specified medication; patients were unable to determine the efficacy or incomplete information; patients did not undergo PCI; patients with CHD chose other treatment options.

### ***Treatment***

Patients in control group were treated by conventional therapy after PCI by Western medicine (such as anticoagulant, anti-platelet aggregation, lipid adjustment) for 12 months. Conventional medicine therapy after PCI was primarily 75 mg of Clopidogrel (Plavix) (oral administration, once a day; Sanofi Pharmaceutical Co., Hangzhou, China), 100 mg of bayaspirin (oral administration, once a day; Beijing, China, Bayer Health Care), 20 mg of atorvastatin (Lipitor) (oral administration, once a day; Pfizer, Dalian, China). Symptomatic treatment under different circumstance were performed to patients associated with other diseases (not affecting the judgment for quality of life), such as antihypertensive drugs or hypoglycemic agents treatment for patients associated with hypertension or diabetes.

In TCM groups, based on the conventional treatment after PCI in Western medicine (such as anticoagulant, anti-platelet aggregation, lipid adjustment), Yiqi Huoxue Tongmai decoction was used, 250 ml for each time, and 2 times a day. The ingredients of Yiqi Huoxue Tongmai decoction were as follows: Astragalus, 30 g; *Polygonatum sibiricum*, 15 g; Atractylodes, 12 g; angelica, 12 g; walnuts, 10 g; safflower, 15 g; Salvia, 15 g; leech, 6 g; Typhae, 12 g; *Daemonorops draco* Bl, 1.5 g; *Citrus aurantium*, 12 g; licorice, 6 g. Subtraction or addition was performed on the medicine dose with the disease condition, the treatment course was 12 months.

### ***Determination of efficacy***

Clinical symptoms, Electrocardiogram (ECG), coronary angiography of the TCM group and the control group after 12 months were taken as the efficacy criteria. The efficacy determination criteria referred to "New Chinese medicine clinical research guidelines" [8] to primarily assess the situation changes of the clinical symptoms, ECG and coronary angiography. Marked: clinical symptoms disappeared; resting ECG showed corrected myocardial ischemia. Effective: part of clinical symptoms disappeared or reduced; and the electrocardiogram showed a significant improvement in myocardial ischemia. Invalid: no improvement in the condition, electrocardiogram showed no improvement. Coronary angiography after PCI showed vascular restenosis with the definition of residual stenosis after interventional treatment < 50%, and the follow-up coronary angiography showing luminal diameter stenosis  $\geq$  50%.

### ***Detection of biochemical indexes***

Before and after treatment, the routine blood, urine and stool indexes, blood lipid indexes including Total Cholesterol (TC), Triglyceride (TG), High Density Lipoprotein Cholesterol (HDL-C), Low Density Lipoprotein Cholesterol (LDL-C), renal function indexes including indexes Blood Urea Nitrogen (BUN) Creatinine (Cr) and myocardial enzyme indexes including Creatine Kinase (CK) and CK-MB were detected using PUZS-300 automatic biochemical analyser (Perlong Medical Equipment Co., Ltd., Beijing, China).

### ***Statistical analysis***

All statistical analysis was carried out using SPSS17.0 software (SPSS Inc., Chicago, IL, USA). Measurement data were presented as mean  $\pm$  SD. The comparison before and after treatment was carried out using paired t test, while comparison between groups using two independent samples t test. Categorical data were analysed using  $\chi^2$  test, and the distribution between independent samples using independent samples nonparametric test.  $P < 0.05$  was considered that the differences had statistically significance.

## **Results**

### ***General data of patients two groups***

General data of patient's two groups were shown in Table 1. There was no significant difference of age, gender, disease duration, risk factor, angina pectoris, myocardial infarction, coronary stenosis degree of or residual stenosis after PCI between TCM and control group ( $P > 0.05$ ). The two groups were comparable.

### ***Comparison of clinical efficacy between two groups***

As shown in Table 2, in TCM group, there were 31, 14 and 4 cases in which the treatment was markedly effective, effective and ineffective, respectively. In control group there were 21, 13

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and 12 cases in which the treatment was markedly effective, effective and ineffective, respectively. The total effective rate in TCM group was 91.84%, which was significantly higher than that in 73.91% in control group ( $P<0.05$ ).

**Comparison of efficacy by ECG between two groups**

In TCM group, there were 30, 13 and 6 cases in which the treatment was markedly effective, effective and ineffective by ECG, respectively. In control group there were 20, 12 and 14 cases in which the treatment was markedly effective, effective and ineffective by ECG, respectively. The total effective rate by ECG in TCM group was 87.76%, which was significantly higher than that in 69.56% in control group ( $P<0.05$ ) (Table 3).

**Comparison of symptom score improvement between two groups**

In TCM group, the scores of chest pain, chest tightness, breath shortness, fatigue and dry mouth after treatment were significantly lower than those before treatment, respectively ( $P<0.05$ ). In control group, the scores of chest pain and chest tightness after treatment were also significantly lower than those before treatment, respectively ( $P<0.05$ ). In addition, after treatment, the scores of chest pain, chest tightness, fatigue and dry mouth in TCM group were also significantly lower than those in control group, respectively ( $P<0.05$ ) (Table 4).

**Comparison of coronary angiography outcome between two groups**

After treatment, there were 1 (2.04%) and 6 (13.04%) cases with restenosis in TCM and control group, respectively. There was significantly difference between two groups ( $P<0.05$ ).

**Table 1.** General data of patients in two groups.

Parameter	TCM group (n=49)	Control group (n=46)	P
Age (years)	61.2 ± 6.3	63.8 ± 5.9	<0.05
Gender (male, n)	28	26	<0.05
Disease duration (years)	4.6 ± 2.1	4.7 ± 1.6	<0.05
Risk factor (n)			<0.05
Smoking	19	17	
Hypertension	22	21	
Diabetes	15	14	
Dyslipidemia	21	20	
Family history	15	13	
Stable angina pectoris (n)	9	7	<0.05
Unstable angina pectoris (n)	22	18	<0.05
Acute myocardial infarction (n)	3	3	<0.05
Old myocardial infarction (n)	5	3	<0.05

**Comparison of blood lipid levels between two groups**

In two groups, the blood TC, TG and LDL-C levels after treatment were significantly lower than those before treatment, respectively ( $P<0.05$ ), and the blood HDL-C level after treatment was significantly higher than that before treatment ( $P<0.05$ ). In addition, after treatment, the blood TC, TG and LDL-C levels in TCM group were also significantly lower than those in control group, respectively ( $P<0.05$ ) (Table 5).

**Effects of treatment on the biochemical indexes of patients**

In TCM group, the routine blood, urine, and stool indexes, liver function indexes (AST and ALT), renal function indexes (BUN, Cr), myocardial enzyme indexes (CK and CK-MB) were all normal before and after treatment. In control group, 2 cases were with increased AST and levels at the 3 month during the treatment course. They turned to normal after liver-protection treatment.

**Adverse cardiovascular events**

Patients in two groups were followed up 3 months to observe the incidence of adverse cardiovascular events including revascularization, coronary artery bypass grafting, fatal or nonfatal myocardial infarction, heart failure, etc. There was no case of death or acute myocardial infarction in each group. In control group, 2 cases received the second PCI due to angina pectoris aggravation.

Coronary stenosis degree (%)	79.34 ± 10.33	81.03 ± 9.56	<0.05
Residual stenosis after PCI (%)	7.67 ± 3.18	8.02 ± 4.34	<0.05

PCI: Percutaneous Coronary Intervention.

**Table 2.** Comparison of clinical efficacy between two groups.

Group	n	Markedly effective (n)	Effective (n)	Ineffective (n)	Total effective rate (%)	$\chi^2$	P
TCM	49	31	14	4	91.84	5.442	0.02
Control	46	21	13	12	73.91		

**Table 3.** Comparison of efficacy by ECG between two groups.

Group	n	Markedly effective (n)	Effective (n)	Ineffective (n)	Total effective rate (%)	$\chi^2$	P
TCM	49	30	13	6	87.76	4.723	0.030
Control	46	20	12	14	69.56		

**Table 4.** Comparison of symptom score improvement between two groups (points).

Group	n		Chest pain	Chest tightness	Breath shortness	Fatigue	Dry mouth
TCM	49	Before	3.45 ± 0.56	3.90 ± 0.71	4.12 ± 1.53	4.21 ± 1.06	3.51 ± 0.92
		After	1.05 ± 0.42 <sup>#</sup>	1.45 ± 0.52 <sup>*</sup>	1.44 ± 0.54 <sup>#</sup>	1.65 ± 0.49 <sup>#</sup>	1.52 ± 0.76 <sup>#</sup>
Control	46	Before	3.87 ± 0.74	3.78 ± 0.65	4.15 ± 1.28	3.96 ± 0.93	3.45 ± 0.92
		After	2.12 ± 0.57 <sup>*</sup>	1.75 ± 0.96 <sup>*</sup>	3.92 ± 0.97	3.72 ± 0.84	2.99 ± 0.64

\*P<0.05 compared with before treatment; #P<0.05 compared with control group.

**Table 5.** Comparison of blood lipid levels between two groups.

Group	n		TC	TG	HDL-C	LDL-C
TCM	49	Before	5.33 ± 1.59	2.80 ± 0.42	0.92 ± 0.48	3.56 ± 0.91
		After	4.52 ± 1.44 <sup>#</sup>	1.78 ± 0.47 <sup>#</sup>	1.34 ± 0.43 <sup>*</sup>	2.33 ± 0.65 <sup>#</sup>
Control	46	Before	5.32 ± 1.72	3.10 ± 0.72	0.95 ± 0.33	3.41 ± 0.82
		After	4.71 ± 1.56 <sup>*</sup>	2.32 ± 0.91 <sup>*</sup>	1.22 ± 0.37 <sup>*</sup>	2.73 ± 0.72 <sup>*</sup>

\*P<0.05 compared with before treatment; #P<0.05 compared with control group. TC: Total Cholesterol; TG: Triglyceride; HDL-C: High Density Lipoprotein Cholesterol; LDL-C: Low Density Lipoprotein Cholesterol.

## Discussion

CHD is one of the major diseases threatening the human health. With the improvement of eating habits and changes of people's living standards, this disease has become a major cause of death in China. Currently, drug therapy, PCI and coronary artery bypass grafting have become the three main treatments for CHD [1,9,10]. The indications for PCI continue to widen, and the success rate of interventional treatment for complex lesions is continuously improved. PCI has become one of the important means of CHD blood supply. Coronary artery PCI is more and more widely clinically used on the basis of its immediately generated noticeable effect. However, the

use of new technology also brings us new challenges, such as the high ISR rate after PCI [11]. According to data, it is indicated that the ISR rate after transluminal coronary artery balloon angioplasty (PTCA) reaches up to 50%, while 20%-30% is after bare metal stent implantation, and still 5%-10% is after drug-eluting stent implantation [12-14]. Some patients undergo PCI revascularization, but the myocardial revascularization has the limitations of no-reflow, ventricular remodeling, ISR, myocardial injury, myocardial stunning and ischemia-reperfusion injury, of which the Western medicine treatment is not effective.

With the large number of stents in PCI, ISR problem has obtained more and more attention. ISR often occurs in the first 6 months after stent implantation. The incidence of ISR is different in different people, and the maximum incidence rate of ISR reaches up to 60% [15]. Clinical factors, stenting procedure, coronary lesions of patients have great influences on the occurrence, development and prognosis of ISR. After stent implantation, the in-stent lumen loss is associated with the thrombosis, neointimal proliferation and vascular remodeling. The neointimal proliferation is the main mechanism of ISR formation. The essence of ISR is an excessive healing response for arterial injury of the body, which is a complex biological process, mediated by a series of inflammatory substances and growth factors [16].

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Commonly used drugs of ISR after PCI are anti-platelet drugs, anticoagulant drugs, lipid-lowering drugs statins, and angiotensin-converting enzyme inhibitors. Although heparin (LMWH used) and prostaglandin I<sub>2</sub> intervention can significantly reduce the early postoperative thromboembolic incidence, they have no apparent effect on the incidence of late ISR. It is found that drugs, including chemotherapy drugs (such as colchicine, vincristine, actinomycin D), angiotensin-converting enzyme inhibitors, platelet-derived growth factor inhibitors and statins trapidil, aim to inhibiting the smooth muscle cell proliferation in laboratory studies, and have the benefits of anti-SMC proliferation. However, there is no exact viable and effective clinical evidence. The originally considered promising platelet IIb/IIIa antagonists are also proved ineffective in recent ERASER study [17].

Integrative prevention of Western and Chinese medicine for ISR after PCI is a new field of contemporary treatment of CHD. Chinese medicine has shown some efficacy and characteristics in the prevention and treatment of ISR after PCI. Modern researches show that, many herbs had many protection effects on endothelial cells such as antioxidation, intervention of endothelial cell apoptosis, inhibiting endothelial cell permeability increase, anti-thrombosis, and inhibiting the expression of adhesion molecules [18,19]. Therefore, the "endothelial recovery" is the key in prevention of ISR after PCI, which is the new direction of integrative therapy. This study investigated the curative effect of Yiqi Huoxue Tongmai decoction on the ISR after PCI in CHD patients. Results showed that, the total clinical effective rate and total effective rate by ECG in TCM group were significantly higher than those in control group ( $P < 0.05$ ). After treatment, the scores of chest pain, chest tightness, fatigue and dry mouth in TCM group were significantly lower than those in control group, respectively ( $P < 0.05$ ). After treatment, the ISR rate in TCM group was significantly lower than that in control group ( $P < 0.05$ ). After treatment, the blood TC, TG and LDL-C levels in TCM group were also significantly lower than those in control group, respectively ( $P < 0.05$ ). In addition, no adverse cardiovascular event occurred in the TCM group. This indicated that, the Yiqi Huoxue Tongmai decoction can mitigate ISR after PCI in CHD patients, with no adverse effect.

In conclusion, Yiqi Huoxue Tongmai decoction has good curative effect on ISR after PCI in CHD patients, and has no obvious toxic side effect. This study still has some limitations. The sample size of this study is relatively small. Larger sample size will make the results more convincing. In our next studies, the sample size should be further increased for obtaining more satisfactory outcomes.

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**\*Correspondence to**

Jinying Zhang

Department of Cardiology

The First Affiliated Hospital of Zhengzhou University

No. 1 Construction East Road

PR China