Effect of Guanxin-V Mixture Combined with Sacubitril Valsartan on Cardiac Function after PCI in STEMI Patients

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Abstract [**Objectives**] To observe the effect of Guanxin-V Mixture combined with Sacubitril Valsartan on cardiac function in patients after PCI for acute ST-segment elevation myocardial infarction (STE-MI). [**Methods**] 41 cases of STEMI patients (qi and yin deficiency and blood stasis and obstruction) hospitalized in Nanjing Hospital of Chinese Medicine affiliated to Nanjing University of Chinese Medicine from January 2020 to June 2021 were randomly divided into 21 cases in the treatment group and 20 cases in the control group, and the two groups were given standardized Western medicine treatment as soon as possible after PCI. The control group was treated with Sacubitril Valsartan, and the treatment group was treated with Guanxin-V Mixture on the basis of treatment in the control group. The patients in the two groups were treated for 3 months, and the TCM syndrome score, left ventricular ejection fraction (LVEF), and N-Terminal Pro-Brain Natriuretic Peptide (NT-proBNP), interleukin-6 (IL-6), and high-sensitivity C-reactive protein (hs-CRP) levels, and the incidence of heart failure and adverse reactions in the two groups after treatment were recorded. [**Results**] After the treatment, the TCM syndrome score and serum NT-proBNP, IL-6 and hs-CRP levels of the two groups significantly decreased ($P<0.05$), and the levels of the treatment group were significantly lower than those of the control group ($P<0.05$); the LVEF of the two groups significantly increased ($P<0.05$), and the level of the treatment group was significantly higher than that of the control group ($P<0.05$). Comparison of the incidence of heart failure and adverse reactions in the two groups showed no statistically significant differences ($P>0.05$). [**Conclusions**] Guanxin-V Mixture combined with Sacubitril Valsartan could significantly improve cardiac function in STEMI patients undergoing PCI, and its effect may be related to the suppression of inflammatory response.

Key words Guanxin-V Mixture, Sacubitril Valsartan, Acute ST-segment elevation myocardial infarction, PCI, Heart failure

1 Introduction

Acute ST-segment elevation myocardial infarction (STEMI) refers to the rupture of plaque in the coronary arteries, developing secondary acute thrombosis, causing acute occlusion of coronary arteries, resulting in acute myocardial ischemia and necrosis caused by hypoxia. Clinically, it is characterized by persistent and severe chest pain, arrhythmia and heart failure, which can easily endanger the lives of patients if are not rescued in time. The most important treatments for STEMI are early opening of the infarct-related vessels to achieve myocardial reperfusion and to reduce the infarct size. However, some clinical studies have shown that STEMI patients can start to develop ventricular remodeling within a short time after the onset of the disease, *i.e.*, ventricular chamber morphology changes such as ventricular enlargement, necrosis, and myocardial thinning, which leads to the reduction of ventricular systolic function, and it is the main pathological basis for the development of post-STEMI heart failure, and one of the most important risk factors for sudden cardiac death in the distant future, so it is of great significance to intervene in STEMI patients after PCI[1]. STEMI is mostly categorized as "true heart pain" and "chest paralysis and heart pain disease" in Chinese medicine, and clinical epidemiological studies have found that qi and yin deficiency and blood stasis are one of the more common syndromes of TCM in patients with coronary heart disease[2]. Mao Jingyuan *et al.*[3] found in their clinical study that patients with coronary heart disease with qi and yin deficiency and blood stasis had poor exercise tolerance and severe coronary artery lesions, suggesting that qi and yin deficiency and blood stasis is a more serious form of coronary heart disease in Chinese medicine. Benefiting qi, nourishing yin and activating blood prescription drugs have obvious advantages in improving ventricular remodeling after STEMI[4]. Guanxin-V Mixture, a preparation developed by Nanjing Hospital of Chinese Medicine, is clinically and widely used in patients with coronary heart disease with deficiency of both qi and yin and blood stasis, and the clinical efficacy is remarkable. This study further observed the effect of Guanxin-V Mixture on cardiac function of STEMI patients after emergency PCI, in order to provide more evidence for its clinical application.

2 Information and methods

2.1 Criteria for case inclusion

2.1.1 Western medicine diagnostic criteria. Refer to the relevant diagnostic criteria of *Guidelines for the Diagnosis and Treatment of Acute ST-Segment Elevation Myocardial Infarction (2019)*[5].

2.1.2 Traditional Chinese medicine diagnostic criteria. The syndrome of deficiency of both qi and yin and blood stasis is determined with reference to *TCM Clinical Diagnosis and Treatment Terminology—Syndrome Part*[6]. Primary symptoms: chest tight-

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ness, chest pain, palpitation, shortness of breath, dry mouth; secondary symptoms: tiredness, weakness, spontaneous sweating, low voice, dark color, cyanosis of lips and mouth; tongue and pulse: tongue is pale, or purplish, or pale dark, or petechial, pulse is thin, or uneven, or irregular. A definite diagnosis can be made if there are 2 or more of the primary symptoms and 2 or more of the secondary symptoms, combined with the tongue and pulse.

2.1.3 Inclusion criteria. Patients aged 18 – 75 years old, who met the standards of Western medicine diagnosis and TCM syndrome, volunteered to participate in the study.

2.1.4 Exclusion criteria. Patients younger than 18 years or older than 76 years; those who did not undergo emergency PCI; patients with severe obesity, radiotherapy and chemotherapy of malignant tumors and severe heart, lung, liver, kidney and other organ insufficiency; those who have not signed the informed consent.

2.2 General information 41 patients who were hospitalized in Nanjing Hospital of Chinese Medicine, affiliated to Nanjing University of Chinese Medicine, for emergency PCI due to STEMI from January 2020 to June 2021 were selected and randomly divided into the treatment group and the control group according to the order of admission. There were 21 cases in the treatment group, including 12 men and 9 women; age (68.5 ± 8.4) years; 12 cases of anterior wall infarctions, 4 cases of lower wall infarctions, and 4 cases of infarctions in other parts of the heart; 12 cases of hypertension and 3 cases of diabetes. There were 20 cases in the control group, including 14 men and 6 women; age (65.4 ± 11.6) years; 13 cases of anterior wall infarctions, 5 cases of inferior wall infarctions, and 2 cases of infarctions in other parts of the heart; 10 cases of hypertension and 5 cases of diabetes. The differences in general information between the 2 groups were not statistically significant ($P > 0.05$) and it was comparable. This study was reviewed and approved by the Ethics Committee of Nanjing Hospital of Chinese Medicine affiliated to Nanjing University of Chinese Medicine (KY2020093).

2.3 Treatment methods Patients in both groups were admitted to the hospital after emergency PCI with reference to the guideline, and were given a standardized antithrombotic regimen, *i.e.*, dual antiplatelet therapy with aspirin combined with clopidogrel or ticagrelor; in addition, they were given standardized treatment for coronary artery disease within 24 h, involving statins, β-blockers, and nitrate preparations. On this basis, the control group was given Sacubitril Valsartan sodium tablets (NovartisPharmaStein-AG, registration number H20170362, specification: 50 mg), with the initial dose of 25 – 50 mg, twice/day, and gradually titrated to the target dose of 200 mg, twice/day. The treatment group was treated with Guanxin-V Mixture (composed of *Codonopsis pilosula*, Radix Ophiopogonis, Radix Salviae Miltiorrhizae, Radix Paeoniae Rubra, Fructus Schisandrae, *etc.*) on the basis of method of the control group. Both groups were treated for 3 months.

2.4 Observation indexes TCM syndrome score, left ventricular ejection fraction (LVEF), N-Terminal Pro-Brain Natriuretic Peptide (NT-proBNP), interleukin-6 (IL-6) and high-sensitivity C-reactive protein (hs-CRP) were observed before and after treatment. The incidence of heart failure and adverse reactions were recorded in the two groups after treatment.

2.5 Statistical methods The data were analyzed by SPSS 21.0 statistical software, and the measurement data were expressed as $\bar{x} \pm s$. The comparison between the two groups was made by independent samples t-test, and the comparison before and after the treatment was made by paired t-test; the count data was tested by X^2, and $P < 0.05$ indicated that the difference was statistically significant.

3 Results and analysis

3.1 Comparison of TCM syndrome score before and after treatment There was no significant difference in TCM syndrome score between the two groups before treatment ($P > 0.05$); after treatment, the TCM syndrome score of the treatment group decreased to (8.81 ± 2.52) points, the TCM syndrome score of the control group decreased to (12.05 ± 3.01) points, and the difference between the two groups was statistically significant ($P < 0.05$) (Table 1).

Table 1 Comparison of TCM syndrome score before and after PCI in two groups of patients with acute ST-segment elevation myocardial infarction ($\bar{x} \pm s$, points)

Group	Number of cases	Before treatment	After 3 months of treatment
Treatment	21	14.57 ± 3.65	8.81 ± 2.52①②
Control	20	15.61 ± 3.49	12.05 ± 3.01①

Note: ①Compared with pre-treatment, $P < 0.05$; ②compared with control group, $P < 0.05$.

3.2 Comparison of NT-proBNP level and LVEF before and after treatment There was no significant difference in NT-proBNP and LVEF between the two groups before treatment ($P > 0.05$). After 3 months of treatment, the levels of NT-proBNP decreased significantly ($P < 0.05$) and the levels of LVEF increased significantly ($P < 0.05$) in the two groups, and the improvement in the treatment group was more significant than that in the control group ($P < 0.05$) (Table 2).

Table 2 Comparison of NT-proBNP level and LVEF in two groups of patients with acute ST-segment elevation myocardial infarction after PCI ($\bar{x} \pm s$)

Group	Number of cases	NT-proBNP//pg/mL		LVEF//%	
		Before treatment	After 3 months of treatment	Before treatment	After 3 months of treatment
Treatment	21	1 571.67 ± 164.93	575.45 ± 83.79①②	49.35 ± 10.71	58.08 ± 5.63①②
Control	20	1 477.83 ± 153.61	704.01 ± 76.35①	46.18 ± 9.79	53.39 ± 4.12①

Note: ①Compared with pre-treatment, $P < 0.05$; ②compared with control group, $P < 0.05$.

3.3 Comparison of serum IL-6 and hs-CRP levels before and after treatment Before treatment, there was no significant difference in serum IL-6 and hs-CRP levels between the two groups ($P>0.05$); after treatment, the levels of serum IL-6 and hs-CRP in the two groups were significantly lower than those before treatment ($P<0.05$), and the levels in the treatment group were significantly lower than those in the control group ($P<0.05$) (Table 3).

Table 3 Comparison of serum IL-6 and hs-CRP levels in two groups of patients with acute ST-segment elevation myocardial infarction after PCI ($\bar{x}\pm s$)

Group	Number of cases	IL-6//pg/mL		hs-CRP//mg/L	
		Before treatment	After 3 months of treatment	Before treatment	After 3 months of treatment
Treatment	21	48.17±11.07	30.56±5.59①②	9.06±3.34	4.47±2.14①②
Control	20	46.99±12.35	38.68±6.13①	9.35±3.63	5.91±2.35①

Note: ①Compared with pre-treatment, $P<0.05$; ②compared with control group, $P<0.05$.

3.4 Comparison of the incidence of heart failure and adverse effects before and after treatment After 3 months of treatment, heart failure occurred in 1 case (4.8%) in the treatment group and 3 cases (15.0%) in the control group, and the difference between the two groups was not statistically significant ($P>0.05$). During the treatment process, one patient in the treatment group had digestive discomfort symptoms, one patient had elevated renal damage, and the incidence rate of adverse reactions was 9.5%; in the control group, one patient had elevated blood potassium, one patient had vomiting symptoms, and the incidence rate of adverse reactions was 10.0%. The difference in the incidence of adverse reactions between the two groups was not statistically significant ($P>0.05$). Under the condition of close monitoring, the digestive tract discomfort symptoms gradually disappeared, the renal function and electrolyte abnormalities were improved of patients in the two groups, and the study was successfully completed.

4 Discussion

With the establishment of chest pain center on a large scale, the popularization of myocardial infarction knowledge and the maturity of emergency interventional technology, the proportion of STEMI patients undergoing emergency PCI and the postoperative survival rate have increased significantly, while the mortality rate in acute stage has decreased significantly. However, the occurrence of long-term heart failure after PCI has become a clinical practical problem that patients with STEMI need to pay close attention to after PCI. This may be related to the occurrence of inflammatory reaction after STEMI and ventricular remodeling caused by the activation of renin-angiotensin-aldosterone system (RAAS), and heart failure after STEMI will ultimately affect the quality of life and prognosis of patients. Thus, for STEMI patients, early administration of drugs to intervene in RAAS activation and inhibit inflammatory response after PCI, thereby inhibiting or delaying the process of ventricular remodeling, will help to reduce the incidence of post-PCI heart failure in STEMI patients, thereby improving cardiac function and improving clinical prognosis.

Sacubitril Valsartan, composed of traditional valsartan combined with sacubitril, has a dual mechanism of blocking the RAAS system and increasing the natriuretic peptide system (NPs), thus exerting an inhibitory effect on ventricular remodeling. Studies have shown that Sacubitril Valsartan can significantly improve cardiac function in patients after myocardial infarction[7] and prevent the occurrence of heart failure and other conditions[8]. Guanxin-V Mixture was developed based on the understanding of the pathogenesis of "chest obstruction and heartache" with deficiency of both qi and yin and blood stasis. *Codonopsis pilosula* in the prescription can invigorate spleen-stomach and replenish qi, *Ophiopogon japonicus* can nourish yin for moistening dryness, relieve dry mouth, and *Schisandra chinensis* can promote fluid production, tonify kidney and calm heart. The first can be used as principal medicine while the latter two can be used as adjuvant medicine. The combination of these three drugs can exert the effects of tonifying, moistening and astringing, and resolving the deficiency of qi and yin. Radix Paeoniae Alba can relieve stasis and pain, Salviae Miltiorrhizae can nourish blood and dissolve stasis and *Rehmannia glutinosa* libosch. can nourish yin and cool blood. These three medicines can be used together to exert the effects of clearing heat and cooling blood, activating blood circulation and removing blood stasis. Previous studies have confirmed that Guanxin-V Mixture has the effect of inhibiting post-inflammatory reaction after myocardial infarction[9], improving cardiac function in patients with coronary heart disease and cardiac insufficiency[10], and inhibiting ventricular remodeling in rats with myocardial infarction[11]. Modern pharmacological studies have found that *Codonopsis pilosula* extract has the effect of improving left ventricular systolic function and increasing cardiac output[12]; *Ophiopogon japonicus* injection can significantly improve the hemodynamics of myocardial infarction model rats, thus improving their left ventricular function[13]; Radix Paeoniae Alba has the effect of deterring cardiomyocyte apoptosis and protecting cardiomyocytes[14]; Tanshinone IIA-sulfonic sodium, an extracted preparation of *Salvia miltiorrhiza*, has the effect of increasing coronary blood flow, improving the anti-hypoxia ability of cardiomyocytes, improving myocardial metabolic disorders, and resisting platelet aggregation in patients with heart failure[15].

This clinical study showed that patients in the treatment group had better clinical symptoms and cardiac function improvement than the control group, and serum IL-6 and hs-CRP levels were lower than those of the control group. It is suggested that on the basis of conventional drug therapy, the early use of the combination of Chinese and Western medicine regimen of Guanxin-V Mixture with Sacubitril Valsartan is more conducive to the improvement of cardiac function after PCI in patients with STEMI, and its mechanism of action may be related to the inhibition of inflammatory response, and the combination with Guanxin-V Mixture did not bring about any significant adverse effects. Guanxin-V Mixture combined with Sacubitril Valsartan in reducing the incidence of

heart failure, did not show a significant advantage. Considering the small sample size and short follow-up time associated with this study, it is necessary to increase the sample size and prolong the follow-up time for further exploration in the future.

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(From page 65)

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