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Original Article

Effects of Xinnaoning combined with trimetazidine on the levels of CK and its isoenzymes, AST, ALT and LDH in patients with myocardial ischemia

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Abstract: Objective: To explore the effect of combin3e uw3 of Xinnaoning and trimetazidine on the levels of creatine kinase (CK) and its isoenzymes (CK-MB), aspartate aminotransferase (AST), alanine aminotransferase (ALT), and lactate dehydrogenase (LDH) in patients with myocardial ischemia (MI). Methods: A total of 137 patients with MI admitted to our hospital were enrolled in our study. Among them, 68 cases in the control group (CG) were treated with trimetazidine and 69 cases in the study group (SG) were treated with Xinnaoning on the basis of the CG. The incidence of adverse events, serum CK, CK-MB, AST, ALT, LDH levels, episodes of angina, lipid levels [total cholesterol (TC), triacylglycerol (TG), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C)], and quality of life (SF-36) scores were compared between the two groups. Results: The total effective rate was 88.41% in the SG, which was higher than 73.53% in the CG ($P < 0.05$). The episodes of angina in the SG were lower than those in the CG after 3 months of treatment ($P < 0.05$). The SG showed decreased serum CK, CK-MB, AST, and ALT and LDH levels compared with the CG ($P < 0.05$). The SG showed increased EF, SV and CO levels compared with the CG after 3 months of treatment. The SG also exhibited lower TC, TG and LDL-C, and higher HDL-C and quality of life than the CG after 3 months of treatment ($P < 0.05$). Conclusion: The regimen of Xinnaoning and trimetazidine could significantly improve cardiac function and serum cardiac enzyme levels, reduce lipid levels, and improve the quality of life in patients with MI.

Keywords: Trimetazidine, Xinnaoning, myocardial ischemia, creatine kinase, glutamate transaminase, alanine aminotransferase, lactate dehydrogenase

Introduction

Myocardial ischemia (MI) occurs when blood flows to heart is reduced, preventing the heart muscle from receiving enough oxygen. The reduced blood flow is usually due to a partial or complete blockage of coronary arteries, which is characterized by chest tightness, shortness of breath, palpitations, dyspnea, etc., and is often complicated by myocardial infarction, arrhythmias, angina, progressing rapidly and causing difficulty in revascularization and poor prognosis [1]. Platelet inhibitor therapy has been administrated as a treatment option, which only alleviates patients' pain to some extent, and the overall efficacy is not satisfactory [2]. The use of trimetazidine in patients with MI could prevent neutrophil coagulation and infiltration, protect cardiac function, slow down glucose fermentation, and reduce the production and secretion of inflammatory mediator, thus effectively protecting the ischemic myocardium [3]. However, in some patients, trimetazidine alone is ineffective in improving overall symptoms, and needs to be combined with other medicines.

Chinese medicine has been gradually considered in the clinical treatment of MI [4]. A study has found that Xinnaoning capsules in combination with Western medicine can significantly reduce the episodes of angina for the treatment of MI in coronary heart disease [5]. Xinnaoning could effectively reduce angiotensin II activity, relax blood vessels, inhibit platelet coagulation and adhesion, reduce blood viscosity, improve microcirculation, enhance cardiac function, and relieve myocardial hypox-

ia-ischemia in patients with MI [6]. When the myocardium is hypoxic-ischemic, creatine kinase (CK), creatine kinase isoenzymes (CK-MB), aspartate aminotransferase (AST), alanine aminotransferase (ALT), lactate dehydrogenase (LDH) and other cardiac enzyme levels will be expressed abnormally high, and too much CK, CK-MB, AST, ALT, LDH will enter the blood circulation, thus resulting in an increase in serum cardiac enzyme levels [7]. Currently, there are few reports on the effect of Chinese medicine on serum cardiac enzyme levels in patients. The present study was conducted to observe the effects of Xinnaoning and trimetazidine on CK, CK-MB, LDH, AST and ALT levels in patients with MI, so as to provide new ideas and directions for the clinical treatment of MI.

Materials and methods

General information

A total of 137 patients with MI admitted to our hospital from August 2016 to October 2019 were divided into the control group (CG, n=68) and the study group (SG, n=69) according to the treatment methods. The CG included 29 females and 39 males, aged 41-76 years, with an average age of (54.32±6.34) years and disease duration of 0.3-3.1 months. The study group included 27 females and 42 males, aged 42-77 years, with an average age of (55.03±5.96) years and disease duration of 0.4-3.2 months. This study was approved by the Ethics Committee of Shengli Oilfield Central Hospital.

Inclusion criteria

This study included the patients who (1) met the diagnostic criteria for MI in the 8th edition of *Internal Medicine* [8] and *Chinese Medicine Diagnostic Efficacy Criteria* [9]; and (2) voluntarily signed the consent form.

Exclusion criteria

(1) Patients who do not cooperate with follow-up investigation; (2) Patients with severe hypotension; (3) Patients with severe liver, kidney, or lung disease; (4) Patients with malignant arrhythmias; (5) Patients with coagulation abnormalities; (6) Patients with allergies or hypersensitivity to the study medications; (7) Patients with low adherence and low compliance were excluded from the study.

Methods

The CG was administered with Trimetazidine (Reyoung Pharmaceutical Group Co., Ltd., SFDA: H20066534) at a dose of 20 mg/time, orally, 3 times/d.

The SG was treated with Xinnaoning (Guizhou Jing Cheng Pharmaceutical Co., Ltd., State, Z20025697) on the basis of the CG at a dose of 1.35 g/time, orally, 3 times/d. Both groups continued treatment for 3 months.

Outcome measurement

(1) Clinical efficacy: ineffective means that the symptoms of fatigue, shortness of breath and chest tightness are not relieved after 3 months of treatment, and the recovery of cardiac function is less than 50%; effective means that the above symptoms improve significantly after 3 months of treatment, and the recovery of cardiac function is greater than 50%; markedly effective means that the above symptoms disappear after 3 months of treatment with normal cardiac function [10]. The effective rate= (Markedly effective + Effective)/Total cases *100%.

(2) Episodes and duration of angina were recorded before and after 3 months of treatment.

(3) Serum CK, CK-MB, AST, ALT and LDH levels: 4 ml of venous blood was collected before and 3 months after treatment, and the supernatant was obtained by centrifugation (2500 r/min, 5 min), and serum CK, CK-MB, AST, ALT and LDH levels were detected using enzyme-linked immunosorbent assay.

(4) Cardiac function (EF, SV, CO) was measured by Vivid E9 color ultrasound (purchased from GE, USA) before treatment and 3 months after treatment.

(5) Blood lipid levels [total cholesterol (TC), triacylglycerol (TG), low-density lipoprotein cholesterol (LDL-C) and high-density lipoprotein cholesterol (HDL-C)] were measured by automatic life analyzer before treatment and 3 months after treatment.

(6) The incidence of adverse reactions (including rash, gastrointestinal discomfort and insomnia) was recorded in the two groups.

Table 1. Comparison of the clinical efficacy of the two groups [n (%)]

Group	Number of cases	Ineffective	Effective	Markedly effective	Total effective rate
Study group	69	8 (11.59)	27 (39.13)	34 (49.28)	61 (88.41)
Control group	68	18 (26.47)	28 (41.18)	22 (32.35)	50 (73.53)
χ^2	-	-	-	-	4.929
P	-	-	-	-	0.026

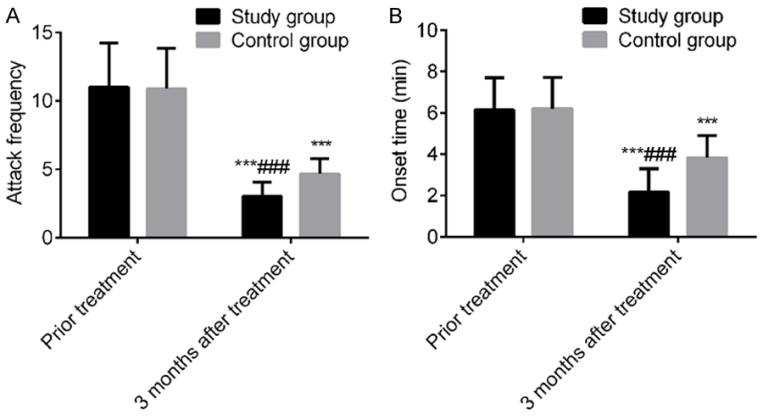

Figure 1. Comparison of the number and duration of angina attacks between the two groups before and after treatment. A: The number of angina attacks; B: The duration of attacks. Compared with the pre-treatment, ***$P < 0.001$; compared with the control group, ###$P < 0.001$.

(7) The quality of life of the two groups was evaluated before and 3 months after treatment using Short Form Health Status Scale (SF-36), covering 0 to 100, with the higher score indicating the better quality of life [11].

Statistical analysis

The results were processed by SPSS 23.0. Measurement data ($\bar{x}\pm s$) were examined by *t* test. Count data [n (%)] were compared by *Chi*-squared test. $P < 0.05$ indicated significant differences.

Results

Comparison of efficacy

The total effective rate of the SG was 88.41%, higher than that of 73.53% in the CG ($P < 0.05$), indicating that Xinnaoning in combination of trimetazidine could significantly improve the clinical efficacy of MI treatment (**Table 1**).

Comparison of the episodes of angina

The SG showed decreased episodes of angina after 3 months of treatment compared with the CG ($P < 0.05$), indicating that the regimen of Xinnaoning and trimetazidine could reduce the episodes of angina (**Figure 1**).

Comparison of cardiac enzyme levels

Those indices in the SG after 3 months of treatment were lower than those in the CG ($P < 0.05$), demonstrating that trimetazidine combined with cardiac enzymes could improve patients' myocardial enzyme levels in the treatment of MI (**Figure 2**).

Comparison of cardiac function

The difference of EF, SV and CO in the SG was higher than that in the CG after 3 months of treatment ($P < 0.05$), indicating that the combination of trimetazidine and cardiac encephalin can significantly improve patients' cardiac function in the treatment of MI (**Figure 3**).

Comparison of blood lipid levels

The differences in TC, TG and LDL-C in the SG were lower than those in the CG, while HDL-C in the SG was higher than that in the CG after 3 months of treatment ($P < 0.05$), suggesting that the combination of Xinnaoning and trimetazidine can significantly improve 'the lipid levels in patients with MI (**Figure 4**).

Comparison of adverse reactions

The total incidence rate of adverse events was 8.70% in the SG and 4.41% in the CG ($P > 0.05$), indicating that combination of Xinnaoning and trimetazidine would not increase the adverse reactions in patients with MI (**Table 2**).

Comparison of SF-36 scores

The SF-36 scores of the SG were higher than those of the CG after 3 months of treatment (*P*

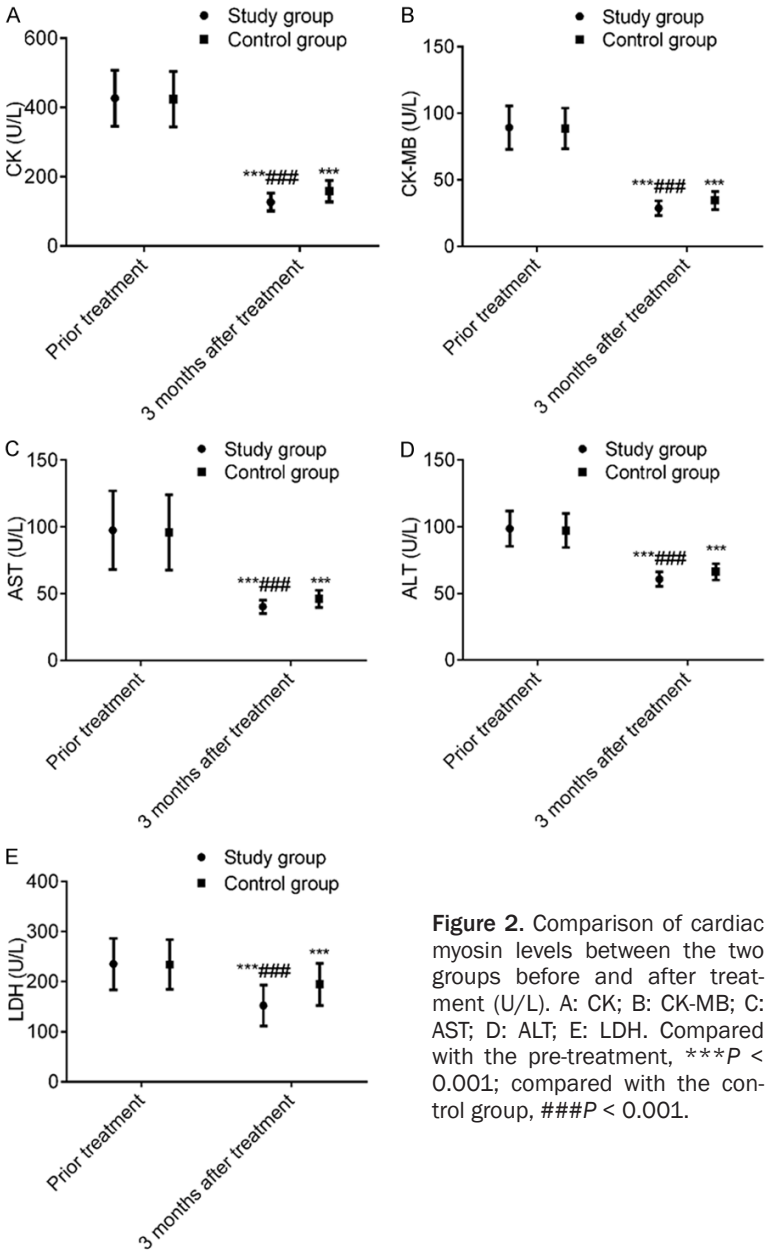

Figure 2. Comparison of cardiac myosin levels between the two groups before and after treatment (U/L). A: CK; B: CK-MB; C: AST; D: ALT; E: LDH. Compared with the pre-treatment, ***P < 0.001; compared with the control group, ###P < 0.001.

< 0.05), suggesting that the combination of trimetazidine and cardiac cerebrospinal can effectively improve the quality of life of patients with MI (**Table 3**).

Discussion

In recent years, the number of patients with MI has been increasing, which seriously affects the quality of life of patients. The key to treat MI is to improve blood circulation, reduce consumption of myocardial oxygen, and improve the tolerance of myocardial tissue to hypoxia [12]. Trimetazidine could improve myocardial energy metabolism and inhibit oxidative stress and inflammation. When administrated in patients with MI, trimetazidine prevents chain fatty acid β oxidation and promotes glucose oxidation by competitively antagonizing the activity of mitochondrial long-chain 3-KAT. It makes full use of limited oxygen to produce and release more ATP, thereby effectively increasing the utilization of oxygen and improving MI [13, 14]. In addition, trimetazidine can antagonize the oxidation of free fatty acids and meanwhile significantly reduce the myocardial fatty acid utilization, effectively improving the intracellular acidosis caused by lactic acid deposition, reducing the calcium overload and inward flow, and preventing mitochondrial swelling caused by excessive calcium ions to enhance the cellular tolerance to hypoxia [15]. Moreover, trimetazidine can attenuate oxygen toxicity, scavenge excessive oxygen free radicals, and reduce their damaging effects on the membrane. Besides, trimetazidine also prevents neutrophil coagulation and infiltration, protect cardiac function, and slow down gluconeogenesis, thus effectively protecting the ischemic myocardium [16].

According to traditional Chinese Medicine, MI belongs to the category of “Chest bi-syndrome”, and is caused by Qi deficiency, and the treatment option should focus on relieving palpitations, promoting blood circulation, nourishing Yin, and benefiting Qi [17]. Geng et al. [18] have found that Xinnaoning capsules can significantly improve the electrocardiogram of patients with unstable angina and coronary heart disease, with a total effective rate of up to 88.50%. The main herbs and ingredients of Xinnaoning are ginseng, angelica, rhizoma chuanxiong, and astragalus, which are often prescribed in the treatment of coronary heart disease, cerebral

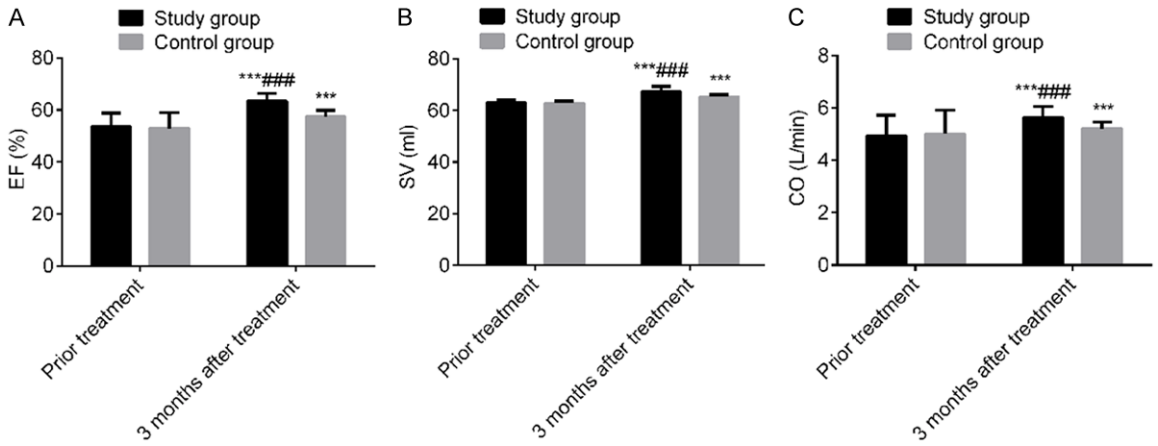

Figure 3. Comparison of myocardial enzymes between the two groups before and after treatment. A: EF; B: SV; C: CO. Compared with the pre-treatment, ***P < 0.001; compared with the control group, ###P < 0.001.

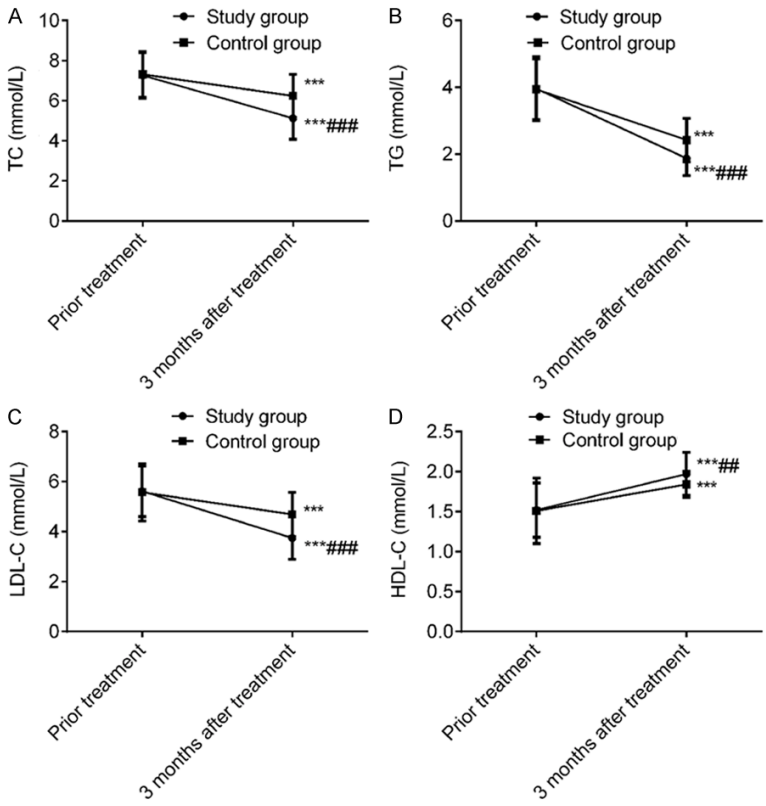

Figure 4. Comparison of lipid levels between the two groups before and after treatment (mmol/L). A: TC; B: TG; C: LDL-C; D: HDL-C. Compared with pre-treatment, ***P < 0.001; compared with the control group, ##P < 0.01, ###P < 0.001.

thrombosis and other cardiovascular and cerebrovascular diseases and have achieved good results [19, 20]. Ginseng has been used in Chinese medicine for thousands of years, which can regulate the Qi, calm the mind, clear the blood vessels, quench thirst, resolve ailments, and tonify the five internal organs. Angelica can invigorate and nourish blood. Rhizoma chuanxiong can subdue Qi, soothe the liver, invigorate blood, clear menstruation, and eliminate stasis. Astragalus can also benefit Qi. Therefore, Xinnaoning exert the effects of resolving stasis, invigorating blood, benefiting Qi and clearing blood vessels [21]. Modern pharmacology confirms that Xinnaoning can effectively reduce angiotensin II activity, relax blood vessels, inhibit platelet coagulation and adhesion, lower blood lipid levels, improve microcirculation, enhance cardiac function, and relieve myocardial hypoxia [22]. This study showed that the total effective rate of the SG was higher than that of the CG, and the EF, SV, CO, and HDL-C in the SG were higher than those in the CG after 3 months of treatment, while the number and duration of angina attacks, TC, TG, and LDL-C were lower than those in the CG (P < 0.05), and the total incidence of adverse reactions was low in both groups, which showed that the combination of Xinnaoning and trimetazidine could

Table 2. Comparison of adverse reactions between the two groups [n (%)]

Group	Number of cases	Skin rash	Digestive discomfort	Insomnia	Total incidence
Study group	69	2 (2.90)	3 (4.35)	1 (1.45)	6 (8.70)
Control group	68	1 (1.47)	2 (2.94)	0 (0.00)	3 (4.41)
χ^2	-	-	-	-	0.445
P	-	-	-	-	0.504

Table 3. Comparison of SF-36 scores between the two groups before and after treatment ($\overline{x}$±s, min)

Timing	Group	Number of cases	Somatic pain	Energies	physiological function	Mental health
Before treatment	Study group	69	43.18±7.28	46.92±8.27	47.51±7.48	47.32±8.04
	Control group	68	44.32±6.37	47.64±6.24	46.98±5.03	46.96±6.87
	t	-	0.974	0.575	0.486	0.281
	P	-	0.331	0.567	0.627	0.779
After 3 months of treatment	Study group	69	82.61±8.04	82.89±7.28	82.34±8.82	84.23±9.08
	Control group	68	74.01±6.83	75.38±5.36	73.62±6.43	75.51±7.86
	t	-	6.742	6.867	6.604	6.006
	P	-	0.000	0.000	0.000	0.000

significantly improve cardiac function and reduce lipid levels with high safety. The reason may be that the regimen of Xinnaoning and trimetazidine can not only dredge blood vessels and improve blood supply to organs, but also effectively improve body function and metabolism as well as myocardial contractility, promoting the recovery of cardiac function [23].

Human myocardial tissues contain enzymes such as CK, CK-MB, AST, ALT, LDH, *etc*., which will change when the organism body is recovering from disease. For example, when the myocardium is hypoxic-ischemic, the levels of CK, CK-MB, AST, ALT, and LDH will show high expression. Therefore, the detection of these serum levels can provide a reliable basis for determining the treatment effect and prognosis of MI [24, 25]. We found that the SG exhibited lower levels of serum CK, CK-MB, AST, ALT and LDH and higher SF-36 scores than the CG after 3 months of treatment ($P < 0.05$).

In summary, the combined treatment of Xinnaoning and trimetazidine in patients with MI could significantly improve the cardiac function and serum myocardial enzymes levels and enhance the quality of life, with high safety. However, the sample size of this study is relatively small. Therefore, the results need to be further confirmed by multi-center studies on lager sample size.

Disclosure of conflict of interest

None.

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