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ORIGINAL RESEARCH ARTICLE

Effects of sodium creatine phosphate on myocardial and left ventricular function in patients with slow / no reflow acute ST segment elevation myocardial infarction during percutaneous coronary intervention

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ABSTRACT

Objective: To investigate the effect of sodium creatine phosphate on myocardial and left ventricular function in patients with slow / no reflow acute ST segment elevation myocardial infarction (STEMI) during percutaneous coronary intervention (PCI). **Methods:** The incidence of major adverse cardiovascular events (heart failure, recurrent myocardial infarction, malignant arrhythmia, cardiac arrest, cardiogenic shock, etc.) Was recorded and compared between the two groups. **Results:** Conclusion sodium creatine phosphate can reduce myocardial injury, improve heart rate variability and left ventricular function, and reduce the risk of major adverse cardiovascular events in STEMI patients with slow / no reflow during PCI.

Keywords: phosphate muscle; sodium acetate; percutaneous coronary intervention; acute st segment elevation myocardial infarction; myocardial injury; left ventricular function

Percutaneous coronary intervention (PCI) plays an important role in the treatment of acute ST - segment elevation myocardial infarction (STEMI). It can improve the blood supply of myocardial tissue and save the dying myocardium by dredging the diseased vessels [1 – 2]. After PCI, patients may have microcirculation disorders (slow / no reflow phenomenon), affect myocardial perfusion, and increase the risk of major adverse cardiovascular events (MACE) such as angina pectoris and recurrence of myocardial infarction [3]. Myocardial injury caused by myocardial ischemia and hypoxia in STEMI patients is an irreversible pathological process, which is often accompanied by abnormal inflammatory reactions. Oxidative free radicals and inflammatory factors can change myocardial membrane potential, thus damaging myocardial cells and tissues, leading to ventricular remodeling and cardiac dysfunction [4]. Creatine phosphate widely exists in cells with vigorous metabolism in the body. It can stabilize the electrophysiological state of cells by participating in energy metabolism of cells, provide energy when myocardial cells are damaged by ischemia and hypoxia, and prevent them from being invaded by oxidative free radicals, so as to play a role in myocardial protection and reduce the risk of

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mace [5]. With small molecular structure, creatine phosphate can directly enter myocardial cells, supplement energy required for myocardial metabolism as soon as possible, effectively block myocardial cell apoptosis and avoid cardiovascular events [6]. The purpose of this study was to investigate the effect of sodium creatine phosphate on myocardial and left ventricular function in patients with STEMI with slow / no reflow. It is reported as follows.

1. Data and methods

1.1. General information

128 STEMI patients admitted to Xingtai Third Hospital (Xingtai cardiovascular hospital) from August 2017 to December 2019 were selected and divided into routine group (n=64) and observation group (n=64) according to the random number table method. Inclusion criteria: (1) met the diagnostic criteria of the "guidelines for the diagnosis and treatment of acute ST segment elevation myocardial infarction" issued by the cardiovascular branch of the Chinese Medical Association in 2015 [7], and was diagnosed as STEMI by coronary angiography; (2) All patients met the indication of PCI and underwent emergency PCI within 12 hours after onset; (3) Slow / no reflow during emergency PCI [thrombosisinmyocardialinfarction (TIMI) blood flow grade ≤ 2]. Exclusion criteria: (1) the time from onset to admission exceeded 12h, or exceeded the time window of direct PCI; (2) Received PCI treatment within half a year; (3) Severe liver and kidney dysfunction; (4) Combined with immune, blood and nervous system diseases and malignant tumors; (5) Heart valve disease, cardiogenic shock, stroke, severe bradycardia and other cardiovascular and cerebrovascular diseases; (6) Allergic to the drugs used in this study, unable to cooperate with the treatment. There was no significant difference between the two groups in gender, age, smoking history, drinking history and other clinical data ($p>0.05$), which was comparable. See Table 1. The study was approved by the hospital ethics committee, and the patients and their families signed the informed consent form.

1.2. Treatment methods

Both groups were treated with PCI within 12 hours after onset. Puncture the right radial artery, place a 5foutlooktig common catheter for coronary angiography, perform angiography on the non criminal vessel side and criminal vessel side in turn, replace the guide catheter according to the angiography results, and perform PCI on the criminal vessel side. During the operation, 100u/kg heparin (Beijing tobisi Pharmaceutical Co., Ltd.; gyzz: h20043741) was given intravenously, and 1000u heparin was added every 1H. After the operation, the radial artery sheath was pulled out and pressed to stop bleeding. Patients in the routine group were given diuretics to reduce cardiac load and β-Receptor blockers reduce heart rate, angiotensin converting enzyme inhibitors reduce blood pressure, antiplatelet and anticoagulant therapy. The patients in the observation group received intravenous drip of sodium creatine phosphate (Harbin laibotong Pharmaceutical Co., Ltd.; gyzz: h20073072) and 1g of sodium creatine phosphate + 250ml of 09% sodium chloride injection during PCI based on the treatment of patients in the conventional group. The drip was completed within 30~45min. On the second day after operation, sodium creatine phosphate was continuously injected intravenously at the above dose, once a day. Both groups were treated for 14 days.

Table 1. Comparison of clinical data between the two groups / case (percentage /%)

Group	Gender		Age (x ± s, years)	Smoke	Drink wine	Chest pain after admission	Time from onset to emergency PCI (U ± s, H)
	Male	Female sex					
General group (n=64)	40(62.5)	24(37.5)	59.43±4.07	27(42.2)	29(45.3)	45(70.3)	7.43±0.78
Observation group (n=64)	35(54.7)	29(45.3)	60.42±4.12	29(45.3)	25(39.1)	48(75.0)	7.62±0.82
T/ χ^2 Value	0.i	805	1.368	0.127	0.513	0.354	1.343
P value	>0	1.05	>0.05	>0.05	>0.05	>0.05	>0.05

Group	Hyperlipidemia	Hypertension	Diabetes	Number of vessel lesions		
				Single branch	Double branch	Three branches
General group (n=64)	32(50.0)	40(62.5)	30(46.9)	28(43.8)	24(37.5)	12(18.7)
Observation group (n=64)	30(46.9)	37(57.8)	26(40.6)	31(48.4)	22(34.4)	11(17.2)
T/ χ^2 Value	0.125	0.293	0.508		0.283	
P value	>0.05	>0.05	>0.05		>0.05	

Group	TIII 1 Blood flow classification			Number of vessel lesions			
	Level 0	Level 1	Level 2	Left anterior descending artery disease	Right circumflex branch lesion	Right coronary artery disease	Left main lesion
General group (n=64)	16(25.0)	26(40.6)	22(34.4)	23(35.9)	8(12.5)	22(34.4)	11(17.2)
Observation group (n=64)	14(21.9)	29(45.3)	21(32.8)	22(34.4)	9(14.0)	19(29.7)	14(21.9)
T/ χ^2 Value		0.320			0.661		
P value		>0.05			>0.05		

1.3. Observation indicators

Efficacy evaluation

Evaluate the clinical efficacy of the two groups after 14 days of treatment [7]. Significant effect: the symptoms of chest tightness, shortness of breath, dyspnea, fatigue, decreased activity tolerance and so on basically disappeared or completely disappeared, and the degree of improvement in the New York heartassociation (NYHA) classification exceeded grade 2, or recovered to grade I. Effective: the clinical symptoms are significantly improved or partially disappeared, and the NYHA grade improvement exceeds grade I, but does not reach grade I status. Invalid: if the above criteria are not met, the condition may worsen.

Total effective rate = (markedly effective + effective) cases / total cases × 100%

Heart rate variability

Holter was used to monitor the heart rate

variability of the two groups before and 14 days after treatment, including the standard deviation of the normal R-R in- interval (SDNN), the percentage of differences exceeding 50 ms of the total number of heart beats analyzed (pnn50) Standard deviation of the average value of normal R-R intervals for 5 min (SDANN) and square root of the mean square differences of successful NN intervals (RMSSD).

Serum myocardial injury index

Before treatment and in the morning after 14 days of treatment, 4 ml of fasting elbow venous blood were collected from the two groups, placed at room temperature for 1 h, centrifuged at 3000 r/min for 15 min, and the supernatant was stored at -80 Zhang for testing. The levels of serum creatine kinase isoenzyme (CK-MB) were measured by enzyme-linked immunosorbent assay. The levels of serum brain natriuretic peptide (BNP) and cardiac troponin I (ctni) were measured by immunopotentiation rate turbidimetry.

Left ventricular function

Before treatment and 14 days after treatment, the patients in the two groups were measured by Sequoia 512 color Doppler echocardiography (Siemens, Germany), and the left ventricular ejection fraction (LVEF), left ventricular end diastolic volume (LVEDV) and left ventricular end systolic volume (LVESV) were calculated.

Major postoperative adverse cardiovascular events

The patients were followed up for 6 months after PCI and followed up by telephone once a month after discharge to record the occurrence of major adverse cardiovascular events (heart failure, recurrent myocardial infarction, malignant arrhythmia, cardiac arrest, cardiogenic shock, etc.) During the follow-up period.

1.4. Statistical methods

Spss200 software was used for statistical analysis. The measurement data in line with normal distribution were expressed as mean ± standard deviation (x ± s). The independent sample t-test was used for inter group comparison, and the paired t-test was used for intra group comparison before and after treatment; the counting data is expressed by example (percentage), and the comparison is made by χ 2 inspection. The difference was statistically significant ($p<0.05$).

2. Results

2.1. Comparison of treatment effect between the two groups

The total effective rate of the observation group was 92.2% (59/64), which was higher than 79.7% (51/64) of the routine group ($p<0.05$). See **Table 2**.

Table 2. Comparison of treatment effect between the two groups / case (percentage /%)

Group	Remarkable effect	Valid	Invalid	Total effective rate /%
General group (n=64)	29(45.3)	22(34.4)	13(20.3)	79.7
Observation group (n=64)	39(60.9)	20(31.3)	5(7.8)	92.2
T/ χ^2 Value				4.137
P value				<0.05

2.2. Comparison of heart rate variability between the two groups

Before treatment, there was no significant difference in SDNN, pnn50, SDANN and RMSSD between the two groups ($p>0.05$). After treatment, the SDNN, pnn50, SDANN and RMSSD of the two groups were higher than those before treatment, and the observation group was higher than that of the routine group, the difference was statistically significant ($p<0.05$). See **Table 3**.

Table 3. Comparison of heart rate variability between the two groups (x ± s)

Group	SDNN/ms		SDANN/ms		RMSSD/ms		PNN50/%	
	Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment
General group	84.12±9.06	96.16±11.14[a]	81.78±8.32	85.21±9.32[a]	20.06±2.32	24.33±2.66[a]	9.42±0.56	14.37±0.52[a]
Observation group	82.65±8.14	100.28±10.75[a]	82.96±7.63	88.76±8.37[a]	20.64±2.18	26.58±2.48[a]	10.48±0.47	16.54±0.56[a]
T value	0.966	2.129	0.836	2.267	1.458	2.750	0.930	3.111
P value	>0.05	<0.05	>0.05	<0.05	>0.05	<0.05	>0.05	<0.05

Note: compared with the group before treatment, a P< zero point zero five

2.3. Comparison of left ventricular function between the two groups

Before treatment, there was no significant difference in LVEF, LVESV and LVEDV between the two groups (p>0.05). After treatment, LVEF of the two groups was higher than that before treatment, and that of the observation group was higher than that of the routine group; LVESV and LVEDV of the two groups were lower than those before treatment, and the observation group was lower than that of the routine group, the difference was statistically significant (p<0.05). See **Table 4**.

Table 4. Comparison of left ventricular function between the two groups (x ± s)

Group	LVEF/%		LVESV/ ml		LVEDV/ ml	
	Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment
General group	46.75±4.47	50.68±5.03[a]	66.02±5.52	61.68±5.24[a]	155.23±12.58	146.74±11.37[a]
Observation group	45.89±4.56	53.46±4.55[a]	64.58±5.43	58.85±5.07[a]	152.93±10.84	142.85±10.16[a]
T value	1.077	3.279	1.488	3.105	1.108	2.041
P value	>0.05	<0.05	>0.05	<0.05	>0.05	<0.05

Note: compared with the group before treatment, [a]p<0.05

Table 5. Comparison of serum myocardial injury indexes between the two groups (x ± s)

Group	CK-MB/U·L-1		Ctn Ⅰ/ng·L-1		BNP/ng·L-1	
	Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment
General group	4157±434	1555±217[a]	24754±3222	18518±2345[a]	46441±5376	30346±3277[a]
Observation group	4061±376	1686±282[a]	25261±3586	20243±2787[a]	46973±5035	34039±3456[a]
T value	1337	2945	0841	3789	0578	4524
P value	>0.05	<0.05	>0.05	<0.05	>0.05	<0.05

Note: compared with the group before treatment, [a]p<0.05

2.4. Comparison of serum myocardial injury indexes between the two groups

Before treatment, there was no significant difference in serum CK - MB, CTN Ⅰ and BNP levels between the two groups (p>0.05). After treatment, the levels of serum CK - MB, CTN Ⅰ and BNP in the two groups were lower than those before treatment, and the levels in the observation group were lower than those in the routine group, the difference was statistically significant (p<0.05). See **Table 5**.

2.5. Comparison of major adverse cardiovascular events between the two

groups

After 6 months' follow-up, 6 cases of angina pectoris, 3 cases of myocardial infarction, 3 cases of heart failure and 1 case of cardiac arrest occurred in the routine group; in the observation group, there were 3 cases of angina pectoris, 1 case of myocardial infarction and 1 case of heart failure. The total incidence of major adverse cardiovascular events in the observation group was 78% (5/64), significantly lower than 20.3% (13/64) in the conventional group ($p<0.05$).

3. Discussion

Acute occlusive thrombosis caused by coronary plaque injury and rupture is the basis of STEMI. If not treated in time, it is easy to lead to serious complications such as hypotension, arrhythmia, heart failure, shock and sudden death [8 - 9]. PCI is a fast and effective method to reconstruct the blood supply of stenosed or blocked vessels. Compared with drug treatment, PCI can recover the ischemic myocardial reperfusion faster and has a better prognosis [10]. However, 10%~30% of ste - MI patients undergoing PCI will have slow / no reflow phenomenon, and the ischemic myocardial tissue cannot be effectively perfused, increasing the risk of myocardial injury, which is an independent risk factor for adverse cardiovascular events [11]. At present, although more and more studies believe that PCI Treatment Combined with drug treatment (such as statins, nicorandil, etc.) Can improve myocardial perfusion and injury, and reduce the risk of slow / no reflow during operation to a certain extent, the clinical efficacy still needs to be fully demonstrated [11 - 12].

Sodium creatine phosphate is a drug that regulates myocardial metabolism. It is widely used in the treatment of myocardial injury related diseases (myocardial ischemia-reperfusion injury, myocardial infarction, heart failure, etc.). Myocardial injury is closely related to slow / no reflow phenomenon. In this study, the patients in the observation group were given intravenous injection of sodium creatine phosphate during and after PCI, and the total effective rate was significantly higher than that in the conventional treatment group, indicating that the combination of sodium creatine phosphate with conventional drugs and PCI treatment can improve NYHA classification, improve dyspnea, chest tightness, shortness of breath and other symptoms, and improve activity tolerance. In patients with slow / no reflow STEMI, the blood oxygen supply of myocardial tissue is blocked, the content of creatine phosphate in myocardial cells is reduced, and the energy metabolism of myocardial cells is abnormal. The slowing down of myocardial oxidative metabolism is an important reason for the slowing down of myocardial cell damage and recovery [13]. Creatine phosphate is the main form of chemical energy stored in myocardial cells. When myocardium contracts, it needs to consume a lot of energy to maintain regular systolic and diastolic functions. Creatine phosphate plays an important role in energy metabolism. Intravenous drip of sodium creatine phosphate during PCI can be used as a stable "buffer" in high energy consuming cells. By supplementing high-energy phosphate groups, adenosine phosphate and adenosine diphosphate can be re phosphorylated, adenosine triphosphate degradation can be reduced, energy can be supplemented to damaged cardiomyocytes in time, high-energy state of cardiomyocytes can be maintained, and damage to cardiomyocytes can be reduced [14 - 15]. The results of this study showed that the levels of left ventricular systolic function indexes (LVEF, LVESV, LVEDV) and myocardial injury indexes (CK - MB, CTN Ⅰ, BNP) in the observation group were significantly better than those in the conventional group, which further confirmed that sodium creatine phosphate could effectively protect the myocardial tissue of STEMI patients with slow / no reflow during PCI and improve

the left ventricular function.

The acceleration of compensatory heart rate in STEMI patients can change the ventricular filling pressure, and then cause the relative prolongation of depolarization and repolarization, resulting in abnormal ECG and heart rate variability. Among them, the decline of SDNN, SDANN and RMSSD can objectively reflect the damage of cardiac autonomic nervous system [16]. Both groups of patients in this study were given routine drug treatment (nitrates, diuretics, and β Receptor blockers, etc.) To reduce heart rate, reduce cardiac load, reverse myocardial remodeling, correct cardiovascular sympathetic and vagal system imbalance, etc. The patients in the observation group were given sodium creatine phosphate, which could play a role in myocardial protection by improving myocardial energy metabolism and microcirculation. Therefore, after treatment, the ventricular function and heart rate variability were significantly improved, and the risk of major adverse cardiovascular events such as angina pectoris and myocardial infarction was reduced. Wanghongwei et al. [17] found that sodium creatine phosphate can reduce the generation of oxygen free radicals by providing a large number of high-energy phosphate bonds, so as to protect the integrity of muscle fiber membrane structure, increase the stability of ischemic myocardial potential changes, block cardiomyocyte apoptosis, restore the regulatory effect of autonomic nervous system on sinus node, improve heart rate variability and reduce the risk of major adverse cardiovascular events.

In conclusion, sodium creatine phosphate can reduce myocardial damage in STEMI patients with slow / no reflow during PCI, improve heart rate variability and left ventricular function, and reduce the risk of major adverse cardiovascular events.

Conflict of interest

The authors declare no conflict of interest.

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