



Effect of nicorandil on the myocardial tissue perfusion and myocardial cell injury in patients with diabetes after PCI

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ABSTRACT

Objective: To study the effect of nicorandil on the myocardial tissue perfusion and myocardial cell damage in patients with diabetes after percutaneous coronary intervention (PCI).

Methods: 68 patients with coronary heart disease and type 2 diabetes mellitus who received PCI in our hospital between May 2011 and September 2015 were collected and then divided into observation group and control group ($n=34$) according to the single-blind randomized control method. Control group of patients received PCI alone, and the observation group of patients received nicorandil therapy after PCI. After treatment, real-time myocardial ultrasound contrast was used to evaluate the myocardial perfusion of two groups of patients; blood biochemical analyzer was used to detect the contents of peripheral blood myocardial enzyme spectrum indexes; the ELISA method was used to detect the contents of serum oxidative stress indicators; RIA method was used to detect the contents of serum apoptosis molecules.

Results: After treatment, the myocardial tissue perfusion parameters plateau peak intensity (A), slope rate of curve (β) and myocardial blood flow ($A \times \beta$) levels of observation group were significantly higher than those of control group ($P < 0.05$); peripheral blood myocardial enzyme spectrum indexes creatine kinase (CK), lactate dehydrogenase (LDH), troponin I (cTnI) and glutamic oxalacetic transaminase (GOT) contents of observation group were significantly lower than those of control group ($P < 0.05$); serum vitamin E (VitE) and vitamin C (VitC) contents of observation group were significantly higher than those of control group while malondialdehyde (MDA), advanced oxidation protein products (AOPPs), soluble apoptosis-associated factor (sFas) and soluble apoptosis-associated factor ligand (sFasL) contents were lower than those of control group ($P < 0.05$). **Conclusion:** Adjuvant nicorandil therapy can improve the myocardial perfusion and reduce the myocardial cell injury in patients with coronary heart disease and diabetes mellitus after PCI.

1. Introduction

Percutaneous coronary intervention (PCI) is the main minimally invasive surgery for coronary heart disease, its reliable curative effect has been proven in many clinical researches, but there are also some researches showing that there is thrombus shedding and

distal vascular embolization in some patients after PCI[1]. Diabetes is an important complication of coronary heart disease, this type of patients is with severer condition, and the risk of myocardial injury is bigger after PCI[2,3]. Nicorandil is ATP-sensitive potassium channel opener, and clinical studies have confirmed that the drug is suitable for all kinds of angina pectoris, and helps to reduce the risk of cardiovascular events[4]. At present, there is no clear report about the effect of nicorandil for peri-PCI treatment in diabetic patients with coronary heart disease. In the following study, the effect of nicorandil on the myocardial blood perfusion and myocardial cell damage in patients with diabetes after PCI was analyzed.

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2. Materials and methods

2.1. Inclusion and exclusion criteria

Inclusion criteria: (1) diagnosed with coronary heart disease by coronary angiography; (2) diagnosed with type 2 diabetes mellitus; (3) complying with the PCI indications; (4) participating in the whole treatment and examination, and with complete clinical data. Exclusion criteria: (1) with previous history of myocardial infarction; (2) with severe liver and kidney dysfunction; (3) associated with systemic infectious diseases; (4) with nicorandil allergy; (5) with recent nicorandil-taking history.

2.2. Clinical information

68 patients with both coronary heart disease and type 2 diabetes mellitus who received PCI in our hospital between May 2011 and September 2015 were collected, and all the patients signed the informed consent. According to the single blind randomized control method, the patients were divided into observation group and control group ($n=34$). Control group of patients included 19 male cases and 15 female cases, they were 43–71 years old, and the body mass index (BMI) was $22\text{--}29\text{ kg/m}^2$ and $(24.71\pm 2.95)\text{ kg/m}^2$ in average; observation group included 18 male cases and 16 female cases, they were 42–73 years old, and the BMI was $21\text{--}29\text{ kg/m}^2$ and $(24.09\pm 2.76)\text{ kg/m}^2$ in average. Two groups of patients were not statistically different in gender, age and BMI distribution ($P>0.05$), and the research was approved by the hospital ethics committee.

2.3. Therapy

Control group received routine treatment before PCI such as anticoagulation, antiplatelet and oxygen uptake, and the observation group received nicorandil therapy on the basis, which was as follows: oral administration of nicorandil tablets (Henan Qianfeng Pharmaceutical Technology Co., LTD., approved by H41024500) 24–72 h before operation, 5–10 mg/times, t.i.d.

2.4. Observation indexes

2.4.1. Myocardial blood perfusion

After treatment, real-time myocardial ultrasound contrast was used to evaluate myocardial perfusion in two groups of patients, and the specific parameters included plateau peak intensity (A), slope rate of curve (β) and myocardial blood flow ($A\times\beta$).

2.4.2. Myocardial enzyme spectrum

After treatment, 2 mL of peripheral venous blood was extracted

from two groups of patients, and blood biochemical analyzer (German Roche Diagnostics Co., LTD., models cobas b) was used to detect the contents of myocardial enzyme spectrum indexes, including creatine kinase (CK), lactate dehydrogenase (LDH), troponin I (cTnI) and glutamic oxalacetic transaminase (GOT).

2.4.3. Serum indexes

After treatment, 2 mL of peripheral venous blood was extracted from two groups of patients, let stand at room temperature overnight and centrifuged at low speed to get supernatant, and the following indexes were detected: (1) oxidative stress indexes: enzyme-linked immunosorbent assay (ELISA) was used to detect serum oxidative stress index levels, including vitamin E (VitE), vitamin C (VitC), malondialdehyde (MDA) and advanced oxidation protein products (AOPPs). (2) Apoptosis molecules: RIA method was used to detect soluble apoptosis-associated factor (sFas) and soluble apoptosis-associated factor ligand (sFasL).

2.5. Statistical analysis

SPSS18.0 software was used for statistical processing, measurement data in the study was in terms of mean \pm standard deviation ($\bar{x}\pm s$), comparison between groups after treatment was by grouping t test and $P<0.05$ indicated statistical significance in differences.

3. Results

3.1. Myocardial blood perfusion of two groups of patients after treatment

After treatment, comparison of myocardial blood perfusion parameters A, β and $A\times\beta$ levels between two groups of patients was as follows: after treatment, the myocardial blood perfusion parameters A, β and $A\times\beta$ levels of observation group were significantly higher than those of control group. Differences in myocardial blood perfusion parameters A, β and $A\times\beta$ levels were statistically significant between two groups of patients after treatment ($P<0.05$), shown in Table 1.

Table 1

Comparison of myocardial blood perfusion parameter levels after treatment ($n=34, \bar{x}\pm s$).

Groups	A (dB)	β (/s)	$A\times\beta$ (dB/s)
Observation group	6.92 ± 0.75	0.84 ± 0.09	6.01 ± 0.65
Control group	6.05 ± 0.67	0.75 ± 0.08	5.17 ± 0.59
t	5.891	5.763	6.091
P	<0.05	<0.05	<0.05

3.2. Myocardial enzyme spectrum of two groups of patients after treatment

After treatment, comparison of peripheral blood myocardial enzyme spectrum indexes CK, LDH, cTnI and GOT contents between two groups of patients was as follows: peripheral blood myocardial enzyme spectrum indexes CK, LDH, cTnI and GOT contents of observation group were significantly lower than those of control group. Differences in peripheral blood myocardial enzyme spectrum indexes CK, LDH, cTnI and GOT contents were statistically significant between two groups of patients after treatment ($P < 0.05$), shown in Table 2.

Table 2

Comparison of peripheral blood myocardial enzyme spectrum index contents after treatment ($n=34, \bar{x} \pm s$).

Groups	CK (ng/L)	LDH (U/L)	cTnI (ng/L)	GOT (U/L)
Observation group	22.98±2.65	194.77±18.23	78.92±8.64	9.15±0.97
Control group	46.25±5.09	241.65±28.84	115.83±10.58	16.42±1.94
<i>t</i>	9.203	8.192	9.827	7.293
<i>P</i>	<0.05	<0.05	<0.05	<0.05

3.3. Oxidative stress indexes of two groups of patients after treatment

After treatment, comparison of serum oxidative stress indexes VitE, VitC, MDA and AOPPs contents between two groups of patients was as follows: serum VitE and VitC contents of observation group were significantly higher than those of control group while MDA and AOPPs contents were significantly lower than those of control group. Differences in serum oxidative stress indexes VitE, VitC, MDA and AOPPs contents were statistically significant between two groups of patients after treatment ($P < 0.05$), shown in Table 3.

Table 3

Comparison of serum oxidative stress index contents after treatment ($n=34, \bar{x} \pm s$).

Groups	VitE (μg/mL)	VitC (μg/mL)	MDA (μmol/L)	AOPPs (μmol/L)
Observation group	7.15±0.82	27.79±3.41	4.09±0.53	2.36±0.35
Control group	6.05±0.65	20.22±2.78	7.53±0.89	5.17±0.68
<i>t</i>	5.882	7.192	6.993	6.281
<i>P</i>	<0.05	<0.05	<0.05	<0.05

3.4. Apoptosis molecules of two groups of patients after treatment

After treatment, comparison of serum apoptosis molecules sFas and sFasL contents between two groups of patients was as follows: serum sFas content (207.58±24.86) pg/mL and sFasL content (147.32±18.56) pg/mL of observation group were significantly lower than sFas content (345.76±41.69) pg/mL and sFasL content (225.58±32.72) pg/mL of control group. Differences in serum apoptosis molecules sFas and sFasL contents were statistically significant between two groups of patients after treatment ($P < 0.05$).

4. Discussion

Many studies have shown that there is myocardial injury after PCI, and the study of Yang *et al* has shown that the incidence of myocardial injury after PCI is as high as 1/3 in patients with stable angina and the probability is higher in patients with unstable angina[5]. Nicorandil is the first ATP-sensitive potassium channel opener applied to clinical practice, it can relax vascular smooth muscle, increase coronary blood flow, inhibit the potential-dependent calcium ions release, and so on, and it can also reduce the myocardial oxygen consumption, increase myocardial oxygen supply and double improve myocardial ischemia state[6,7]. Myocardial ultrasound contrast was first introduced in this study to define the myocardial blood supply after PCI, and it was found that compared with the control group, the observation group of patients were with higher postoperative myocardial ultrasound contrast parameters A, β and $A \times \beta$ levels. A represents myocardial blood flow, β represents myocardial blood flow velocity, $A \times \beta$ is on behalf of the myocardial blood flow, and the above results show that preoperative intravenous nicorandil can increase myocardial blood supply, which is consistent with previous research results, and once again confirming the role of the drug in the optimizing patients' myocardial function after PCI.

Myocardial dysfunction after PCI is directly related to myocardial ischemia-reperfusion injury and the resulting inflammatory and oxidative stress response, nicorandil can simulate ischemic preconditioning, and therefore, it has obvious myocardial protective effect[8,9]. When myocardial injury occurs, a large number of enzymes indexes are produced, and their contents are positively correlated with the degree of myocardial injury[10]. CK, LDH, cTnI and GOT are all commonly studied clinical myocardial enzyme spectrum indexes, and comparison of the above indicator levels between two groups of patients in this study showed that compared with the control group of patients, the observation group of patients were with lower peripheral blood CK, LDH, cTnI and GOT contents ($P < 0.05$), indicating that the intravenous nicorandil before PCI can reduce the myocardial enzyme spectrum index contents in the blood circulation, and is the visual symbol of relieved myocardial injury in patients.

Oxidative stress is an important part of the myocardial injury after PCI, and nicorandil can strengthen mitochondria potassium ion reflux and depolarization, and inhibit myocardial cell calcium ion reflux and intracellular mitochondria ischemia so as to reduce reactive oxygen species[11,12]. It has been found in the oxidative stress rat models that nicorandil can realize the inhibitory effect on oxidative stress by NO/cGMP and ATP-sensitive potassium channels[13,14]. In the study, serum oxidative stress indicator contents of two groups of patients were detected after treatment, and it was found that compared with the control group of patients, the observation group of patients were with higher VitE and VitC contents, and lower MDA and AOPPs contents after treatment

($P < 0.05$). VitE and VitC are the typical antioxidant vitamins, their contents are in a stable state in the body, and when a large number of oxygen free radicals are produced, VitE and VitC are neutralized and lowly expressed. Both MDA and AOPPs are lipid oxidation metabolites, and their contents are in line with the levels of oxidative stress in the body. The above results show that nicorandil application before PCI for coronary heart disease patients with diabetes mellitus can inhibit systemic oxidative stress state, and this is the one of the important mechanisms for it to exert myocardial protective effect.

There is myocardial cell dysfunction after myocardial ischemia, and there is irreversible apoptosis in the case of severe ischemia. Nicorandil belongs to nicotinamide derivative, and can produce nitric oxide (NO) and combine its effect on reducing myocardial cell calcium overload to realize the effects of relaxing vascular smooth muscle, expanding capillaries and improving the myocardial perfusion[15,16]. Myocardial perfusion improvement can reduce myocardial cell apoptosis, and the reduced myocardial cell apoptosis is the intuitive performance of good myocardial perfusion. sFas and sFasL are the most typical myocardial apoptosis molecules, and the sFas and sFasL are produced in great quantities in cells of patients with coronary heart disease in the case of acute myocardial infarction attack, they cross the damaged cell membrane and are released into the blood, and high serum levels of sFas and sFasL are the most intuitive indexes for myocardial cell injury and apoptosis[17,18]. In the study, serum apoptosis molecule contents of two group of patients were detected, and it was found that compared with the control group of patients, the observation group of patients were with lower serum sFas and sFasL contents after treatment ($P < 0.05$), it confirms that adding nicorandil before PCI can inhibit myocardial cell apoptosis, and this is the composite results after the drug increases myocardial perfusion, inhibits oxidative stress, etc.

Nicorandil has positive value for peri-PCI application in patients with both coronary heart disease and diabetes mellitus, it can improve the myocardial perfusion after PCI and reduce myocardial cell injury, and it's worthy of popularization and application in clinical practice in the future.

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