Tropical Journal of Pharmaceutical Research January 2019; 18 (1): 123-127
ISSN: 1596-5996 (print); 1596-9827 (electronic)

Available online at http://www.tjpr.org
http://dx.doi.org/10.4314/tjpr.v18i1.18

Original Research Article

Effect of recombinant human brain natriuretic peptide on myocardial enzymes and cardiac function after percutaneous coronary intervention in patients with acute myocardial infarction

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Sent for review: 15 October 2018 *Revised accepted: 23 December 2018*

Abstract

Purpose: *To study the effect of recombinant human brain natriuretic peptide rhBNP on myocardial enzymes and cardiac function following percutaneous coronary intervention (PCI) in acute myocardial infarction (AMI) subjects.*

Methods: *Patients with AMI (124 cases) subjected to PCI for 2 years were used as subjects in this investigation. Two groups of patients were used (62 patients per group). One group received rhBNP while the other group served as control. The patients consisted of 76 males and 48 females (mean age, 63.54 ± 12.31 years). The two groups of patients received 75 mg/kg body weight of clopidogrel orally and aspirin (300 mg/kg) 2 h before PCI. The peaks of creatine kinase (CK), creatine kinase MB (CK-MB), and the levels of troponin I (cTnI) were assayed at pre-determined intervals with an automated biochemical analyzer, and changes in the enzyme levels were recorded. Echocardiography (ECG) parameters were also measured.*

Results: *Lower peaks of CK, CK-MB and levels of cTnI were seen in rhBNP-treated patients, when compared with controls ($p < 0.05$). Total effectiveness was markedly higher in rhBNP-treated group than in control group ($p < 0.05$). Moreover, myocardial infarct size was significantly lower in rhBNP treatment group than in control group ($p < 0.05$).*

Conclusion: *Treatment with rhBNP before PCI in patients with AMI increases coronary blood flow, ameliorates perfusion injury, inhibits left ventricular remodeling, reduces myocardial cell necrosis, and improves cardiac function and prognosis.*

Keywords: *Recombinant human brain natriuretic peptide (rhBNP), Acute myocardial infarction, percutaneous coronary intervention, Myocardial enzymes, Cardiac function*

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INTRODUCTION

Acute myocardial infarction (AMI) refers to myocardial necrosis caused by acute and persistent ischemia and hypoxia in coronary arteries. The most common clinical manifestation of AMI is angina pectoris. In Europe and the United States, about 1.5 million people suffer

from myocardial infarction annually, and in China its incidence has gradually risen in recent years. At present, available treatment options for AMI include drug therapy, bone marrow mesenchymal stem cell (BMSCS) transplantation, and percutaneous coronary intervention (PCI) [1].

Clinically, PCI not only reduces the incidence of myocardial infarction, but also confers protection to the myocardium [2]. Although PCI is an effective procedure, direct and elective PCI come with some risk, because they may lead to distal thrombotic obstruction. Thus, the myocardial tissue may not achieve blood perfusion in the infarct area, which inevitably leads to different degrees of deterioration of cardiac functions in patients [3]. In a previous study, it was reported that some patients usually come down with heart failure after PCI [4].

Recombinant human brain natriuretic peptide (rhBNP) is a first-line drug for the treatment of AMI because it can significantly increase myocardial blood supply and coronary blood flow in patients with heart failure. This investigation was carried out to study the effect of rhBNP on myocardial enzymes and heart function after PCI in patients with AMI.

EXPERIMENTAL

Patients and general information

Patients with AMI (124 cases) subjected to PCI for two years were used as subjects in this investigation. The patients were randomly assigned to two groups of 62 patients each: patients treated with rhBNP and control group. The AMI subjects consisted of 76 men and 48 women (mean age = 63.54 ± 12.31 years). Patients who met the criteria for AMI by World Health Organization (WHO) were selected. The exclusion parameters were: (1) patients who had cardiogenic shock, insufficient circulating blood volume, or other clinical conditions; (2) patients whose angiography results showed distal and proximal indicators of thrombolysis in myocardial infarction (TIMI) grade > 0; (3) patients who had liver, kidney, and heart diseases; (4) patients with a history of myocardial infarction; and (5) patients who were allergic to rhBNP. The patients signed written informed consent with their family members. Age, risk factors and time of onset were comparable between the two groups of patients.

This study received approval from Ethical Committee of Cardiology Department, Provincial Hospital Affiliated to Shandong University, Jinan, Shandong (approval no. 20183143), and carried out in line with the guidelines of Helsinki Declaration of 1964, as amended [5].

Treatment regimen

The two groups of patients received 75 mg/kg of clopidogrel orally and aspirin (300 mg/kg) 2 h before PCI.

Control group

Immediately after the onset of symptoms, heart function was controlled in the patients by intravenous injection of nitroglycerin at doses based on hemodynamics and blood pressure.

RhBNP treatment group

Intravenous bolus dose of 1.5 μg/kg rhBNP was given within 90 sec and the drip was controlled at a rate of 0.015 to 0.030 μg/kg min according to the patient's blood pressure and hemodynamics. The duration of treatment in the two groups was 7 days. During the course of treatment, anti-platelet drugs and blood lipid-lowering drugs were administered according to relevant guidelines based on the patient's clinical condition.

Assessment indices

Blood was drawn at intervals of 2 h after admission and 1 day after surgery, and at the end of the second day, blood was taken at intervals of 12 h. The peaks of creatine kinase (CK), CK-MB, and the levels of troponin I (cTnI) were determined using an automated biochemical analyzer, and changes in the enzyme dynamics were recorded.

Echocardiography (ECG) was performed at 1, 4, and 12-week intervals after surgery, and the left ventricular end diastolic diameter (LVEDD), left ventricular ejection fraction (LVEF), stroke volume (SV), and left ventricular diastole were also measured, and their mean values taken.

TIMI blood flow classification

Grade 0 = no perfusion; grade II = partial perfusion; and grade III = complete perfusion [6].

Evaluation of efficacy

This was determined based on Killip Grading Standard as follows: Level 2 and above = markedly effective; level 1 = improved; and level 0 = ineffective. The total effectiveness was calculated using the formula:

$TE\ (\%) = \{(S + I)/43\}100$ …… (1)

where *TE* is total effectiveness; *S* is significant effectiveness; *I* is improved effectiveness

Statistical analysis

The results are presented as mean ± SEM, and were analyzed with SPSS version 20.0. Groups were compared with *t*-test. Quantitative data were compared between groups using χ^2 test. Fisher's exact probability test was employed for analysis of TIMI grades after PCI. Statistical significance was fixed at $p < 0.05$.

RESULTS

Cardiac function after PCI

As shown in Table 1, significantly lower peaks of CK, CK-MB and lower cTnI levels were seen in the rhBNP-treated patients, relative to the control group ($p < 0.05$).

Table 1: Cardiac function after PCI

Group	CK Peak (mol/l)	CK-MB Peak (mol/l)	cTnI (µg/l)
Control	1586.64 ± 847.52	161.63 ± 82.45	15.67 ± 2.40
rhBNP	1167.51 ± 721.23*	112.73 ± 65.42*	10.35 ± 2.34*
χ^2	2.97	3.66	12.50
p	0.0036	0.0004	< 0.01

Electrocardiography results

There were no significant differences in LVEDD, LVEDV, LVESV, LVEF and SV between the control and rhBNP treatment groups 1 week after surgery ($p > 0.05$). At the end of 4 weeks post-operation, LVEDD, LVEDV and LVESV were markedly lower in the rhBNP-treated patients, relative to the control group ($p < 0.05$). However, LVEF and SV were significantly higher in rhBNP-treated patients than in control patients ($p < 0.05$). At 12 weeks post-operation, LVEDD, LVEDV and LVESV were significantly lower in rhBNP-treated patients than in controls, but LVEF and SV in the rhBNP patients were significantly higher ($p < 0.05$, Table 2).

Therapeutic effectiveness

Table 3 shows that total effectiveness in the rhBNP treatment group was significantly higher than that in the control group ($p < 0.05$).

Infarct-related angiography and myocardial infarction size

As shown in Table 4, pre-operative TIMI grading and immediate post-operative TIMI in both groups were comparable ($p > 0.05$). However, rhBNP treatment brought about significant decrease in myocardial infarct size ($p < 0.05$).

Table 2: ECG parameters

Group	LVEDD/mm	LVEDV/mm	LVESV /ml	LVEF/%	SV/ml
Control					
1 post-surgery	57.91 ± 1.92	79.19 ± 6.24	29.85 ± 3.87	48.20 ± 5.13	48.22 ± 6.05
4 weeks post-surgery	58.42 ± 4.95	80.19 ± 6.03	29.99 ± 3.51	51.62 ± 5.31	47.83 ± 7.64
12 weeks post-surgery	57.74 ± 2.92	80.96 ± 5.89	29.89 ± 3.47	51.25 ± 4.79	50.72 ± 4.78
RhBNP treatment					
1 week post-surgery	58.21 ± 3.03	81.28 ± 6.43	29.89 ± 2.73	49.87 ± 4.35	49.04 ± 6.26
4 weeks post-surgery	56.21 ± 4.37*	72.76 ± 4.82*	25.40 ± 2.40*	55.19 ± 5.94*	49.27 ± 5.08*
12 weeks post-surgery	55.02 ± 2.34#	71.25 ± 4.35#	24.98 ± 2.37#	56.08 ± 5.86#	53.91 ± 5.53#

*$P < 0.05$, relative to control; #$p < 0.01$, relative to levels at same time point

Table 3: Therapeutic efficacy (N, %)

Group	Significant effect	Improved	Ineffective	Overall efficacy
Control	24 (38.71)	21 (33.87)	17 (27.42)	45 (72.58)
RhBNP	33 (53.22)	23 (37.10)	6 (9.68)	56 (90.32)*
χ^2				6.4589
P-value				0.0110

*$P < 0.05$, relative to control group

Table 4: Infarct-related angiography and myocardial infarction size (n, %)

Parameter	Control (n = 62)	rhBNP-treated (n = 62)	t/χ^2	*P*-value
Preoperative TIMI classification (grade)				
0	47 (75.81)	50 (80.65)	0.4261	0.5139
Ⅰ	11 (17.74)	9 (14.52)	0.2385	0.6253
Ⅱ	4 (6.45)	3 (4.84)	0.0000	1.0000
Immediately after surgery TIMI (case)				
Ⅰ	1 (1.61)	0 (0.00)	-	0.6336
Ⅱ	6 (9.68)	4 (6.45)	0.4351	0.5095
Ⅲ	55 (88.71)	58 (93.55)	0.8978	0.3434
Myocardial infarct size (cm^2)	8.72 ± 2.15	7.75±1.38*	37.4871	< 0.01

*P < 0.05, relative to control

DISCUSSION

Acute myocardial infarction (AMI), a critical condition caused by the rupture of vascular plaque, causes thrombosis which leads to acute occlusion of blood vessels. The incidence, mortality and disability caused by AMI are on the increase, with age, history of diabetes, systolic blood pressure, left ventricular ejection fraction, and myocardial enzymes as risk factors associated with complications of the disease [7]. Creatine kinase (CK) and CK-MB are myocardial enzymes which reflect myocardial damage. The activities of these enzymes increase to varying degrees when myocardial damage or necrosis occurs. Clinically, CK and CK-MB are used as common indicators for monitoring the development of AMI.

Troponin I (cTnI) is one of the three subunits of cardiac and skeletal muscle contractile regulatory proteins (troponin), and it is often used as an indicator in the diagnosis of myocarditis [8]. Direct PCI in the treatment of AMI can reduce or slow down recurrent myocardial ischemia, recurrent myocardial infarction, stroke and death. When compared to drugs used in perfusion therapy, direct PCI can reduce the mortality rate of AMI to 4 - 6 % [9]. Brain natriuretic peptide (BNP) is produced in the ventricle and it serves as a quantitative marker of heart failure, reflecting left ventricular systolic dysfunction, right ventricular diastolic dysfunction, valvular dysfunction, and right ventricular dysfunction [9].

RhBNP is a synthetic endogenous hormone with the same amino acid sequence as BNP in dilated blood vessels. It exerts the same biological effect as BNP in protecting the heart [10].

In the present study, the peaks of CK, CK-MB and levels of cTnI in the rhBNP-treated patients were significantly decreased. The LVEDD, LVEDV, LVESV, LVEF and SV were comparable between the control and rhBNP treatment group at 1 week after surgery. At the end of 4 weeks post-operation, LVEDD, LVEDV and LVESV were significantly lower in the rhBNP treatment group than in the control group.

However, the LVEF and SV in the rhBNP treatment group were significantly higher than those in the control group. At 12 weeks post-operation, LVEDD, LVEDV and LVESV were significantly decreased in the rhBNP-treated patients, while LVEF and SV were markedly increased in the patients treated with rhBNP. It has been suggested that rhBNP can significantly improve myocardial injury caused by ischemia and hypoxia, probably by increasing coronary blood flow, reducing resistance to circulation, delaying or preventing ventricular remodeling, and preventing the expansion of myocardial infarct size, thus protecting heart function [11]. Similar findings have been reported in other studies [12,13].

Treatment with rhBNP resulted in markedly higher clinical effectiveness, when compared with patients who were not exposed to rhBNP. This indicates that early treatment with rhBNP is very effective in patients undergoing PCI. The myocardial infarct size in the rhBNP-treated patients was markedly decreased, when compared with that in the control group. These results demonstrate that rhBNP inhibits left ventricular myocardial remodeling after an AMI event, which is in agreement with earlier findings [14]. It is possible that rhBNP may prevent and improve the level of ventricular remodeling by inhibiting growth factors and the proliferation, differentiation and protoplast synthesis of cardiac fibroblasts. In a previous study, it was reported that early use of rhBNP in patients with AMI can

significantly reduce myocardial cell necrosis, improve left ventricular remodeling, and improve cardiac function [15].

Limitations of the study

This research was followed up for only 12 weeks. Thus, long-term effectiveness of the treatment is unclear.

CONCLUSION

Treatment with rhBNP before PCI in patients with AMI improves cardiac function and prognosis.

DECLARATIONS

Conflict of Interest

No conflict of interest associated with this work.

Contribution of Authors

We declare that this work was done by the author(s) named in this article and all liabilities pertaining to claims relating to the content of this article will be borne by the authors. All authors read and approved the manuscript for publication. Lianqun Cui conceived and designed the study. Yuntao Cheng, Guangxia Yang, Yuansheng Tang, Chuanfang Li, Meng Zhang and Lianqun Cui collected and analyzed the data. Yuntao Cheng wrote the manuscript.

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