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Influence of recombinant human B-type natriuretic peptide on improving ventricular function in patients with ST elevation myocardial infarction

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Abstract. – OBJECTIVE: The aim of this study was to investigate the effect of recombinant human B-type natriuretic peptide (rhBNP) on improving ventricular function in patients with ST-elevation myocardial infarction (STEMI).

PATIENTS AND METHODS: In this retrospective study, 96 patients with STEMI admitted to Cangzhou Central Hospital from June 2017 to June 2019 were recruited and randomized to either a control group or an experimental group, with 48 patients in each group. Patients in both groups were given conventional pharmacological therapy, and an emergency coronary intervention was performed within 12 hours. Patients in the experimental group received rhBNP intravenously postoperatively, whereas patients in the control group received an equal amount of 0.9% NaCl solution through an intravenous drip. Postoperative recovery indicators were compared between the two groups.

RESULTS: Patients treated with rhBNP showed better postoperative respiratory frequency, heart rate, blood oxygen saturation, pleural effusion, acute left heart remodeling after surgery and central venous pressure at 1-3 days after surgery than those without ($p<0.05$). Early diastolic blood flow velocity/early diastolic motion velocity (E/Em) and wall-motion score indices (WMSI) of patients in the experimental group were markedly lower compared to the control group one week after surgery ($p<0.05$). Patients receiving rhBNP had better left ventricular ejection fraction (LVEF) and WMSI six months after surgery and higher left ventricular end diastolic volume (LVEDV) and LVEF one week after surgery than the controls ($p<0.05$). Administration of rhBNP for patients with STMI provided a higher treatment safety by significantly reducing the incidence of left ventricular remodeling and complication than conventional medication ($p<0.05$).

CONCLUSIONS: Intervention with rhBNP in STEMI patients could effectively inhibit ventricular remodeling, alleviate symptoms, reduce adverse complications and improve ventricular function.

Key Words:
Recombinant human B-type natriuretic peptide, ST-segment elevation myocardial infarction, Myocardial infarction, Ventricular function, Surgery.

Introduction

Acute myocardial infarction is the most common cardiovascular disease in middle-aged and elderly people. In recent years, its clinical incidence has increased significantly, along with the aging of the population and changes in diet. Additionally, massive myocardial ischemia and hypoxia cause cardiac pump failure, which leads to systemic multi-organ insufficiency and even sudden death. Therefore, acute myocardial infarction combined with left-heart failure has become a health concern in China. Its treatment and prevention have become an important topic of research[1,2]. The term ST-segment elevation in myocardial infarction (STEMI) is defined as the electrocardiograph (ECG) presentation of patients with myocardial infarction[3]. The disease is primarly caused by a plaque in the coronary arteries. Plaque rupture or formation of blood clots in vessels will cause ischaemia and hypoxia, leading to necrosis of the heart muscle cells and serious damage to the heart[4].

Currently, this disease is managed with emergency percutaneous coronary intervention,

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which yields a satisfactory outcome. However, it is associated with arterial dysfunction or necrosis after successfully opening the artery, leading to poor prognoses such as arrhythmia and heart failure. Recombinant human B-type natriuretic peptide (rhBNP) is a peptide equivalent in amino acid sequence to human BNP made by recombinant DNA technology and has a dilating effect on normal coronary arteries. It has been reported[5] that rhBNP could specifically bind to natriuretic peptide receptor A, thereby increasing the content of cyclic guanosine phosphate in cells, activating protein kinase and protecting the myocardium.

In traditional Chinese medicine, myocardial infarction belongs to the category of 'chest paralysis', 'syncopalgia' and 'true heart pain', and the cause of myocardial infarction is the deficiency of heart Qi or/and Yin. The TCM medical book The Yellow Emperor's Internal Canon of Medicine[6] records that "the heart is the master of the five viscera and harbors the spirit, and injury to the heart causes pain". Yang deficiency leads to a deficiency of heart Qi and poor blood flow, thereby blocking the blood vessels and triggering 'chest paralysis'. Thus, the main treatment should lie in Yang promotion and paralysis clearance. However, there are fewer studies on the clinical therapy of STEMI patients. To this end, 96 STEMI patients who attended our hospital were selected for a retrospective study to examine the effect of rhBNP on ventricular function, with the aim of providing theoretical support for the clinical treatment of STEMI.

Patients and Methods

Participants

The clinical data of 96 STEMI patients admitted to Cangzhou Central Hospital from June 2017 to June 2019 were collected for prospective analysis, and they were randomized into the control group and the experimental group at a ratio of 1:1. The participants consisted of 63 males and 33 females, aged 61-82 years. Patients in both groups received conventional medical treatment, and the appropriate emergency coronary intervention was performed within 12 hours. The two groups were well-balanced in terms of baseline patient profiles.

The randomization was carried out using an online web-based randomization tool (freely available at http://www.randomizer.org/). For concealment of allocation, the randomization procedure and assignment were managed by an independent research assistant who was not involved in screening or evaluation of the participants.

The original sample size calculation estimated that 45 patients in each group would be needed to detect a 3-point difference between groups in a 2-sided significance test with a power of 0.8 and an alpha error level of 0.05.

Inclusion and Exclusion Criteria

A total of 105 patients were recruited originally, and 96 eligible participants were finally enrolled after excluding 9 patients who met the exclusion criteria. The flow chart of this study is shown in Figure 1.

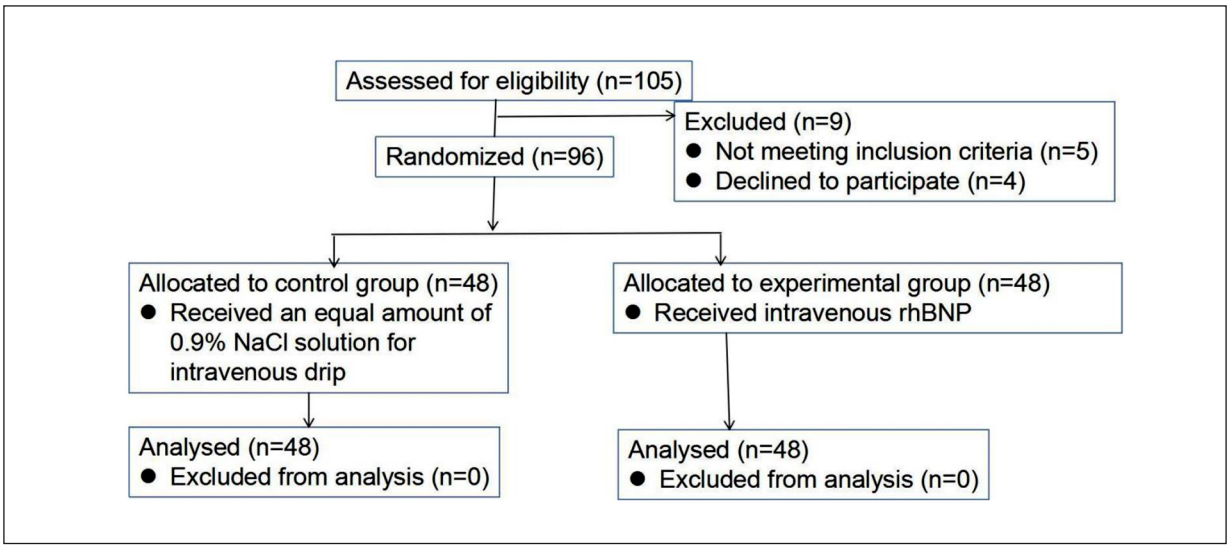

Figure 1. Flow chart of the study.

Inclusion criteria

1. Patients who met the clinical diagnostic criteria of STEMI;
2. Patients with first onset and with emergency coronary interventional therapy implemented within 12 hours after onset;
3. Patients with complete clinical medical records;
4. The patients' family members were aware of the purpose and process of this experimental study, and signed an informed consent form.

Exclusion criteria

1. Patients with co-morbidities of the brain, heart, kidney, liver and other organ tissue diseases;
2. Patients with severe aortic valve stenosis;
3. Patients with mental or other cognitive impairment or refused to cooperate in the experiment;
4. Patients with pulmonary heart disease or pulmonary hypertension induced by other causes;
5. Patients with a history of myocardial infarction, valvular heart disease, dilated cardiomyopathy, heart failure and hypertrophic cardiomyopathy, etc.

Methods

All patients were given the appropriate emergency treatment within 12 hours of disease onset. Postoperatively, both groups of patients received conventional STEMI treatment. The treatment drugs include clopidogrel tablets (specification: 75 mg×7 tablets, Lepu Pharmaceutical Co., Ltd., Beijing, China, NMPA approval number H20123116), aspirin (specification: 100 mg× 30 tablets, Bayer Healthcare Co., Ltd., Whippany, NJ, USA, NMPA approval number J20130078), Tirofiban (specification: 5 mg/100 ml, Hangzhou Zhongmei Huadong Pharmaceutical Co., Ltd., Hangzhou, China, NMPA approval number H20060265), Atorvastatin (specification: 10 mg×7 tablets, Pfizer Pharmaceutical Co., New York, USA, Ltd., NMPA approval number H20051407), Nitroglycerin (specification: 0.5 mg/tablet, Harbin Pharmaceutical Group Sixth Pharmaceutical Factory, Harbin, China, NMPA approval number H23021574), and small dose angiotensin-converting-enzyme inhibitors and B receptor blockers[7-9].

Patients in the experimental group received rhBNP (specification: 1 mg, Beijing Biolab Technology Co., Ltd., Beijing, China, NMPA approval number JN1946) on the basis of conventional treatment. The initial dose of 1.5-2.0 μg/kg was administered, and intravenous bolus was completed within 3 minutes, followed by intravenous infusion with a dose of 0.008 μg/(kg/min) for 3 days postoperatively[10-14]. Patients in the control group were given an equivalent amount of 0.9% NaCl solution.

The treatment duration in both groups spanned 1 week.

Additioanally, both groups were given Shenshu Yixin Tang on the basis of the prescription of 12 g of Ginseng, 15 g of Largehead Atractylodes Rhizome, 30 g of *Astragalus mongholicus*, 15 g of White Peony Root, 15 g of *Ligusticum wallichii*, 15 g of *Radix Salivae Miltiorrhizae*, 15 g of *Rhizoma Corydalis*, 10 g of *Panax notoginseng,* 15 g of peach kernel, 10 g of *Dalbergia odorifera*, 10 g of Scorpio, 6 g of Liquorice. The above materials were decocted in 450 mL of water and administered daily, with *Panax notoginseng*, *Dalbergia odorifera* and Scorpio being taken in powder. All the above materials were provided by the Chinese pharmacy of our hospital. The course of treatment for both groups was 14 days.

Indices Assessed

Postoperative clinical symptoms and vital signs

Indicators tested include respiratory frequency, heart rate, systolic blood pressure, blood oxygen saturation and chest X-ray. The ratio of acute left-side heart failure to pleural effusion after operation, and the levels of central venous pressure before operation, immediately after operation, as well as 1, 2, 3 and 7 days after operation were compared between the two groups.

Electrocardiography indicators

All patients underwent electrocardiography (ECG) examination one week after surgery, and the left ventricular end systolic volume (LVESV), left ventricular end diastolic volume (LVEDV), early diastolic blood flow velocity (E), mitral valve late diastolic blood flow velocity (A), early diastolic motion velocity (Em) of the valve annular and other related indicators were recorded to calculate the patient's left ventricular ejection fraction (LVEF), E/Em, E/A and wall-motion score index (WMSI). Patients were followed-up for six months after discharge, their ECG was reviewed, and the WMSI, LVEDV and LVEF were compared between the two groups.

Serum CTGF content and miR-92a expression level

The levels of serum connective tissue growth factor (CTGF) content and miR-92a were determined preoperatively, 24 h postoperatively and 1 week postoperatively.

Serum CTGF was determined using an enzyme-linked immunosorbent assay. Detection of miR-92a expression of miR-92a using the All-in-One™ miRNAqRT-PCR detection kit, and specific detection of the target gene miR-92a expression using a fluorescence real-time polymerase chain reaction instrument (Roche LightCycler 96, Basel, Switzerland).

Postoperative left ventricular remodeling

Based on the patient's ECG examination results, the left ventricular end-diastolic volume growth rate was calculated as ΔLVEDV% = [(LVEDV at half a year after surgery-LVEDV at 1 week after surgery)/LVEDV at 1 week after surgery]×100%, with ΔLVEDV ≥15% defined as ventricular remodeling and ΔLVEDV <15% as non-remodeling.

Complications

The number of complications of patients such as heart failure, recurrent myocardial infarction, arrhythmia, post-infarction angina, cardiogenic shock, and cardiac death was counted in both groups, and the incidence of complications was calculated.

Statistical Analysis

The data in this research was processed using the SPSS Statistics v. 22 (IBM Corp., Armonk, NY, USA), and GraphPad Prism 7 (GraphPad Software, San Diego, CA, USA) was used to plot graphics of this study. Normally distributed measures are expressed as mean plus or minus standard deviation ($\bar{x} \pm s$). Differences between groups were compared using One-Way analysis of variance, followed by Student's *t*-test, Wilcox rank-sum test, or Tukey's test. Differences with a *p*-value <0.05 were considered statistically significant.

Results

The Postoperative Vital Signs and Clinical Index Changes

Patients treated with rhBNP showed better postoperative respiratory frequency, heart rate, blood oxygen saturation, pleural effusion, acute left heart remodeling after surgery and central venous pressure at 1-3 days after surgery than those without ($p<0.05$). There was no statistical difference in postoperative systolic blood pressure and central venous pressure between the two groups before, immediately after and one week after surgery. ($p>0.05$) (Table I).

Comparison of the Postoperative ECG Indexes

In the experimental group, the E/Em and WMSI indicators were significantly lower than those of the control group one week after surgery ($p<0.05$), and the differences in LVEDV, LVESV, LVEF and E/A were not statistically significant ($p>0.05$). Patients receiving rhBNP had better LVEF and WMSI six months after surgery and higher LVEDV and LVEF one week after surgery than the controls ($p<0.05$), and the levels of LVEDV and LVEF were significantly higher at

Table I. Comparison of postoperative vital signs and clinical index changes in the two groups of STEMI patients (n=48).

Indexes	Control group	Experimental group	χ^2/t	*p*
Respiratory frequency (times/min)	33 ± 9	21 ± 5	8.0751	0.001
Systolic blood pressure (mmHg)	91 ± 10	92 ± 15	0.3843	0.7016
Heart rate (times/min)	98 ± 17	70 ± 14	8.8086	0.001
Blood oxygen saturation (%)	84 ± 15	91 ± 16	2.2113	0.0294
Pleural effusion (n)	33 (68.75)	11 (22.92)	20.3077	0.001
Acute left heart failure (n)	25 (52.08)	7 (14.58)	15.1875	0.001
Central venous Pressure (cmH_2O)				
Before operation	12 ± 2	11 ± 3	1.9215	0.0577
Immediately after operation	13 ± 4	11 ± 6	1.9215	0.0577
1 day after operation	16 ± 4	14 ± 3	2.7713	0.0067
2 days after operation	19 ± 5	13 ± 4	6.4920	0.001
3 days after operation	18 ± 6	14 ± 3	4.1312	0.0001
1 week after operation	15 ± 6	14 ± 5	0.8871	0.3773

Table II. Postoperative ECG indexes of the two groups of patients (n=48, $\bar{x} \pm s$).

Indexes	Control group	Experimental group	χ^2/t	p
One week before operation				
LVEDV (ml)	115 ± 16	113 ± 15	0.6318	0.5291
LVESV (ml)	63 ± 12	61 ± 13	0.7832	0.4355
LVEF (%)	45 ± 8	47 ± 8	1.2247	0.2237
E/A	1.3 ± 0.3	1.4 ± 0.3	1.6320	0.1058
E/Em	16 ± 5	12 ± 2	5.1461	≤ 0.001
WMSI	2.71 ± 0.46	1.70 ± 0.15	14.4624	≤ 0.001
Half a year after operation				
LVEDV (ml)	135 ± 47	128 ± 42	0.7694	0.4436
LVEF (%)	46 ± 8	53 ± 11	3.5656	0.0006
WMSI	2.01 ± 0.47	1.54 ± 0.33	5.6701	≤ 0.001

six months postoperatively compared to one week postoperatively (t=2.3302, 3.0562, and p=0.0219, 0.0029, respectively) (Table II).

Comparison of the Serum CTGF and MiR-92a Expression Levels

Figure 2 shows the serum CTGF levels of the two groups of patients before surgery, 24 hours after surgery, and one week after surgery.

Figure 3 shows the expression levels of miR-92a before, 24 hours after, and one week after operation.

Comparison of Left Ventricular Remodeling

Significant differences were identified in left ventricular remodeling between the two groups half a year after operation (p<0.001) (Table III).

Comparison of the Incidence of Postoperative Complications

Six months following surgery, the experimental group reported fewer postoperative complications than the control group (p<0.05) (Table IV).

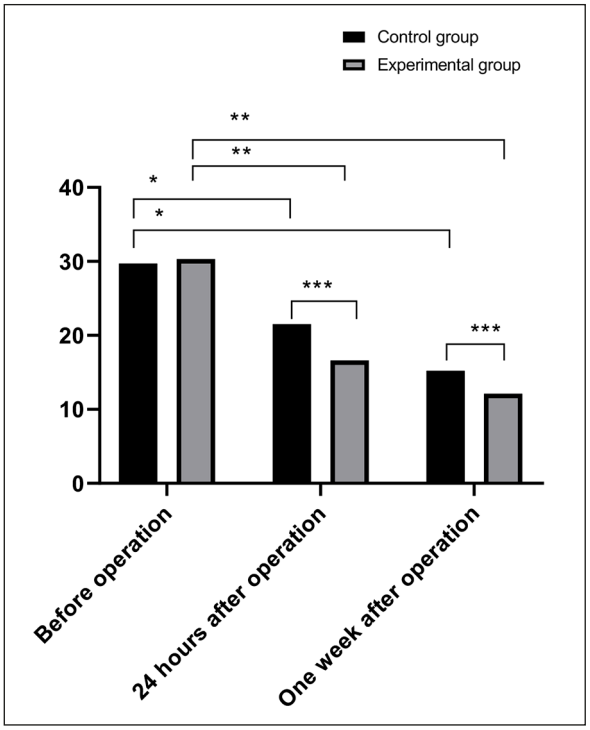

Figure 2. Serum CTGF levels of two groups of patients. The abscissa indicates the time point of the patient's serum test, including before operation, 24 hours after operation, and 1 week after operation, and the ordinate indicates serum CTGF content (μg/L). The serum CTGF levels of patients in the control group before operation, 24 hours after operation and 1 week after operation were 29.7±4.9 μg/L, 21.5±4.1 μg/L, 15.2±3.1 μg/L. The serum CTGF levels of patients in the experimental group before operation, 24 hours after operation and 1 week after operation were 30.3±5.0 μg/L, 16.6±3.4 μg/L, 12.1±2.7 μg/L. *From top to bottom, the CTGF content of the control group 24 hours after surgery and 1 week after surgery was significantly lower than that before surgery (t=8.8920, 17.3257, p<0.001). **From bottom to top, the levels of CTGF in the experimental group 24 hours after surgery and 1 week after surgery were significantly lower than that before surgery (t=15.6978, 22.1900, p<0.001). ***From left to right, the CTGF content of the experimental group at 24 hours and 1 week after surgery was significantly lower than that of the control group (t=6.3736 and 5.2244, p<0.001).

Discussion

This is the first study to assess the efficacy of rhBNP intervention and TCM, so as to preserve myocardial structure and function in humans with STEMI. This strategy, to be tested in a single center, randomized, double-blind, placebo-controlled trial, is designed to complement myocardial revascularization, with the hypothesis that the cardiac hormone BNP will prevent adverse post-acute myocardial infarction (AMI) LV remodeling when combined with interventional and conventional therapy and TCM.

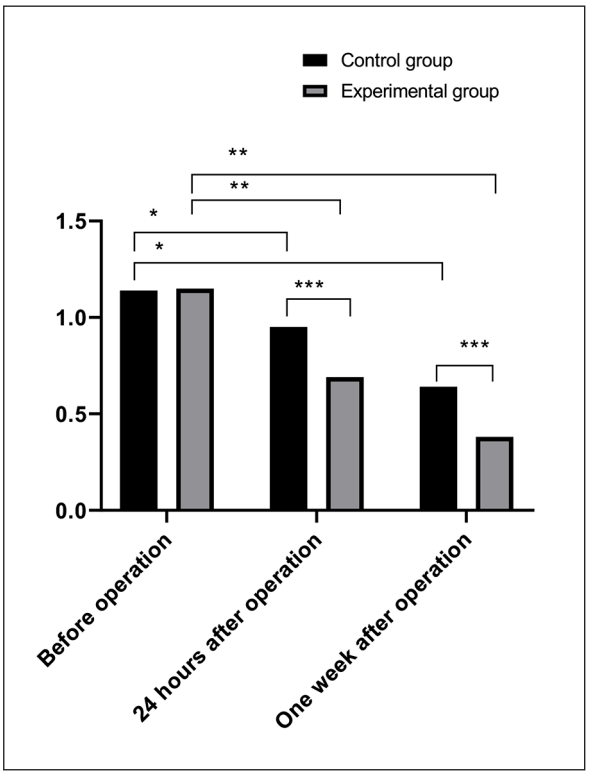

Figure 3. Serum miR-92a expression levels of two groups of patients. The abscissa represents the time point of patient serum testing, including before operation, 24 hours after operation, and 1 week after operation, and the ordinate represents the expression level of miR-92a. The expression levels of miR-92a in the control group before operation, 24 hours after operation and 1 week after operation were 1.14±0.32), 0.95±0.23, 0.64±0.16. The expression levels of miR-92a in the experimental group before operation, 24 hours after operation and 1 week after operation were 1.15±0.32, 0.69±0.16, 0.38±0.05. *From top to bottom, the expression levels of miR-92a in the control group at 24 hours and 1 week after surgery were significantly lower than those before surgery (t=3.3403 and 8.7903, both p<0.05). **From bottom to top, the expression levels of miR-92a in the experimental group at 24 hours and 1 week after surgery were significantly lower than those before surgery (t=8.9079, 16.4711, p<0.001). ***From left to right, the expression levels of miR-92a in the experimental group at 24 hours and 1 week after surgery were significantly lower than those in the control group (t=6.4292, 10.7459, respectively, p<0.001).

Acute myocardial infarction is one of the most critical diseases in the elderly, and left heart failure is its most serious clinical manifestation, which may lead to sudden death in severe cases. Currently, it is mostly managed with oxygenation, thrombolysis, anticoagulation, volume expansion, myocardial nutrition and antibiotic prophylaxis of infection[15,16]. Ventricular remodeling is based on edema or necrosis of cardiomyocytes following an acute myocardial infarction. Percutaneous coronary intervention is an effective method for early treatment of myocardial infarction, as it unblocks the infarcted artery to relieve symptoms and save the lives of STEMI patients. Re-perfusion of the infarcted artery may lead to myocardial instability, arrhythmia and enlargement of the infarcted region, as well as additional ischemia-reperfusion injury[17-20]. It has been found[21] that ischemia-reperfusion injury mainly involves immediate necrosis and subsequent apoptosis, whereas the opening of the mitochondrial membrane permeability transition pore plays a key role in post-reperfusion necrosis of cardiomyocytes. There are certain limitations to the effect of antagonists on perfusion injury. As a result, percutaneous coronary intervention (PCI) combined with medication treatment significantly minimizes ischemia and reperfusion injury and provides improved myocardial protection in STEMI patients. B-type natriuretic peptide is an endogenous active component that inhibits ventricular remodeling and provides cardioprotection[22].

In the present study, it was observed that postoperative respiratory frequency, heart rate, blood oxygen saturation, pleural effusion, acute left heart failure after operation, and central venous pressure at 1 to 3 days postoperatively were significantly improved after the administration of rhBNP than controls. The reason may be that recombinant human B-type natriuretic peptide is synthesized using recombinant DNA technology and has diuretic and vasodilator effects. It reduces blood volume, decreases cardiac load, relieves cardiac function, protects cardiomyocytes, and reduces myocardial cell damage through

Table III. Left ventricular remodeling of the two groups of patients (n=48) [n(%)].

Groups	ΔLVEDV% ≥ 15%		ΔLVEDV% < 15%
Control group	17 (35.42%)		31 (64.58%)
Experimental group	2 (4.17%)		46 (95.83%)
χ^2		14.7642	
p		≤ 0.001	

Table IV. Comparison of postoperative complications of the two groups of STEMI patients (n=48) [n(%)].

Groups	Arrhythmia	Heart failure	Post-infarction angina pectoris	Complication rate
Control group	11 (22.92%)	2 (4.17%)	2 (4.17%)	15 (3.125%)
Experimental group	2 (4.17%)	1 (2.08%)	0 (0%)	3 (6.25%)
χ^2				9.8462
p				0.002

anti-inflammatory, anti-oxidant and endothelial cell growth antagonistic effects. In addition, recombinant human B-type natriuretic peptide has neuroendocrine regulatory effects, antagonizes the renin-angiotensin-aldosterone system and endothelin, and blocks sympathetic excitability to myocardial and vasoconstriction, thereby exerting myocardial protective effects[23,24].

Moreover, the E/Em and WMSI indexes of patients in the experimental group were lower than those of the control group at 1 week after surgery, and the LVEF and WMSI indexes of patients in the experimental group were significantly higher than those of the control group six months after surgery, indicating that rhBNP binds to receptors *in vivo*, effectively dilates arteries, inhibits sympathetic nerves, improves the hemodynamic status of STEMI patients, and reduces the patient's myocardial fibrosis. It also blocks ventricular remodelling, which is essential for maintaining ventricular function. The results of the present study were consistent with the findings of Song et al[25], in which rhBNP effectively inhibits heart failure after myocardial infarction, protects the heart function of patients, and reduces oxidative stress damage. This may be related to the vasodilatory effects of BNP through multiple pathways, including nitric oxide (NO), prostaglandin release, ATP-sensitive potassium channels and inhibition of endothelin action. BNP increases intracellular cyclized guanosine monophosphate concentration by activating the membrane-coupled guanylate cyclase receptor A, thereby mediating the dilation of vascular smooth muscle[26]. The distribution of natriuretic peptide receptors on the coronary vessels of the heart suggests that BNP may have a coronary artery-dilating effect. Another study[27] found that the dilation of coronary vessels by BNP could be inhibited by NO synthase inhibitors and cyclooxygenase inhibitors (anti-inflammatory pain), while the dilation of vessels pretreated with glibenclamide, an endothelin or ATP-sensitive potassium channel inhibitor, was significantly increased, suggesting that one pathway of coronary dilation was blocked and that rhBNP may achieve its dilation of coronary vessels through multiple pathways.

In TCM, acute myocardial infarction is categorized as 'true heart pain'. Qi and blood are the most basic substances that constitute the human body. In cardiovascular terms, blood flow and heart activity are closely related to the driving effect of heart Qi. Smooth blood flow and abundant heart Qi are the material basis for the heart to perform its normal physiological functions. Ginseng in Shenshu Yixin Tang is a powerful tonic for vital energy; it restores the pulse, fixes the detachment, and generates fluid to nourish the blood. Largehead Atractylodes Rhizome benefits Qi and strengthens the spleen. White Peony Root nourishes the blood to regulate menstruation and relieve pain. *Ligusticum wallichii* promotes blood and Qi circulation to dispel wind and relieve pain. *Radix Salivae Miltiorrhizae* resolves blood stasis to relieve pain. *Rhizoma Corydalis* disperses stasis and relieves pain. *Panax notoginseng* disperses blood stasis to relieve pain and swelling. Peach kernel activates blood circulation and dispels blood stasis. *Dalbergia odorifera* reduces blood stasis, stops bleeding, regulates Qi and relieves pain. Scorpio disperses nodules and relieves pain. Liquorice harmonizes the herbs. Throughout the entire prescription, the main effects are to benefit Qi, invigorate blood and resolve blood stasis to relieve pain. Modern pharmacological studies[28-31] have shown that Shenshu Yixin Tang could effectively inhibit neutrophil chemotaxis, mitigate inflammatory responses, reduce vascular endothelial cell injury, and improve myocardial contractile function and microcirculation. Thus, the overall efficiency of the patients with acute myocardial infarction in the experimental group was higher than that of the control group, demonstrating that Shenshu Yixin Tang could reduce the symptoms and improve the efficacy.

This study, therefore, lays the foundation for a paradigm shifting concept which includes the combined use of acute revascularization to regain

myocardial perfusion, which may limit infarct size, remarkably inhibit ventricular remodeling, alleviate clinical symptoms, reduce the occurrence of adverse complications and improve ventricular function, so as to prevent unfavorable LV remodeling, preserve LV function and ultimately reduce the burden of heart failure.

Limitations

This study has some limitations, including the short period of follow-up, although we have tried to extend the follow-up duration. The age range of participants was limited and a wider age range will be investigated in the future. There is also a need to evaluate larger numbers of participants to assess more fully the safety of a relatively new therapy.

Conclusions

RhBNP intervention in STEMI patients can significantly inhibit ventricular remodelling, alleviate clinical symptoms, reduce the occurrence of adverse complications and improve ventricular function.

Conflict of Interest

The Authors declare that they have no conflict of interests.

Ethics Approval

The study protocol was approved by the Ethics Committee of Cangzhou Central Hospital [Approval No. 2020-065-01(Z)], and all processes complied with the Declaration of Helsinki Ethical Guidelines for clinical research.

Informed Consent

Informed consent was obtained from patients and signed prior to enrolment in the study.

Authors' Contribution

L. Yao and C.-J. Liu designed the research study. L. Zhang, Y. Lin and Y.-M. Hu performed the research, analyzed the data. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript.

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Availability of Data and Materials

All data generated or analysed during this study are included in this published article.

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