

Original Article

Effects of recombinant human brain natriuretic peptide on renal function in patients with acute heart failure following myocardial infarction

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Abstract: Objective: To investigate the effect of recombinant human brain natriuretic peptide (rhBNP) on renal function in patients with acute heart failure (AHF) following acute myocardial infarction (AMI). Methods: Consecutive patients with AHF following AMI were enrolled in this clinical trial. Eligible patients were randomly assigned to receive rhBNP (rhBNP group) or nitroglycerin (NIT group). Patients in the rhBNP group received rhBNP 0.15 µg/kg bolus injection after randomization followed by an adjusted-dose (0.0075-0.020 µg/kg/min) for 72 hours, while patients in NIT received infusion of nitroglycerin with an adjusted-dose (10-100 µg/kg/min) for 72 hours in NIT group. Standard clinical and laboratory data were collected. The levels of serum creatinine (SCr), urea, β-2 microglobulin and cystatin C were measured at baseline and repeated at the end of the 24, 48 and 72 hours after infusion. The primary end point was the incidence of acute renal dysfunction, which was defined as an increase in SCr > 0.5 mg/dl (> 44.2 µmol/L) or 25% above baseline SCr value. The occurrence of major adverse cardiac event (MACE) was followed up for 1 month. Results: Of the 50 patients enrolled, 26 were randomly assigned to rhBNP and 24 to nitroglycerin (NIT). There were no significant differences in baseline characteristics between the two groups (all $P > 0.05$). The baseline concentrations of SCr, urea, β-2 microglobulin and cystatin C at admission were similar in the two groups. However, the concentrations of SCr and urea were significantly higher in rhBNP group than those in NIT group at hour 24 and 48 after treatments (all $P < 0.01$). For both groups, the concentrations of SCr, urea, β-2 microglobulin and cystatin C were not significant changed compared with baseline levels. The levels of systolic blood pressure (SBP) and diastolic blood pressures (DBP) at admission were also similar between the two groups. In rhBNP group, levels of SBP and DBP decreased significantly at hour 24, 48 and 72 (all $P < 0.05$). In NIT group, levels of SBP decreased significantly at hour 48 and 72. The level of SBP at hour 24 and DBP at hour 48 after treatment were lower in rhBNP group than those in NIT group ($P < 0.01$). The occurrence of MACE was not significantly different. The incidence of acute renal dysfunction in rhBNP group was higher (9/26 vs. 2/24, $P = 0.040$). The results of multiple logistic regression found that the use of rhBNP was an independent predictor of acute renal dysfunction in patients with AHF following AMI (OR, 0.162; 95% CI, 0.029 to 0.909; $P = 0.039$). Conclusion: the incidence of acute renal dysfunction in rhBNP group was higher, and the use of rhBNP was an independent predictor of acute renal dysfunction in patients with AHF following AMI. (ChiCTR-IPR-15005796).

Keywords: Acute heart failure, acute myocardial infarction, recombinant human brain natriuretic peptide, renal function

Introduction

Acute heart failure (AHF) is a common complication following acute myocardial infarction (AMI), which is a major public health problem throughout the world and its importance is continuing to grow [1, 2]. One of the main challenges in the treatment of AHF following AMI is worsened renal function [3]. Patients with AHF following AMI are at higher risk of acute renal dysfunction even in patients with normal base-

line renal function [4, 5]. Several conditions may contribute to the development of renal dysfunction, such as reduction of renal perfusion caused by hypotension, vasoconstrictive factors resulting in medulla ischemia, and the damage caused by contrast used during coronary interventions [6]. Recombinant human brain natriuretic peptide (rhBNP), approved by the Food and Drug Administration in 2001 [7]. Although its primary mechanism of action is as a systemic and pulmonary vasodilator, it has

multiple effects on the kidneys, including promoting natriuresis, diuresis, and inhibiting the renin-angiotensin-aldosterone axis [8, 9]. Retrospective analyses have raised concerns that it may cause worsened renal function [10, 11]. However, all previous studies focused on this field excluded patients with AMI [12], to date no randomized clinical trials have been reported focusing on its effect on renal function in patients with AHF following AMI. This clinical trial was to investigate the effect of rhBNP on renal function in patients with AHF following AMI.

Materials and methods

Study population

From January 2015 to June 2015, all consecutive AMI patients within 24 hours from onset of symptoms who were admitted in the Cardiology Department of the Second Hospital of Hebei Medical University were enrolled.

Patients must meet all of the following inclusion criteria: (1) first myocardial infarction; (2) left ventricular function between Killip grade II and III; (3) clinical symptoms and initial laboratory tests indicating AHF; (4) need of intravenous vasodilation therapies; (5) ineligibility to receive, or refusal to accept thrombolytic therapy or primary percutaneous coronary intervention on admission.

The diagnosis of AMI was established according to symptoms of ischemia, ECG changes and part of biochemical examinations in all patients immediately after admission.

Patients who met one or more of the following criteria were excluded from this study: (1) cardiogenic shock: systolic blood pressure (SBP) \leq 90 mmHg for more than 30 min with signs of low peripheral perfusion such as cyanosis or cold extremities; (2) concomitant valvular heart disease, or hypertrophic cardiomyopathy or restrictive cardiomyopathy; (3) coronary bypass surgery in the past 6 months; (4) presence of contraindications for anticoagulation therapies, such as recent stroke, major surgery, trauma, or cardiac resuscitation for more than 10 min; (5) requirement for mechanical ventilation; (6) severe hepatic (aspartate aminotransferase or alanine aminotransferase elevation of more than 2 times of the normal value) or renal dysfunction (blood creatinine $>$ 221 μ mol/l); (7) refused to participate.

The study protocol was approved by the Ethical Committee of the Second Hospital of Hebei Medical University. Informed consents were obtained from all the patients. All the protocol was in compliance with the Declaration of Helsinki. The registration number is ChiCTR-IPR-15005796.

Study protocols

After their written informed consent, eligible patients were randomly assigned to receive rhBNP (rhBNP group) or nitroglycerin (NIT group) by means of random number table. Patients in the rhBNP group received rhBNP 0.15 μ g/kg bolus injection after randomization followed by an adjusted-dose (0.0075-0.020 μ g/kg/min) for 72 hours, while patients in NIT received infusion of nitroglycerin with an adjusted-dose (10-100 μ g/kg/min) for 72 hours in NIT group. The bolus dose could have been withheld by the treating physician if a potential for significant hypotension was present at the time of initial therapy (SBP $<$ 90 mmHg, history of significant hypotension from vasodilator therapy, or labile blood pressures). Standard clinical and laboratory data were collected, including patient demographics, medical history, vital signs (including blood pressure, heart rate, and oxygen saturation), left ventricle ejection fraction, Killip classification, medications, electrocardiogram, and routine hematologic and blood chemistry tests. Standard treatments [angiotensin-converting enzyme inhibitors (ACEI), angiotensin-receptor blockers (ARB), spironolactone, β -blockers] were administered to the patients according to current best practice. The use of diuretics was at the discretion of the treating physician. Digitalis was forbidden during the first 24 hours from symptom onset.

Left ventricular function was evaluated by echocardiography in all patients within 24 hours after admission. Investigators involved in the procedures and those reading echocardiograms were all blind to the randomized treatment.

According to the study design, levels of serum creatinine (SCr), urea, β -2 microglobulin and cystatin C were measured at baseline and repeated at the end of the 24, 48 and 72 hours infusion. Total fluid input and output during the 72 hours study period were recorded. Blood concentrations of sodium were measured before and daily during the course of therapy. The

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Table 1. Baseline characteristics between the two groups

	rhBNP group (n = 26)	NIT group (n = 24)	P value
Age (yr.)	62.73±15.43	59.88±10.49	0.220
Male-n (%)	21 (80.8)	17 (70.8)	0.514
Hypertension-n (%)	14 (53.8)	13 (54.2)	1.000
Diabetes-n (%)	10 (38.5)	7 (29.2)	0.559
ST-elevation myocardial infarction-n (%)	22 (84.6)	22 (91.7)	0.669
Anterior myocardial infarction-n (%)	16 (61.5)	11 (45.8)	0.265
Time from onset of chest pain to hospital admission (hour)	13.73±11.47	8.79±7.44	0.076
Killip classification-n (%)			0.779
II	15 (57.7)	15 (62.5)	
III	11 (42.3)	9 (37.5)	
eGFR (ml/min/1.73 m ²)	87.90±20.89	91.01±17.75	0.571
BNP (pg/ml)	998.15±850.42	929.00±685.42	0.754
Peak CK-MB (U/L)	312.12±159.10	316.16±156.80	0.982
Peak cTnl (ng/ml)	82.54±21.12	85.63±17.55	0.587
Heart rate (beat per minute)	85.46±21.30	78.46±15.62	0.194
ACEI/ARB-n (%)	17 (65.4)	14 (58.3)	0.608
B-blocker-n (%)	18 (69.2)	17 (70.8)	0.902
Spironolactone-n (%)	14 (53.8)	12 (50.0)	0.786
Statins-n (%)			
LVEF (%)	49.87±9.24	53.47±7.81	0.145
Thrombolysis-n (%)	4 (15.4)	3 (12.5)	0.771
Primary PCI-n (%)	14 (53.8)	16 (66.7)	0.354

Note: eGFR: estimated glomerular filtration rate; BNP: B-type natriuretic peptide; ACEI/ARB: angiotensin converting enzyme inhibitors, angiotensin-receptor blockers; LVEF: left ventricle ejection fraction.

primary end point was the incidence of acute renal dysfunction, which was defined as an increase in SCr > 0.5 mg/dl (> 44.2 μmol/L) or 25% above baseline SCr value. Estimated glomerular filtration rate (eGFR) was calculated by the simplified modification of diet in renal disease study equation (MDRD): $eGFR = 186 \times \text{Serum creatinine}^{-1.154} \times \text{age}^{0.203}$ (female $\times 0.742$).

The occurrence of major adverse cardiac event (MACE) was followed up for 1 month, including death, sustained ventricular tachycardia, target vessel revascularization and readmission due to worsening of heart failure.

Statistical analysis

All calculations were computed with the aid of SPSS 19.0 statistical software. The continuous variables were reported as means ± SD, and the categorical variables were presented as percentages. Continuous variables were compared using the t test for normally distributed

value; and the Mann-Whitney U test was used. Proportions were compared using Fisher's exact test when the expected frequency was < 5; and the chi-square test was applied. Multivariate test of repetitive measure ANOVA was used to compare the different renal functions and blood pressures before and after the procedure in each group. Multivariate logistic models were used to identify the independent predictors of acute renal dysfunction. The ORs and their corresponding 95% CIs are provided. A P value of less than 0.05 (2-tailed) was considered statistically significant.

Results

Baseline data

Of the 50 patients enrolled, 26 were randomly assigned to rhBNP and 24 to nitroglycerin (NIT). All patients received the assigned treatment. There were no significant differences in baseline characteristics, including mean age, gender distribution, risk factors, and clinical pre-

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Table 2. Impact of rhBNP on renal functions and blood pressures

	rhBNP group (n = 26)				NIT group (n = 24)			
	Before	24 h	48 h	72 h	Before	24 h	48 h	72 h
Serum creatinine (μmol/L)	81.39±15.24	94.12±29.24*	92.94±35.04*	87.42±26.92	76.29±10.43	73.83±15.67	75.30±15.51	78.03±18.58
Urea (mmol/L)	6.50±0.63	7.16±0.62*	7.78±0.63*	7.90±0.73*	5.09±0.31	4.71±0.26	4.74±0.33	5.24±0.43
β-2 microglobulin (mg/L)	1.58±0.20	1.68±0.22	1.77±0.21	1.97±0.22	1.33±0.13	1.37±0.08	1.39±0.08	1.49±0.08
cystatin C (mg/L)	1.51±0.12	1.60±0.11	1.66±0.11	1.59±0.10	1.31±0.08	1.40±0.08	1.38±0.06	1.42±0.09
SBP (mmHg)	121.38±1.90	109.88±2.84#,*	107.69±2.45#	111.58±2.89#	125.63±2.37	119.17±3.36	115.08±3.30#	111.46±2.74#
DBP (mmHg)	76.69±1.11	69.54±1.88#	67.31±1.64#,*	67.19±1.36#	75.58±1.67	75.54±2.68	74.29±2.26	70.38±2.46

Note: SBP: systolic blood pressure; DBP: diastolic blood pressure; *: compared with NIT group, $P < 0.01$; #: compared with baseline, $P < 0.05$.

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Table 3. Adverse events and outcomes

	rhBNP group (n = 26)	NIT group (n = 24)	P value
Urinary specific gravity	1.017±0.019	1.016±0.006	0.783
Acute renal dysfunction	9 (34.6)	2 (8.3)	0.040
IV furosemide during infusion (mg)	63.08±21.68	93.75±32.14	0.000
Net fluid balance (ml)	-1435, 750	-327.5, 112.5	0.040
Hyponatremia-n (%)	12 (46.2)	6 (25)	0.207
Hypotension-n (%)	8 (30.8)	4 (16.7)	0.327
MACE-n (%)	5 (19.2)	2 (8.3)	0.420
Death	1 (3.8)	1 (4.5)	1.000
Sustained ventricular tachycardia	1 (1.38)	0 (0)	1.000
Target vessel revascularization	1 (1.38)	0 (0)	1.000
Readmission due to worsening of heart failure	2 (7.7)	1 (4.2)	1.000

Note: MACE: major adverse cardiac event.

Table 4. Multivariate logistic regression analysis of the association between clinical characteristics and acute renal dysfunction

Variables	Acute renal dysfunction		
	OR	95% CI	P value
AnteriorMI	0.926	0.203-4.219	0.921
eGFR	1.892	0.339-10.575	0.467
Contrast used during coronary interventions	1.216	0.234-6.315	0.816
rhBNP	0.162	0.029-0.909	0.039
Hypotension	0.700	0.106-4.616	0.711

sentations between the two groups (all $P > 0.05$). The laboratory results and medications used during the procedure were not significantly different. The level of eGFR on admission was also similar between the two groups (**Table 1**).

Changes of renal functions and blood pressures during treatment

The baseline concentrations of SCr, urea, β -2 microglobulin and cystatin C at admission were not significantly different between the two groups (**Table 2**). However, the concentrations of SCr and urea were significantly higher in rhBNP group than those in NIT group at hour 24 and 48 after treatments (all $P < 0.01$). For both groups, the concentrations of SCr, urea, β -2 microglobulin and cystatin C were not significantly changed compared with baseline levels.

The levels of systolic and diastolic blood pressures at admission were also similar between the two groups (**Table 2**). In rhBNP group, levels of SBP and DBP decreased significantly at

hour 24, 48 and 72 (all $P < 0.05$). In NIT group, levels of SBP decreased significantly at hour 48 and 72. The level of SBP at hour 24 and DBP at hour 48 after treatment were lower in rhBNP group than those in NIT group ($P < 0.01$).

Outcomes and adverse events

The incidence of acute renal dysfunction in rhBNP group was higher (9/26 vs. 2/24, $P = 0.040$). The levels of urinary specific gravity were similar between the two groups. The dose of furosemide used rhBNP group was lower in rhBNP group (63.08±21.68 mg vs. 93.75±32.14 mg, $P < 0.001$). The

volume of net fluid was significantly increased in rhBNP group than that in NIT group ($P = 0.040$). No significant differences in incidences of hyponatremia and hypotension were found in both groups. The occurrence of MACE was similar (**Table 3**).

Results of multiple logistic regression analysis

The results of multiple logistic regression found that the use of rhBNP was an independent predictor of acute renal dysfunction in patients with AHF following AMI (OR, 0.162; 95% CI, 0.029 to 0.909; $P = 0.039$) (**Table 4**).

Discussion

The main finding of this study was that the incidence of acute renal dysfunction in rhBNP group was higher, and the use of rhBNP was an independent predictor of acute renal dysfunction in patients with AHF following AMI.

In spite of the improvements in the treatment for AMI, it can lead to AHF characterized by sys-

tolic and/or diastolic dysfunction with decreased cardiac output [13]. Several conditions may contribute to the development of renal dysfunction in the treatment of AHF following AMI, such as reduction of renal perfusion caused by hypotension, vasoconstrictive factors resulting in medulla ischemia, and the damage caused by contrast used during coronary interventions [6]. Recognizing the limitations of having varied definitions, acute renal dysfunction occurs in approximately 25-33% of patients admitted with AHF following AMI [14]. It is an important consequence of hospitalization with a myriad of implications in terms of diagnosis, prognosis and a more complex management [3]. Any of these clinical conditions can cause worsening renal function, which is related to increased hospital stay, morbidity and mortality [15]. As a result, renal protection plays an important role on the treatment for AHF following AMI.

rhBNP is the recombinant form of endogenously produced human B-type natriuretic peptide (BNP) and is approved by the Food and Drug Administration for management of patients with decompensated congestive heart failure [16]. Several clinical studies have demonstrated the beneficial effects of intravenous administration of rhBNP on vasodilatation, sodium excretion, diuresis and neuroendocrine regulation [17-19], but the data on the renal benefits of rhBNP have been conflicting. Some studies demonstrated that increased acute renal dysfunction was noted for rhBNP group and the main contributing factor might be hypotension [9-11, 20, 21]. Others including the ASCEND-HF study revealed no difference in renal function. However in the ASCEND-HF study, patients with acute myocardial infarction were excluded [12]. Because AHF is a main complication of AMI, in this study, we hypothesized that the incidence of acute renal dysfunction might be related to the infusion of rhBNP in the treatment of AHF following AMI. This significant reduction in systolic blood pressure may have influence on the results.

There are many important differences between our study and earlier trials [22-24]. Firstly, the hemodynamic characteristics of AHF following AMI is different from AHF caused by other diseases because of cautiously uses of positive inotropic medications and serious change of hemodynamics. Secondly, in this study, nitro-

glycerine was used in control group, which is more common in the use of AHF following AMI than saline or sodium nitroprusside. Thirdly, a low-dose, slow-velocity, and intravenous infusion of rhBNP were administered in our study. As a result, the renal functions were recovered in most patients, and no symptomatic hypotension and significant increase of MACE were found in both group. Fourth, the levels of urea, β -2 microglobulin and cystatin C were used as markers of renal function except for SCr in this study, and the evaluation for renal function was much more comprehensive than precious studies.

Limitation of the study: This is a small scale study. Therefore, further adequately powered studies will be required to determine whether these physiological observations can be translated to improve patient outcomes and to assess the safety of this strategy.

In conclusion, the incidence of acute renal dysfunction in rhBNP group was higher, and the use of rhBNP was an independent predictor of acute renal dysfunction in patients with AHF following AMI.

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