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		PAPER ID	91448990

Protective effect of rhBNP on contrast-induced nephropathy in elderly acute myocardial infarction patients: A randomized controlled trial

Zhang YJ *et al*. rhBNP against CIN after PCI

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Abstract

BACKGROUND

To explore whether recombinant human brain natriuretic peptide (rhBNP) protects against contrast-induced nephropathy (CIN) in elderly acute myocardial infarction (AMI) patients after percutaneous coronary intervention (PCI).

AIM

To explore the effective of rhBNP on CIN in elderly AMI patients after PCI.

METHODS

One hundred and thirty-one elderly AMI patients underwent PCI from Jan 2017 to Jul 2021. Control group patients (n = 66) were given 1 mL 0.9% normal saline/ (kg/h) for 72 h after PCI and those within rhBNP treatment group (n = 65) received intravenous rhBNP [1.5 mg/kg followed by 0.0075 mg/ (kg/min)] for 72 h. Serum creatinine, cystatin C levels, creatinine clearance rate, and eGFR were measured at 24 h, 48 h, and 72 h after PCI. Research nurses collected data on handwritten forms, and then stored them in password-protected electronic databases.

RESULTS

The creatinine clearance rate and eGFR were increased, while the creatinine level and cystatin C level were decreased significantly in rhBNP treatment group compared to the control group at 48 h, 72 h. The incidence of CIN (P = 0.028) and acute heart failure (P =

0.017) also significantly decreased in the rhBNP group. No significant difference between the two groups in cardiac death and recurrent AMI.

CONCLUSION

An early application of rhBNP could protect renal function and decrease the incidence of CIN after primary PCI, decreasing the incidence of acute heart failure.

Key Words: Natriuretic peptide; Myocardial infarction; Contrast media; Acute myocardial infarction; Percutaneous coronary intervention

Zhang Y, Yin L, Li J. Protective effect of rhBNP on contrast-induced nephropathy in elderly acute myocardial infarction patients: A randomized controlled trial. *World J Clin Cases* 2022; In press

Core Tip: Increasing evidence indicates that emergency percutaneous coronary intervention (PCI) play an important role and also was most effective methods for the treatment of acute myocardial infarction (AMI). However, with the increase of emergency PCI, contrast-induced nephropathy (CIN) is becoming more and more common, which also leads to the increase of the proportion of patients with renal dysfunction, aggravating the cost of hospitalization, and prolonging the length of hospital stay. CIN cannot be managed or prevented by current medications. Recombinant human B-type natriuretic peptide (rhBNP) is the natriuretic peptide receptor A, increasing reports have demonstrated that rhBNP can improve AMI and heart failure. However, whether it can improve renal function and decrease the risk of CIN in elderly patients is still unclear. We explored the effectiveness of rhBNP treatment in post-operative CIN in elderly AMI patients. In this study, we found that early application of rhBNP after primary PCI could protect renal function, reduce serum creatinine and cystatin C levels, improve creatinine clearance rate, and decrease

the risk of CIN and acute heart failure in AMI patients. We show rhBNP as an effective drug to prevent CIN in the elderly after PCI.

INTRODUCTION

There are more than a billion people worldwide who die from cardiovascular diseases every year, most of these cases are attributable to ischemic heart diseases[1]. Increasing evidence indicates that percutaneous coronary intervention (PCI) and coronary artery bypass grafting has replaced drug therapies and become the most important and effective treatment for acute myocardial infarction (AMI)[2,3]. Now, increasing studies has reported that PCI has become the best and preferred treatment option to AMI, and saving many lives. With the popularization of PCI technology and more patients undergoing PCI operation, there has been an increase in the cases of contrast-induced nephropathy (CIN), which was one of the major reasons lead to iatrogenic renal failure, increasing the risk of death during hospitalization, hospitalization expenses, and hospital stays[4-6]. There are many side effects of drug therapy in elderly patients with cardiovascular diseases in China, leading to higher incidents of PCI and a higher incidence of CIN. Sun *et al*[7] found that the overall incidence of CIN was 8.38% after PCI. Moreover, CIN increases hospitalization expenses and hospital stays and also plays an important predictor for unfavorable early and long-term outcomes[8-10]. Hydration therapy effectively prevents CIN, but its efficacy is inadequate and can aggravate strain on the heart[11]. CIN cannot be managed or prevented by current medications.

Recombinant human B-type natriuretic peptide (rhBNP) is the natriuretic peptide receptor A, which can decrease the preload, afterload, and pulmonary capillary wedge pressure. It also can increase cardiac output, urinary output, glomerular filtration rate, restrain the renin-angiotensin-aldosterone system and improve diastolic function[12,13]. Multiple reports have demonstrated that rhBNP can improve AMI and heart failure[14-16]. However, whether it can improve renal function and decrease the risk of CIN in

elderly patients is still unclear. Therefore, we explored the effectiveness of rhBNP treatment in post-operative CIN in elderly AMI patients.

MATERIALS AND METHODS

Study design

From January 2017 to July 2021, a prospective clinical randomized controlled trial was conducted with 131 elderly patients. This study evaluates the value of the rhBNP intervention in post-operative CIN in elderly AMI patients. The study protocol was registered and approved by the Wuxi Taihu Hospital Clinical Research Ethics Committees (2016-YXLL-051). Patients were randomly assigned (1:1) to receive intravenous rhBNP (1.5 mg/kg, followed by 0.0075 mg/ (kg/min)) for 72 h or placebos of 1 mL 0.9% normal saline/ (kg/h) for 72 h after PCI (Figure 1)[12,13]. Written informed consent was obtained from patients or family members. Three days after PCI, the final follow-up was performed.

Patients' inclusion and exclusion criteria

Eligible patients diagnosed with acute ST-segment elevation AMI and received PCI. Inclusion criteria: (1) Age > 60 years; (2) can be randomized and receive either rhBNP or placebo within 72 h after PCI; (3) the electrocardiogram was consistent with the characteristics of AMI; and (4) from the onset of chest pain to less than 12 h after operation, the serum creatine kinase isoenzyme was more than 2 times the normal value or troponin I was significantly increased. Exclusion criteria: (1) Likely patients who were critically ill or close to death on admission; (2) patients with cardiomyopathies, pericarditis, primary pulmonary hypertension, and severe valvular heart disease; (3) diagnosed with connective tissue disease, autoimmune tissue disease; (4) AMI with other complications; and (5) contrast agent and/or rhBNP allergy.

Randomization and masking

Permuted-block randomization was performed using SPSS (version 19.0, SPSS Institute) with an allocation list generated with random numbers (in a 1:1 ratio). An independent statistician conducted this analysis to ensure blinding and study integrity. To keep track of the results of randomization, sequentially numbered envelopes were sealed at the investigation site and stored until the study was finished. The research drugs were administered by a research nurse in accordance with the sequence of randomization. All patients and study members were blinded to the study medication allocation. It is possible to request the unmasking of the treatment allocation in emergency situations, such as a severe hepatic failure, and, if necessary to adjust or stop the study drug in case of an emergency. A thorough documentation of all events took place, including the demographics of the patient, their medical history, and any relevant investigation results.

Sample size estimates

In the pilot preliminary experiment study and previous clinical data, 72 h Creatinine clearance rate in the placebo and rhBNP treatment groups were 1.12 ± 0.31 and 1.20 ± 0.38, respectively. The sample size was calculated according to the alpha of 0.05 and the statistical power of 80%, which decided to enroll 126 patients (63 in each category). We decided to enroll 130 patients (65 in each category). The study database included all baselines and outcome data was entered by a study nurse.

Perioperative management

As soon as the patients were admitted to the cardiology intensive care unit (CICU), they were assessed by two CICU physicians, and recorded all clinical data. Routine admission examination included electrocardiograms, chest radiographs, blood chemistry, arterial blood gas, serum electrolyte levels, and clotting function. All patients received similar treatment after definitive diagnosis, including 0.3 g aspirin, 180 mg ticagrelor, 40 mg atorvastatin, and 20 mg rabeprazole sodium enteric-coated tablet. Patients were transferred to the interventional operating room, and the Judkins method

was used to perform coronary angiography by puncturing radial or femoral arteries. Intraoperatively, the isotonic contrast agent iodixanol was used, and PCI was performed according to the characteristics of the lesions (balloon dilation or stent implantation). Coronary angiography was performed after PCI to check if TIMI grade 3 blood flows was restored and the patient's chest pain was significantly relieved. After PCI, all patients received dual antiplatelet, lipid regulation, ACEI/ARB, b- receptor blockers, and anticoagulators. Additionally, rhBNP group received intravenous rhBNP [1.5 mg/kg, followed by 0.0075 mg/ (kg/min)] for 72 h, whereas the control group received 1 mL 0.9% normal saline/ (kg/h) for 72 h after PCI. All patients' blood pressure was maintained at 120-140 mmHg during the study period, and urapidil was injected if necessary. At the same time, a balance of liquid was maintained in elderly AMI patients with an intravenous infusion of frontal fluid of approximately 1000 mL and an appropriate increase in oral rehydration solution after PCI.

Outcome assessment and efficacy evaluation

All patients' clinical and imaging data were collected and evaluated by an independent, masked diagnostic and assessment two-person committee. The two-person committee was formed of researchers who had been trained before the study and not associated the patient's management. The primary outcome was a renal function at 72 h, and the secondary outcomes were the incidences of CIN, acute heart failure, and complications. All patients' serum samples were collected before the operation and after 24 h, 48 h, and 72 h of PCI. The Cockcroft-Gault formula (Creatinine clearance rate = ([140-Age (years)] × Weight (kg))/(7.2 × SCr (mg/dL)) × 0.85 (if female)) was used to calculated the creatinine clearance rate, and the MDRD formula (eGFR = 186 × $(SCr)^{-1.154}$ × $age^{-0.203}$ × 0.742 (if female)) was used to calculate the estimated glomerular filtration rate. Creatinine clearance rate and eGFR made the diagnosis more accurate as some impaired renal function patients can have normal creatinine clearance. Left ventricular ejection fraction (LVEF) was detected by cardiac color ultrasound. Major adverse cardiovascular events and CIN were monitored.

Statistical analysis

All continuous variables were presented as the mean ± SD. SPSS 19.0 statistical software was used for the statistical analyses. Measurement data of non-normal distribution was represented by M (Q1, Q3). Independent-samples *t*-tests were used to assess for quantitative data. Qualitative data were compared with chi square test or Fisher's exact *t*-test. A value of $P < 0.05$ was considered statistically significant.

RESULTS

A total of 167 elderly patients were assessed from Jan 2017 to Jul 2021, and 36 were excluded according to the exclusion criteria. 131 patients were randomly assigned to receive either rhBNP ($n = 65$) treatment or placebo ($n = 66$) treatment. The baseline data of the two groups were compared, and no significant difference was found (Table 1). No patients were lost follow-up at the end, the final visit of the last randomized patient at Dec 15, 2021, and 131 patients were included in the final analyses (Figure 2).

Comparison of renal function indexes after primary PCI

After primary PCI, the serum creatinine and cystatin C levels were elevated significantly ($P < 0.05$). Compared to the preoperative levels, the postoperative creatinine clearance rate and eGFR were reduced significantly ($P < 0.05$). Moreover, compared to the placebo group at 48 h and 72 h after primary PCI, the serum creatinine and cystatin C levels were reduced significantly ($P < 0.05$) in the rhBNP treatment group, and the creatinine clearance rate and eGFR levels were elevated significantly in the rhBNP group ($P < 0.01$, Table 2).

Clinical outcomes and complications

We found that the incidence of CIN ($P = 0.017$) and acute heart failure ($P = 0.028$) in the rhBNP group was lower than the placebo group after primary PCI, the difference was statistically significant (Table 3). We also evaluated the complications after PCI and did

not find any significant difference in cardiogenic death and recurrent myocardial infarction during hospitalization ($P > 0.05$, Table 3).

DISCUSSION

The condition of AMI is critical in most patients and requires coronary angiography and opening of the diseased vessels as soon as possible. Hence, almost all patients fail to undergo preoperative hydration therapy leading to the utilization of more contrast agents during PCI, especially in complex lesions. This results in a high incidence of post-operative contrast agent nephropathy, which severely affects the prognosis of the patients[17]. A recent study reported that CIN was the third most common reason for hospital-acquired renal failure, 49% of CIN occurs after cardiac catheterization and coronary angioplasty[18]. Although renal replacement therapy is rarely required for CIN patients, it increased the incidence of acute heart failure and stent thrombosis in the short-term and long-term follow-up compared to patients without CIN. Therefore, they risk lengthy hospital stays, hospitalization costs, and other hazards[19].

The exact reason for CIN is unclear and might be related to hemodynamic changes, renal vasoconstriction resulting in medullary hypoxemia, direct toxicity of renal tubular epithelial cells, and oxygen-free radical injury[20]. However, common renal ischemia induced by decreased renal blood flow and increased direct tubular toxicity mediated by oxygen free radicals and large amounts of iodine contrast agents is considered a significant reason for CIN. The potential mechanisms of pathological changes include contrast agent-induced sodium and diuretic drainage, and activation of tubule-glomerular feedback, resulting in glomerular afferent arteriole vasoconstriction, thereby reducing glomerular filtration rate[21]. Recent researches have demonstrated that N-acetylcysteine, hemofiltration, hemodialysis, and the hypotonic or isotonic contrast agent can reduce the incidence of CIN[22-24]. Continuous hydration treatment is still considered the clinically effective methods to against CIN. However, the effect of other methods or drugs in patients with AMI, mostly combined with heart failure, resulting

in complex hydration measures, is unclear. Hence, new drugs are required to improve CIN after PCI in older patients.

rhBNP is the natriuretic peptide receptor A, and recent studies have found that rhBNP can prevent CIN[12,25]. Meng *et al*[26] reported that rhBNP could improve the clinical prognosis of patients with right ventricular dysfunction caused by acute pulmonary embolism who underwent catheter-directed therapy. A recent meta-analysis also indicated that rhBNP could markedly improve the clinical outcome of AMI, and decrease their length of stay without elevating the rate of adverse reactions[27]. In anterior myocardial infarction complicated by cardiogenic shock, low-dose rhBNP can improve pulmonary capillary wedge pressure and does not increase drug-related severe adverse events[28]. Liu *et al*[29] reported that pre-treatment with rhBNP before coronary angiography or PCI could improve renal function and decrease CIN incidence. Due to their unique situation, more elderly AMI patients cannot receive hydration therapy, and the effectiveness of rhBNP in these patients after PCI was unclear. Here, for the first time, we established that rhBNP administration could protect renal function, decrease the risk of CIN and acute heart failure in elderly AMI patients, and not increase the adverse drug effects.

In this study, we found that early application of rhBNP after primary PCI could protect renal function, reduce serum creatinine and cystatin C levels, improve creatinine clearance rate, and decrease the risk of CIN and acute heart failure in elderly AMI patients. Together, our study demonstrated rhBNP as an effective drug to prevent CIN in the elderly after PCI.

Further clinical studies are needed to address several limitations of the present study. A number of additional clinical factors must be considered, including all-cause mortality rate, activities, and daily life, should be examined. A long-term follow-up study is required to further clarify the clinical efficacy of the rhBNP after primary PCI. Furthermore, the small sample size was from a single center. To determine whether or not this treatment is effective, a multicenter, randomized, controlled trial is required.

CONCLUSION

Our study suggests that early rhBNP treatment might help to protect renal function and decrease the risk of CIN in elderly AMI patients after primary PCI, decreasing the incidence of acute heart failure. There was no corroborating evidence to support the claim that low-dose rhBNP enhanced the risk of post-surgical complications. However, long-term outcome and adverse effect are still uncertain after rhBNP treatment. More research is required with patients who received varied dosages and longer-term follow-up to understand the prospective application of rhBNP in post-operative elderly patients.

ARTICLE HIGHLIGHTS

Research background

The overall incidence of contrast-induced nephropathy (CIN) was high after percutaneous coronary intervention (PCI), and lead unfavorable early and long-term outcome.

Research motivation

How to decreased the risk of CIN after PCI, and explore clinical drugs to improve the outcome of elderly acute myocardial infarction (AMI) patients.

Research objectives

To explore the clinical effective of recombinant human brain natriuretic peptide (rhBNP) on CIN in elderly AMI patients after PCI.

Research methods

131 elderly AMI patients underwent PCI, control group (n = 66) were given 1 mL 0.9% normal saline/(kg/h) for 72 h after PCI and rhBNP group (n = 65) received intravenous rhBNP [1.5 mg/kg followed by 0.0075 mg/(kg/min)] for 72 h. Serum creatinine,

cystatin C levels, creatinine clearance rate, and eGFR were measured at 24 h, 48 h, and 72 h after PCI.

Research results

The creatinine clearance rate and eGFR were increased, while the creatinine level and cystatin C level were decreased significantly in the rhBNP group compared to the control group at 48 h and 72 h. The risk of CIN and acute heart failure also significantly decreased in the rhBNP group. We found no statistic difference between two groups in cardiac death and recurrent AMI.

Research conclusions

Early application of rhBNP can protect the renal function and decrease the incidence of CIN in elderly AMI patients after primary PCI, decreasing the incidence of acute heart failure.

Research perspectives

Our study suggests that early rhBNP treatment might help to protect renal function and decrease the incidence of CIN in elderly AMI patients after primary PCI, decreasing the incidence of acute heart failure. Based on these results, rhBNP treatment can be widely promoted. Also, more research is required with patients who received varied dosages to understand the prospective application of rhBNP in post-operative elderly patients.

ACKNOWLEDGEMENTS

We thank Jiangsu Brilliant Biological Technology Co., Ltd. for providing technical and linguistic help. We thank Bullet Edits Limited for the linguistic editing and proofreading of the manuscript.

Figure Legends

Figure 1 Study design.

Figure 2 Trial profile.

Table 1 Demographic and baseline characteristics of the study population in the two groups

	Placebo group	rhBNP group	*P* value
Age (mean ± SD)	75.42 ± 12.88	75.58 ± 12.69	0. 943
Male, *n* (%)	49 (74.2)	43 (66.2)	0.311
Hypertension, *n* (%)	36 (54.5)	32 (49.2)	0. 543
Diabetes, *n* (%)	7 (10.6)	8 (12.3)	0. 760
Hyperlipemia, *n* (%)	46 (69.7)	43 (66.2)	0. 664
Smoking, *n* (%)	18 (27.3)	15 (23.1)	0.580
Killip (mean ± SD)	2.15 ± 0. 52	2. 09 ± 0.49	0. 498
B natriuretic peptide [M (Q_1, Q_3)]	69 (18,384)	78 (35,621)	0. 752
Troponin I (ng/L, mean ± SD)	55.18 ± 10.22	53.29 ± 11.08	0. 312
Treatment, *n* (%)			0.635
Coronary arteriography	9 (13.6)	11 (16.9)	0. 759
PCI	57 (86.4)	54 (83.1)	0. 787
Lesion location, *n* (%)			
Left main	7 (10.6)	5 (7.7)	0.563
Left anterior descending branch	30 (45.5)	34 (52.3)	0.433
Left circumflex branch	12 (18.2)	9 (13.8)	0.499
Right coronary artery	17 (25.7)	17 (26.2)	0.959
LVEF (%, mean ± SD)	59.47 ± 3.29	60.16 ± 3.15	0.223
Contrast agent dosage [mL, M (Q_1, Q_3)]	135 (60,175)	130 (70,160)	0.912
Intro-operative IABP, *n* (%)	7 (10.6)	8 (12.3)	0.760
Hospitalizated, *n* (%)			
ACEI/ARB	35 (53.0)	32 (48.5)	0.664
Receptor antagonist	52 (78.8)	56 (86.2)	0.268
Calcium channel blocker	29 (43.9)	27 (41.5)	0.781
Natriuretic agent	22 (33.3)	25 (38.5)	0.541

rhBNP : Recombinant human brain natriuretic peptide.

Table 2 The renal index ratio after primary percutaneous coronary intervention between two groups

	Placebo	rhBNP	*P* value
Serum creatinine (mol/L)			
Preoperative	72.35 ± 15.38	74.13 ± 16.28	0.521
24 h	85.74 ± 19.21	83.26 ± 18.12	0.449
48 h	101. 55 ± 21.22	80.59 ± 19.46	0.001
72 h	88.15 ± 18.72	76.29 ± 16.55	0.007
Cystatin C (mg/L)			
Preoperative	0.91 ± 0.22	0.93 ± 0.21	0.596
24 h	0.95 ± 0.25	0.96 ± 0.31	0.839
48 h	1.07 ± 0.37	0.93 ± 0.32	0.020
72 h	1.02 ± 0.30	0.88 ± 0.25	0.004
Creatinine clearance rate (mL/min)			
Preoperative	1.12 ± 0.31	1.15 ± 0.38	0.621
24 h	0.95 ± 0. 32	1.03 ± 0.34	0.168
48 h	0.82 ± 0.29	0.95 ± 0.28	0.010
72 h	0.86 ± 0.25	1.05 ± 0.37	0.001
eGFR [mL/(min/1.73 m^2)]			
Preoperative	85.76 ± 22.46	86.35 ± 21.27	0. 877
24 h	78.43 ± 9.12	82.11 ± 10.23	0. 030
48 h	76.82 ± 8.55	83.27 ± 10.13	0.001
72 h	77.432 ± 5.120	85.38 ± 7.22	0. 001

rhBNP: Recombinant human brain natriuretic peptide.

Table 3 Clinical outcomes and complications between two groups

	Placebo	rhBNP	*P* value
Cardiogenic death, *n* (%)	6 (9.1)	5 (7.7)	0.773
Recurrent myocardial infarction, *n* (%)	3 (4.5)	3 (1. 5)	1.000
Acute heart failure, *n* (%)	15(22.7)	5 (7.7)	0.017
CIN, *n* (%)	14(21.2)	5 (9.2)	0.028

CIN: Contrast-induced nephropathy.

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