Clinical therapeutic strategy of recombinant human brain natriuretic peptide and dopamine in cardiorenal syndrome type 4 patients combined with hypotension

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Abstract: Aim of the present study is to investigate the clinical efficacy of recombinant human brain natriuretic peptide (rhBNP) and dopamine combination treatment in patients with cardiorenal syndrome type 4 (CRS4) combined with hypotension. A total of 160 CRS4 patients admitted to our hospital from July 2010 to December 2014 were recruited, and were randomly divided into two groups, the observational group (n=80) and the control group (n=80). CRS4 patients treated with dopamine were recruited into the control group. Patients in the observational group were given rhBNP and dopamine combination treatment once every 8 h. Both groups received conventional treatments and the course of treatment was 7 days. Systolic blood pressure (SBP), diastolic blood pressure (DBP), mean arterial pressure (MAP), heart rate (HR), serum creatinine (SCr), N-terminal brain natriuretic peptide precursor (Nt-proBNP), creatinine clearance (CCr), left ventricular end-diastolic diameter (LVEDd), left ventricular ejection fraction (LVEF), Stroke volume (SV), urine volume and adverse reactions before and after treatment were compared. The observational group showed significant changes in the levels of SBP, DBP and HR compared with the control group ($P<0.05$). The levels of SCr and Nt-proBNP decreased significantly in the observational group than those in the control group ($P<0.05$). The levels of CCr, LVEF, SV and urine volume increased significantly in the observational group than those in the control group ($P<0.05$). Patients in the observational group had mild and tolerable adverse reactions. rhBNP combined with dopamine infusion has good clinical efficacy and mild adverse effects in treatment of CRS4.

Keywords: Cardiorenal syndrome type 4 (CRS4), hypotension, rhBNP, ; dopamine, outcome, adverse reaction.

INTRODUCTION

Progressive renal failure caused by chronic refractory heart failure is definite as cardiorenal syndrome type 4 (CRS4), which is highly linked with hypotension incidence (Ronco *et al.*, 2008). CRS4 refers to the injury of cardiovascular structure and function in the setting of chronic kidney disease (CKD) and is also called chronic renocardiacsyndrome (Tumlin *et al.*, 2013). Recombinant human brain natriuretic peptide (rhBNP) is a type of endogenous hormonal substance, which could not only benefitnatriuretic diuresis, but also suppress the sympathetic nerve and renin-angiotensin-aldosterone system (RAAS) to improve the cardiac function in patients with HF and the related clinical manifestations (Bello *et al.*, 2005). However, previous studies have reported that rhBNP could lead to kidney function impairment and does-dependent hypotension (Jha *et al.*, 2013). Although there are new advances in clinical treatment for both cardiovascular and renal diseases, the treatment for CRS4 remains a challenge. Small dose of dopamine could stimulate β1 receptor, active the renal vascular dopamine receptor and increase glomerular filtration rate (Clementi *et al.*, 2013). Nevertheless, high dose of dopamine could accelerate the heart rate (HR), increase the myocardial contraction and lead to hypotension (Clementi *et al.*, 2013). In this study, we observed the effects of rhBNP-dopamine combination onCRS4 patients with hypotension.

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MATERIALS AND METHODS

Clinical data

A total of 160 CRS4 patients combined with hypotension were included in this study between January 2012 and December 2014. CRS4 was defined to have cardiac abnormalities such as decreased cardiac function in the setting of primary CKD (Ronco *et al.*, 2008). The inclusion criteria were: 1) New York heart association (NYHA) classification standard defined as Ⅲ~Ⅳ level; 2) Left ventricular ejection fraction (LVEF) ≤40% determined by two-dimensional echocardiography; Serum creatinine (SCr) 133~442mu mol/L; 3) Blood pressure between 80/50mmHg and 90/60 mmHg. The exclusion criteria were: Primary renal disease, kidney transplantation, autoimmune diseases, neoplasm, malignant tumors, cerebrovascular diseases, severe psychiatric diseases, pregnancy, infectious diseases, hematological diseases and acute or chronic inflammatory diseases. The patients included were randomly divided into two groups, the observational group (80) and the control group (80). There were 45 male and 35 female in the control group with disease course of 3.1 to 19.7 years

and the mean age was 58.2±5.7 years (range: 29-87), including 14 coronary heart diseases, 20 cases of dilated cardiomyopathy (DCM) and 46 hypertensive cardiovascular diseases. While there were 38 male and 42 female cases in the observational group, with disease course of 3.3 to 18.5 years and the mean age was 56.8±6.4 years (range: 26-88), including 16 coronary heart diseases, 23 cases of dilated cardiomyopathy (DCM), and 41 hypertensive cardiovascular diseases, There were no statistically significant differences of clinical data between the two groups (table 1). The study conformed to the Helsinki Declaration. The Ethics Committee of approved the protocol. Written informed consent was obtained from all the patients.

Treatments

The patients in control group were received routine HF treatments, including of removing induced factors, curing the primary diseases, oxygen inhalation, restricting diets, diuretic treatments, nitrates administration, dopamine treatments (4μg/kg, min). Patients in observational group were received routine HF treatments plus combination treatment of rhBNP (Chengdu Rhodiola Bio-Pharmacy, Chengdu, China) and dopamine. rhBNP was administered as an intravenous bolus of 1.5μg/kg followed by continuous infusion in doses of 0.0075-0.01μg/kg/min according to each patient's clinical status. Dopamine was administered as an intravenous bolus of 4ug/kg, min. In case the patients suffered from sustained hypotension, the diuretic dose should be reduced and dopamine dose should be increased to 10ug/kg, min untill the blood pressure return to the normal level. In cases that HR>100 beats/min, cedilnid should be administrated with small does appropriately. Both of the groups received treatment for one week.

Observational parameters

(1) The mean arterial pressure (MAP) was calculated by the systolic blood pressure (SBP) and diastolic blood pressure (DBP) before and after treatment (24h) relatively in the two groups;(2) fasting venous blood was drawn in the morning of the patients before treatment and at the 8^{th} receiving treatment to test SCr, N-terminal pro-brain natriuretic peptide (Nt-proBNP) and to calculate the creatinine clearance (CCr) according to the Cockcroft-Gault formula;(3) the left ventricular end-diastolic diameter (LVEDd) and stroke volume (SV) were detected by the ultrasonocardiogram before treatment and at the 8^{th} day; (4) the urine volume was calculated before treatment and at the 1^{st} ,2^{nd}, 3^{rd} day following drug administration; (5) Doses of the dopamine, diuretics, cedilanid were recorded during the treatments; (6) the symptoms of electrolyte disorder, persistent hypotension and low perfusion (hyperhidrosis, thirsty, nausea, vomiting, oliguria, intravenous collapsibility) and other adverse reactions were observed during treatments.

STATISTICAL ANALYSIS

Statistical analysis was performed with Sigma Stat 3.5 (Systat Software, Point Richmond, CA, USA) statistical software. Quantitative data are presented as mean ± standard deviation (SD). Comparisons between the two groups were made using a two-sample t-test for continuous variables and chi-squared test or Fisher exact test for categorical data. Differences were considered significant at $P<0.05$.

RESULTS

Comparisons of blood pressure and HR between the two groups

Ambulatory changes in blood pressure (SBP, DBP and MAP) and HR were monitored pre- and post-treatment. As shown in table 2, compared with pre-treatment, the SBP, DBP and MAP values were significantly increased in both groups, but the HR value was significantly decreased ($P<0.05$). Moreover, the SBP, DBP and MAP values were significantly increased in the observation group compared with those in the control group ($P<0.05$). However, the HR value was significantly decreased compared with that in the control group ($P <0.05$).

Comparison of SCr, CCr and Nt-proBNP levels between the two groups

Alterations in SCr, CCr and Nt-proBNP level were analyzed to assess the therapeutic efficacy. As shown in table 3, the levels of SCr and Nt-proBNP decreased remarkably in rhBNP and dopamine combination treatment group compared with those in the control group. Whereas, the level of CCr increased significantly in the observational group ($P<0.05$), demonstrating that rhBNP and dopamine combination treatment displayed superior therapeutic efficacy.

Comparisons of the echocardiogram indexes between the two groups

Compared with the control group, LVEF and SV were both increased in the observation group and the differences were statistically significant ($P<0.05$). Nevertheless, no statistically significant difference of LVEDd was found between the two groups ($P>0.05$), which is shown in table 4.

Comparison of the urine volume between the two groups

The 24h urine volume of the control group before treatment was (794.5±168.3) ml and the urine volume at the 1^{st}, 2^{nd} and 3^{rd} were (1221.6±241.3), (1774.5±346.8), (1683.2±315.7) ml, respectively. While the 24h urine volume of the observational group before treatment was (820.1±188.3) ml and the urine volume at the 1st, 2nd and 3rd were (1780.1±337.4), (3067.5±433.7), (3163.4± 507.9) ml. The urine volume after treatment was significantly increased of the two groups and the increase was more significant in the observational group. The difference was statistically significant ($P<0.05$).

Table 1: Baseline characteristics of study population

	Control group	Observational group
Age, years	58.2±5.7	56.8±6.4
Male, n (%)	45 (56.2)	38 (47.5)
Body mass index, kg/m^2	26.5±4.1	27.2±3.6
Hg Systolic blood pressure, mm	124.7±22.0	125.3±18.4
Hg Diastolic blood pressure, mm	67.2±10.1	65.7±9.8
Plasma total cholesterol, mmol/l	4.6±1.3	4.1±1.5
HDL cholesterol, mmol/l	1.1±0.3	1.5±0.2
LDL cholesterol, mmol/l	2.7±0.7	2.2±0.4*
NYHA Grade		
III	32(40)	34(42.5)
IV	48(60)	46(57.5)
Protopathy		
Coronary heart disease	14(17.5)	16(20)
Dilated cardiomyopathy	20(25)	23(28.8)
Hypertensive cardiovascular disease	46(57.5)	41(51.2)
Haemoglobin, mmol/l	7.4±0.8	7.3±0.6
Estimated creatinine clearance, ml/min	24(30)	26(32.5)
Serum urea, mmol/l	12.2±1.3	13.1±2.4
NT-proBNP, pg/ml	1689.2±334.1	2047±578.4
Ejection fraction, %	46.3±13.2	43.4±11.8
Diabetes mellitus, n (%)	22(27.5)	26(32.5)
Smoker, n (%)	17(21.2)	28(35)

Note: values are presented as n (%), mean±SD or median (IQR). No statistical differences were found between the observational group (n=80) versus the control group (n=80). NA, not available; CRS, cardiorenal syndrome; HDL/LDL, high/low density lipoprotein

Table 2: Comparison of blood pressure and HR before and after treatments (x±s)

Group	n	SBP (mmHg)		DBP (mmHg)		MAP (mmHg)		HR (bmp)	
		Pre-treatment	Pro-treatment	Pre-treatment	Pro-treatment	Pre-treatment	Pro-treatment	Pre-treatment	Pro-treatment
Control group	80	87.1±3.5	97.1±5.7*	56.3±2.8	60.3±2.9*	66.8±4.3	81.7±3.6*	104.4±8.5	94.1±5.4*
Observational group	80	85.4±4.7	108.6±5.2$^{*\#}$	54.5±3.0	68.4±2.1$^{*\#}$	65.3±3.9	72.8±4.1$^{*\#}$	105.7±6.4	82.7±3.3$^{*\#}$

Table 3: Comparison of SCr、CCr、Nt-proBNP before and after treatments ($\bar{x}$±s)

Group	n	SCr(μmol/L)		CCr(mL/min)		Nt-proBNP(pg/mL)	
		Pre-treatment	Pro-treatment	Pre-treatment	Pro-treatment	Pre-treatment	Pro-treatment
Control group	80	227.3±24.6	156.7±11.0*	35.5±9.1	39.6±6.2*	3382.5±356.2	2291.6±241.0*
Observational group	80	236.2±21.7	140.5±13.8$^{*\#}$	33.3±8.4	45.8±4.9$^{*\#}$	3453.8±326.7	1504.3±233.1$^{*\#}$

Table 4: Comparison of ultrasonic cardiogram between the groups ($\bar{x}$±s)

Group	n	LVEDd(mm)		LVEF(%)		SV(mL)	
		Pre-treatment	Pro-treatment	Pre-treatment	Pro-treatment	Pre-treatment	Pro-treatment
Control group	80	54.4±5.8	52.4±5.8	37.3±5.7	41.3±3.5*	42.6±5.8	50.3±5.5*
Observational group	80	52.7±6.4	54.3±4.7	38.6±4.5	49.5±4.1$^{*\#}$	43.4±5.0	63.7±4.8$^{*\#}$

Note: compared with the same group before treatment, *P<0.05; compared with the control group, $^{\#}$P<0.05

Incidence of the adverse effects

There were no arrhythmia, nausea, abdominal distension, peripheral low perfusion and other side effects in the observational group during treatments. There was one case of hypotension incident (80/50 mmHg), and the treatment dosage of dopamine was modified to 7 μg/(kg.min) till the blood pressure elevated gradually to 90/60 mmHg.

DISCUSSIONS

Growing attention has been paid toCRS4 due to its high morbidity and mortality. The patients in the late stage of HF will suffer from the decreased of GFR due to the insufficient of renal perfusion caused by the reduced cardiac output (Wehbe *et al.*, 2015). Patients with HF are more risky to suffer from renal failure and the incidence rate of the renal failure among the patients with GFR<60 ml/min is between 20% and 67% (Zamora *et al.*, 2014). Heart and kidney are highly linked to each other and mutual affect each other from the hemodynamic, neuroendocrine active factors, endocrine, immunology and other aspects (Steiniger *et al.*, 1984). Patients with CRS combined with hypotension will suffer from even more severe symptoms (Kim, 2013). The prognosis is extremely worse and the mortality is extremely high (Palazzuoli and Ronco, 2011). Currently, the main drugs of CRS treatment are sodium nitroprusside, diuretics, beta-blockers, renin-angiotensin-aldosterone system agonist, statins, erythropoietin (Hayes-Jordan *et al.*, 2016). These methods are effective to some extent; however, they work slow and need a longer time to recover of the renal functions. Whereas the effectiveness and safety of the vasopressin receptor antagonist, selective adenosine receptor antagonist and continuous renal replacement therapy still need further clinical research. Patients with CRS combined with hypotension mainly manifest congestion and insufficiency of circumfusion perfusions. Additionally, some of the interventions mentioned above could lead to hypotension and reduce perfusion. rhBNP has an effect on kidney and cardiovascular system directly and regulates the blood pressure and balances the blood volume to alleviate the retention of water and sodium, increase GFR and inhibit the reflective tachycardia (Liu *et al.*, 2014). Its main role for kidney is to inhibit the angiotensin II endothelin and norepinephrine to improve the perfusion, expand the afferent arterioles (Erskine *et al.*, 2016). Meanwhile, it also suppresses the aldosterone and renin synthesis to restrain the Na^+ reabsorption to inhibit the retention of water and sodium, increase potassium secretion and increase the urine volume (Qian *et al.*, 2013). In the late stage of HF, the body cannot produce sufficient amount of urinary sodium brain peptide (BNP) to compensate leading to water-sodium retention and significant ventricular pressure, which suggests relatively insufficient of endogenous BNP or BNP resistance(Brunner-La Rocca *et al.*, 2002). RhBNP injection will lead to the BNP multiplied increase, and prevent HF progress. Previous studies have shown that rhBNP could relief the condition of patients with severe heart failure (Lv *et al.*, 2016; Zhang *et al.*, 2013). It was illustrated that rhBNP caused kidney damage and does-dependent hypotension. Combined dopamine could compensate the side effects caused by rhBNP treatment. Dopamine is type of sympathomimetic agent and low dose of dopamine could active the dopamine receptors in coronary artery, cerebrovascular, kidneys and mesentery, which could not only strengthen the heart's functions but also expand the renal blood vessels to increase GFR. The effects of expansion of renal blood vessels and the myodynamia will benefit the diuretic phenomenon among the patients with HF. Enhancing the dose of dopamine will increase the arterial pressure, peripheral vascular resistance and myocardial contraction to increase the HR and blood pressure (Sanada *et al.*, 2000). Though this effect will result in elevated oxygen demands, if the volume of the heart reduced and the cardiac function improved, the demands of the oxygen will not be necessarily increased. Therefore, rhBNP combined dopamine treatment ofCRS4 could both play their own roles and reduce the side effects. Yu et al. reported that rhBNP could lower the SBP for those SBP were relatively high, whereas rhBNP has no adverse influence on SBP whose SBP were low before treatment (Yu *et al.*, 2014).

Our study shows that there are no significant changes of the blood pressure among the patients during the rhBNP combined dopamine treatments, which illustrates that the combined treatment is relatively safe for those patients with hypotension. According to the previous studies, rhBNP has no significant effects on HR, and dopamine could increase the HR through activating the β1 receptor (Miles *et al.*, 2013). Our study illustrates that the HR decreased in the observational group and control group, especially in the observational group, the HR decreased more significantly. Patients' CCr increased after rhBNP treatment and there were no renal function impairments. While during treatments, the dropping speed was regulated according to the blood pressure. The urine volume of the observational group increased significantly, and the summit function of rhBNP was at the first 24^{th}. Comparing with the control group, the dose of dopamine and diuretics were significantly reduced in the observational group. It is possible that rhBNP is natriuretic, inhibit RAAS activating, improve cardiac function, strengthen the myocardial contractility, and maintain the renal perfusion while increase the blood pressure.

CONCLUSION

The present study was planned to investigate the clinical efficacy of rhBNP and dopamine combination treatment

in patients with CRS4 combined with hypotension. Our data confirmed that the combination treatment can inhibit RAAS, relieve fluid retention, cardiac load, increase the cardiac quantity, expand the renal blood vessels and increase GFR to further improve the renal function. It is especially benefit CRS4 patients with hypotension without obviously side effects.

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