**Original
Article**

Early Results of Human Atrial Natriuretic Peptide Infusion in Non-Dialysis Patients with Chronic Kidney Disease Undergoing Isolated Coronary Artery Bypass Grafting: the NU-HIT Trial for CKD-II

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Background: Chronic kidney disease (CKD) is an important risk factor for cardiac surgery. In the most recently reported NU-HIT trial for CKD with CKD patients underwent coronary artery bypass grafting (CABG) as subjects, carperitide was reported to be effective in terms of renal function. In the present study, a subanalysis was performed on patients registered in the NU-HIT trial for CKD from the standpoint of renin-angiotensin system, natriuresis and renal function.

Methods: 303 patients with CKD who underwent isolated CABG were divided into a group that received carperitide infusion and another group without carperitide. The renin activity, angiotensin-II, aldosterone, urine-sodium, urine-creatinine, fractional sodium excretion, renal failure index, and BNP levels.

Results: There were significant lower in hANP group than the placebo group, in angiotensin-II at one day postoperatively, and in aldosterone from 0 day to one month postoperatively. FENa was significantly lower in the hANP group at 3 day and one week postoperatively.

Conclusions: In on pump isolated CABG patients with CKD, carperitide showed a potent natriuretic action and inhibited the renin-angiotensin system, suggesting that it prevented deterioration of postoperative renal function. Our findings raise new possibilities for the perioperative and postoperative management of patients undergoing surgery with cardiopulmonary bypass.

Keywords: CPB physiology/pathophysiology, kidney, surgery complications

Introduction

Chronic kidney disease (CKD) is a risk factor for coronary artery disease and the survival prognosis

becomes worse as the stage of CKD becomes higher.^{1–3} In coronary artery bypass grafting (CABG), CKD is a complication in 12.2%–37% of patients.^{4–6} In a cohort study on about 30,000 patients who underwent CABG, it was reported that the degree of postoperative increase in serum creatinine (sCr) is correlated with aggravation of CKD and mortality.⁷ In a large multicenter study on 19,558 patients with CABG, the 5-year survival rate was 91.0% in non-CKD patients and 71.4% in CKD patients; CKD patients showed significantly lower rates.⁸ The hospital mortality rate in patients with preoperative sCr of 2.5 mg/dl or higher was 33%, worse than in dialysis patients. The rate of patients

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requiring postoperative hemodialysis was reported to be high at 33%.⁹⁾

We previously performed a randomized controlled trial (RCT) known as the NU-HIT trial (the Nihon University Working Group Study of low-dose hANP infusion therapy during cardiac surgery), in which human atrial natriuretic peptide (hANP: carperitide: Suntory Inc., Osaka, Japan and Daiichi-Sankyo Pharmaceutical Inc., Tokyo, Japan) was administered perioperatively for cardiac and renal protection. Because carperitide inhibits the renin-angiotensin-aldosterone system (RAAS) and has a potent natriuretic effect, we have found that it can compensate for the adverse effects of extracorporeal circulation and can inhibit left ventricular remodeling,^{10–12)} showing effective cardiac protection, not only in the acute stage but also over the long-term, and reduced cardiac and renal events.¹²⁾

In a randomized controlled study (NU-HIT trial for CKD) for 303 patients with CKD who underwent on-pump isolated CABG, perioperative low-dose carperitide infusion has renal protective effects, enabling patients to avoid dialysis and cardiac events not only on the early postoperative stage but also up to one year postoperatively. A carperitide showed strong cardiorenal protective effects that prevented postoperative cardiac events and initiation of dialysis.

In the most recently reported NU-HIT trial for CKD with CKD patients as subjects, carperitide was reported to be effective in terms of renal function (sCr and eGFR).¹³⁾ In the present study, a subanalysis was performed on patients registered in the NU-HIT trial for CKD from the standpoint of RAAS and natriuresis. The efficacy on renal function in the NU-HIT trial for CKD was also investigated in detail.

Methods

Study protocol

Study protocol was similar to the protocol of NU-HIT trial for CKD.¹³⁾ The NU-HIT trial for CKD-II was a randomized double-blind placebo-controlled study of patients with preoperative CKD (preoperative eGFR <60 ml/min/1.73 m²)¹⁴⁾ without dialysis treatment, who underwent isolated CABG with cardiopulmonary bypass (CPB). We excluded patients with cardiogenic shock, dialysis, or off-pump CABG. 303 were enrolled in this trial. 303 patients were enrolled in this trial. They were randomized by the lottery method into two groups, which were a hANP group that received an infusion of carper-

itide from the initiation of CPB and a placebo group that received an infusion of physiological saline. Since carperitide is approved for treatment of acute cardiac failure in Japan, but not for administration during cardiac surgery, approval for this study was obtained from the Ethics Committee of Nihon University Itabashi Hospital, the details of the study were explained to subjects, and informed consent was obtained from each patient. This study was registered with the University Hospital Medical Information Network (UMIN) (study ID: UMIN000001462). Infusion of carperitide is performed from a starting dose of 0.1 µg/kg/min for acute cardiac failure, but a lower initial dose of 0.02 µg/kg/min was selected for this study because the subjects did not have cardiac failure. Administration of carperitide or placebo was initiated at the start of CPB. The infusion rate was decreased to 0.01 µg/kg/min at the commencement of oral medication, and then infusion was discontinued after another 12h. CPB was performed with nonpulsatile low-temperature perfusion (target rectal temperature: 34°C).

Subanalysis items

The renin activity, angiotensin-II, and aldosterone levels were measured at 0, and 1 days, 1 week, and 1 month postoperatively. The urinary sodium (U-Na), urinary creatinine (U-Cr), fractional sodium excretion (FENa = [U-Na/Na] X [Cr/U-Cr] X 100) and renal failure index (RFI = [U-Na X Cr]/U-Cr) were measured at 0, 1, and 3 days, and 1 week postoperatively. The brain natriuretic peptide (BNP) level was measured at 0, 1, and 3 days, 1 week, 1 month, 6 month, and 1 year, postoperatively.

Statistical analysis

Data are expressed as the mean ± the standard deviations (SD). Data were analyzed with repeated measures of ANOVA. In this study, a p value of <0.05 was taken to be a statistically significant difference in all cases. All analyses were conducted with SPSS software (SPSS Inc., Chicago, Illinois, USA).

Results

Patient enrollment: Initially, 303 patients were enrolled in this trial, but three patients were switched to off-pump CABG, and 15 patients who underwent concomitant operations (mitral valve plasty, mitral valve replacement, and graft replacement), in addition to CABG and thus, were excluded from the trial, leaving 285 patients. Among these 285 patients, 141 were assigned to the hANP

Fig. 1 Renin, angiotensin II, and aldosterone levels.

group, and 144 formed the placebo group.¹³⁾

Preoperative patient characteristics showed no significant differences between the two groups.¹³⁾ Although there were no in-hospital deaths in the hANP group, four patients died in the placebo group, and there was no significant difference of in-hospital deaths between the two groups. The cause of death was heart failure in two patients, and cerebral infarction and arrhythmia in one patient each. Perioperative complications occurred in 10 patients from the hANP group and 20 patients from the placebo group. There were fewer complications in the hANP group, but the difference was not significant. In the hANP group, four patients had heart failure (including one with LOS), two each had mediastinitis and cerebral infarction, and one each had acute renal failure and hemorrhage. In the placebo group, seven patients had acute renal failure, five had heart failure (including two with LOS), three had cerebral infarction, two had refractory arrhythmia, and one each had mediastinitis, pneumonia, and gastrointestinal bleeding. During the early postoperative period, dialysis was required by one patient in the hANP group and eight in the placebo group. Although there were no significant differences in postoperative dopamine, dobutamine, and norepinephrine use, the furosemide dose was significantly higher in the placebo group.¹³⁾

Subanalysis items:

1) Renin, angiotensin II, and aldosterone levels (**Fig. 1**): The renin level immediately at 0 day postoperatively was significantly lower in the hANP group. Subsequently, no significant differences were noted, although the hANP group had lower values. Angiotensin II was significantly lower in the hANP group at one day postoperatively, but no significant differences were found thereafter. Aldosterone was significantly lower in the hANP group from 0 day to one month ($p < 0.01$).

2) U-Na and U-Cr (**Table 1**): U-Na showed no signif-

icant differences between the two groups. However, when compared with the preoperative values only in the hANP group, significant increases occurred at 0, 3 days postoperatively ($p = 0.034$, $p = 0.0012$). U-Cr was significantly higher on 1 and 3 days postoperatively in the hANP group than in the placebo group.

3) FENa and RFI (**Table 1**): FENa was significantly lower in the hANP group at 3 day and one week postoperatively while RFI was lower from 0 day to 1 week postoperatively.

4) BNP (**Fig. 2**): BNP was significantly lower than in the hANP group at 1 week, 6 month, and 1 year, postoperatively.

Discussion

This study demonstrated that infusion of carperitide in patients with preoperative CKD undergoing CABG could improve renal function, indicating that carperitide has a potent natriuretic effect in the acute postoperative period. Carperitide inhibits RAAS activity during the acute postoperative period, even in patients with CKD, and it is an especially strong inhibitor of aldosterone. The postoperative BNP is reduced by inhibition of aldosterone in the acute stage. In a comparative study on carperitide and nitroglycerin in patients with AMI, the carperitide group showed greater inhibition of RAAS than the nitroglycerin group, and it was reported that this is related to the inhibitory effects on LV remodeling.^{15–17)} In the NU-HIT trial on patients with left ventricular dysfunction, BNP was significantly reduced from early postoperatively for the long term in the hANP group compared with the placebo group. The cardioprotective effects in the postoperative acute stage were also expressed in the long-term postoperative BNP values, and it appeared that long-term cardiac-related deaths

Table 1 Renal functions after operation

		Preoperative	Day 0	Day 1	Day 3	Week 1
Serum- creatine (mg/dl)	hANP	1.26 ± 0.41	1.18 ± 0.03	1.34 ± 0.05**	1.27 ± 0.06**	1.20 ± 0.05**
	placebo	1.24 ± 0.03	1.24 ± 0.04	1.49 ± 0.05	1.46 ± 0.06	1.39 ± 0.06
Urine-sodium (mEq/l)	hANP	76.64 ± 29.90	93.86 ± 31.37	85.12 ± 75.19	102.36 ± 35.63	81.31 ± 35.46
	placebo	88.71 ± 28.47	93.62 ± 26.39	78.34 ± 42.42	97.72 ± 41.20	78.92 ± 40.74
Urine-creatinine (mg/dl)	hANP	85.73 ± 62.43	18.32 ± 26.27	75.85 ± 59.55**	72.15 ± 70.95*	95.22 ± 46.51
	placebo	89.25 ± 57.01	13.71 ± 40.72	51.07 ± 33.07	56.00 ± 30.14	84.61 ± 38.54
FENa (%)	hANP	2.33 ± 7.18	11.91 ± 12.89	2.12 ± 3.07	1.95 ± 2.25*	0.87 ± 0.79**
	placebo	2.11 ± 9.51	14.60 ± 13.48	2.99 ± 4.74	2.81 ± 4.47	1.24 ± 1.15
RFI	hANP	1.85 ± 1.64	15.51 ± 14.62*	2.97 ± 4.28*	2.70 ± 3.07*	1.21 ± 1.10**
	placebo	1.78 ± 1.56	20.34 ± 19.00	4.16 ± 6.48	3.89 ± 6.11	1.73 ± 1.59

*: $p < 0.05$, **: $p < 0.01$. FENa: fractional excretion of sodium; RFI: renal failure index

Fig. 2 Postoperative brain natriuretic peptide level.

and cardiac events were avoided.¹²⁾ The effects of atrial natriuretic peptide (ANP) on the periglomerular cells and renin were inhibited, decreasing angiotensin-II and aldosterone. Receptors of ANP are present in the adrenal cortex and aldosterone synthesis is inhibited by ANP.^{18,19)} In an animal study on an acute heart failure model, Fett, et al. compared a furosemide group, ANP + furosemide group and untreated group and found that urinary sodium excretion and fraction excretion of sodium were significantly increased in the furosemide group and ANP + furosemide group when compared with baseline. GFR showed no differences from baseline in the ANP + furosemide group and untreated group, but it was significantly decreased after administration in the furosemide group. Renin activity and aldosterone increased significantly only in the furosemide group.²⁰⁾ Catapitti, et al. compared a furosemide group and furosemide + BNP group and found increased urinary volume after treatment in both groups although GFR decreased in the furosemide

group but increased in the furosemide + BNP group. Renin activity and aldosterone did not change in the furosemide + BNP group but increased in the furosemide group.²¹⁾ The level of inhibition of RAAS that is rapidly exacerbated by cardiopulmonary bypass is important to reduce postoperative complications such as renal disorders. Focusing our attention on the reciprocal disadvantages of the cardiopulmonary bypass and the advantages of carperitide, we performed the NU-HIT trial. It was clear from this study, and our past research that the RAAS exacerbated by CPB was inhibited by carperitide.¹⁰⁻¹²⁾

In the present study, FENa values were lower in the hANP group compared with the placebo group. However, U-Na showed no significant difference between the two groups. When compared with the preoperative values, U-Na showed a significant increase only in the hANP group, indicating natriuretic effects. Sica, et al. performed very interesting research on this point. They conducted a comparative study on acute heart failure patients divided into three groups: nesiritide, furosemide, and nesiritide and furosemide concomitantly. In the furosemide group, the urinary sodium excretion rate was significantly higher than in the nesiritide group, but the aldosterone value was significantly lower in the nesiritide group than in the furosemide group, indicating that neurohormonal activation plays an important role in shaping diuretic responsiveness in heart failure patients.²²⁾ In this study, there were three reasons why the FENa value was high in the placebo group. The first reason is that the furosemide dose was significantly higher in the placebo group (hANP group: 11.5 ± 28.0 mg, placebo group: 54.0 ± 69.5 mg, $p < 0.0001$). Furosemide has strong natriuretic action, but it exacerbates the RAAS. The use of carperitide can maintain a good renal environment when the dose of furosemide is reduced. The second reason is that the

significantly high U-Cr in the hANP group results in decreased FENa. The high U-Cr is considered to show good glomerular function. The RFI results showed that carperitide has good effects on the glomeruli. The third reason is that in the hANP group, the aldosterone values were significantly lower after administration. In the placebo group, they were high, and this effect appears to be related to Na excretion. However, this point is still not completely clear and requires further study.

The usefulness of dopamine and furosemide in preventing postoperative renal damage has been reported in patients with cardiac surgery. For dopamine, many reports on increased renal blood flow and urinary volume by the renal vasodilator action of low-dose dopamine have been published. However, it had also been reported that, when compared with the untreated group, dopamine increased urinary volume but worsened tubular disorders at an early stage and the renal protective effects of dopamine were not verified.^{23–26)} In a study on cardiac surgery patients with normal renal function divided into furosemide, dopamine, and untreated groups, the sCr increase rate was significantly higher in the furosemide group than in the other two groups. Creatinine clearance was significantly lower and none of the patients in the other two groups required hemodialysis, but the sCr increase was 4.9% in the furosemide group. In the dopamine group, the rate of sCr increase was low when compared with the furosemide group but no difference from the untreated group was reported.²³⁾

Furosemide increased the urinary volume because of its potent natriuretic action, but increases in sCr, decreases in eGFR, exacerbation of the RAAS and conversely, aggravated renal dysfunction has also been reported.^{20,23,27,28)} In the present research, strong natriuresis was observed in the placebo group. The reason for this appeared to be that many patients in the placebo group used furosemide. However, in the placebo group, the sCr increase rate was high and eGFR was significantly lower than in the hANP group, as in a previous report.¹³⁾ Good glomerular function was found from the results for U-Cr and RFI.

This study showed that carperitide not only inhibited RAAS exacerbated by cardiopulmonary bypass and increased the urinary volume but also increased both GFR and natriuresis. Renal protective effects with the physiological renal environment more improved in the early postoperative stage were obtained. This appeared to be associated with the effects of avoiding dialysis and decreasing cardiac events and renal events observed at one year postoperatively in the results of the NU-HIT

trial for CKD.

Conclusion

In on pump isolated CABG patients with CKD, carperitide showed a potent natriuretic action and inhibited the renin-angiotensin system, suggesting that it prevented deterioration of postoperative renal function. Our findings raise new possibilities for the perioperative and postoperative management of patients undergoing surgery with cardiopulmonary bypass.

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Disclosure Statement

None of the authors have any conflicts of interest associated with this study.

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