Original Paper

Effects of Carperitide on Contrast-Induced Acute Kidney Injury with a Minimum Volume of Contrast in Chronic Kidney Disease Patients

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Key Words

Contrast-induced acute kidney injury · Carperitide · Chronic kidney disease · Contrast medium volume

Abstract

Background/Aims: Although contrast-induced acute kidney injury (CIAKI) is a major complication associated with angiography, the prophylaxis is not well established. Use of a low dose of carperitide for preventing CIAKI remains controversial. We examined the protective effect of carperitide on CIAKI after coronary angiography with a small contrast volume in chronic kidney disease (CKD) patients with coronary artery disease. **Methods:** We randomly assigned 112 consecutive patients to a carperitide or a control group. The contrast volume was kept under 150 ml. The primary endpoint was the incidence of CIAKI defined by a serum creatinine of ≥25% or a serum creatinine of ≥0.5 mg/dl from baseline within 48 h. The secondary endpoint was a change in renal function at 1 week after the procedure. **Results:** The baseline characteristics and contrast volumes (carperitide group: 67.4 ± 38.2 ml vs. control group: 64.8 ± 20.5 ml, p = 0.661) were comparable in the two groups. The incidence of CIAKI was similar in the two groups (carperitide group: 8.5% vs. control group: 5.7%, p = 0.564). A multivariate analysis revealed that a hypotension ≥20 mm Hg was a significant predictor of developing CIAKI in the carperitide

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304

Okumura et al.: Effects of Carperitide on Contrast-Induced Acute Kidney Injury with a Minimum Volume of Contrast in Chronic Kidney Disease Patients

group (p = 0.015). The incidence of CIAKI in the carperitide group without hypotension was rare, but not significantly different (carperitide group: 2.4% vs. control group: 5.7%, p = 0.432). **Conclusions:** This study indicated that the use of a small contrast volume suppressed the incidence of CIAKI and that carperitide had no prophylactic effect against CIAKI. Our results also revealed the impact of hypotension on the development of CIAKI in the carperitide group.

Introduction

Contrast-induced acute kidney injury (CIAKI) is one of the major critical complications of coronary angiography (CAG) and/or percutaneous coronary intervention (PCI), and is associated with increased morbidity and mortality [1, 2].

The overall incidence of CIAKI in patients with chronic kidney disease (CKD) is extremely higher, at 10–25% [3, 4], than in the general population. Diabetes mellitus, high-dose administration of contrast media, hypotension, anemia, and CKD are reported as the risk factors for CIAKI [4]. To date, there is no sound evidence supporting the routine use of prophylactic drugs to prevent CIAKI; however, it is potentially possible to diminish the incidence by reducing the volume of contrast media.

Since recently, technical advances allow performing CAG or PCI with a very small amount of contrast media. The toxicity of contrast media on the kidneys is dose dependent [5], and a recent report revealed that a volume of contrast medium of ≥ 155 ml is a risk for CIAKI [6].

The pathogenesis of CIAKI is considered to be mainly dependent on renal hypoperfusion and ischemia [7, 8]. Carperitide, a member of the natriuretic peptide family with a vasodilating function [9, 10], was found to have various renoprotective effects, such as improvement of renal plasma flow, reducing the plasma levels of several vasoconstrictors [11–13]. Morikawa et al. [6] reported that the beneficial effect of low-dose carperitide on renal function is maintained for up to 1 month after contrast medium use. However, another study failed to prove any beneficial effect of carperitide on the incidence of CIAKI [14].

The aim of this prospective, randomized, open-label, blinded endpoint (PROBE) study was to determine whether low-dose carperitide has a prophylactic effect against CIAKI under CAG/PCI with a minimum volume of contrast medium in patients with CKD.

Materials and Methods

Study Population

We enrolled a total of 125 consecutive CKD patients undergoing CAG or PCI. CKD was defined as a baseline estimated glomerular filtration rate (eGFR) < 60 ml/min/1.73 m^2, which was calculated by the Modification of Diet in Renal Disease formula modified for Japanese subjects: eGFR = 194 $\times$ serum creatinine$^{-1.094}$ $\times$ age$^{-0.287}$ $\times$ 0.739 (if female) [15, 16]. The exclusion criteria included hypersensitivity to contrast media or carperitide; a baseline systolic blood pressure < 110 mm Hg; the use of vasopressors before the procedure; current hemodialysis; planned post-contrast medium dialysis; major surgery or contrast medium use within 10 days before the study; acute coronary syndrome; multiple myeloma; parenteral use of diuretics, and the administration of N-acetylcysteine, metformin, sodium bicarbonate, fenoldopam, mannitol, or nonsteroidal anti-inflammatory drugs (NSAIDs). We excluded the patients who required cardiac mechanical support (intra-aortic balloon pumping or percutaneous cardiopulmonary support) during the procedure.

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305

Okumura et al.: Effects of Carperitide on Contrast-Induced Acute Kidney Injury with a
Minimum Volume of Contrast in Chronic Kidney Disease Patients

We calculated the sample size assuming a CIAKI rate of 20% in the control group based on the incidence rate previously reported in CKD patients undergoing CAG [3, 4]. Also, we assumed that the incidence of CIAKI decreases to almost one seventh through the administration of carperitide [13]. Based on these assumptions, we calculated that 57 patients were needed in each treatment group to detect a statistically significant difference between treatment groups using the log-rank test with $\alpha = 0.05$ (two-sided) and $1 - \beta = 0.80$.

The study protocol and chart reviews were approved by our institutional ethics committee. Written informed consent was given by all patients prior to the procedure.

Study Protocol

Patients were randomly assigned to receive either carperitide (Daiichi-Sankyo Co., Ltd., Tokyo, Japan) in addition to intravenous hydration with 1.0 ml/kg/h of saline (carperitide group) or only hydration with saline (control group) for 12–18 h before and for 6 h after contrast administration. Carperitide was dissolved in a 5% carbohydrate solution and adjusted to 0.025 μg/kg/min. Iohexol (Omnipaque 350; Daiichi-Sankyo Co., Ltd.), a nonionic, low-osmolality contrast medium, was used in all patients. When the systolic blood pressure decreased below 90 mm Hg, carperitide was reduced to half a dose. When we recognized a consistent decrease in the systolic blood pressure (to <90 mm Hg) or when the patients' symptoms were dependent on blood pressure oscillations, we excluded the patients from this study.

The primary endpoint was the incidence of CIAKI defined as a 25% increase in creatinine or an increase in creatinine by 0.5 mg/dl from baseline at the maximum value obtained within 48 h after the procedure [4, 5]. The serum creatinine and cystatin C levels were measured at 12–24 h before the procedure, and at 24–48 h and 1 week after the procedure. The secondary endpoint was the changes in the serum creatinine and serum cystatin C concentrations at 1 week after procedure.
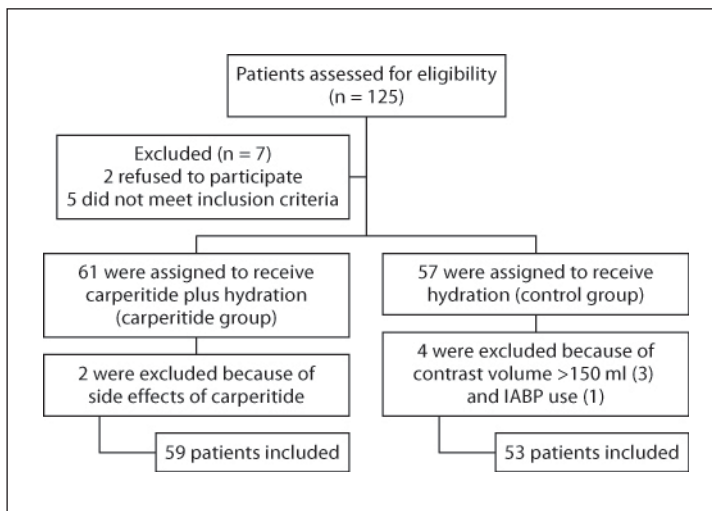
Statistical Analysis

The STATA/SE11 software program was used for all statistical analyses. We tested the distribution of continuous variables for normality with a one-sample Kolmogorov-Smirnov test. Continuous variables were presented as the means (standard deviations), and differences between the two groups were evaluated by Student's unpaired t test or the Wilcoxon test if the distribution was abnormal. Comparisons across the two groups were performed by the χ^2 test. We used a logistic regression analysis for the multivariable analysis. After initial therapy, the statistical analysis was based on an intention-to-treat analysis.

Results

Seven patients (2 refused to participate in the study, 5 did not meet the inclusion criteria) did not participate in this study. Two patients with symptomatic hypotension were excluded because of their intolerance to carperitide. After CAG, 4 patients (3 who received a dose of contrast medium >150 ml, and 1 who required intra-aortic balloon pumping) were excluded. Therefore, 112 patients were eligible for this study (carperitide group: n = 59, placebo group: n = 53) (fig. 1).

Table 1 shows the baseline clinical characteristics of the enrolled patients. There were no significant differences between the two groups. Also, the patients' baseline renal function was comparable.

The volume of contrast medium used (table 2) was similar in both groups (carperitide group: 67.4 ± 38.2 ml vs. control group: 64.8 ± 20.5 ml, p = 0.661). When compared with the control group, carperitide infusion produced a significant decrease in the systolic blood pres-

306

Okumura et al.: Effects of Carperitide on Contrast-Induced Acute Kidney Injury with a
Minimum Volume of Contrast in Chronic Kidney Disease Patients

Fig. 1. Randomization and clinical diagnoses of all patients. IABP = Intra-aortic balloon pumping.

Table 1. Baseline characteristics of study patients

	Carperitide group (n = 59)	Control group (n = 53)	p value
Age, years	74 (8.9)	73.0 (6.3)	0.566
Male, %	68	83	0.080
Body mass index	23.9 (3.1)	23.6 (3.4)	0.682
Systolic blood pressure, mm Hg	129.9 (17.6)	135.1 (20.7)	0.152
Hypertension, %	83	77	0.449
Diabetes mellitus, %	59	45	0.137
History of myocardial infarction, %	15	15	0.981
History of congestive heart failure, %	8	9	0.859
Medication, %			
ACE inhibitors	18	8	0.158
ARBs	56	63	0.513
Calcium channel blockers	52	42	0.306
Diuretics	34	38	0.718
Statins	68	65	0.721
LVEF, %	62.6 (12.4)	59.0 (15.7)	0.198
Current smoker, %	24	38	0.121

Data are presented as means (SD) for continuous variables, and percentages for categorical variables. ACE = Angiotensin-converting enzyme; LVEF = left ventricular ejection fraction.

sure at 12 h [–3.5 (–7 to 2) vs. –14 (–20 to –8.5) mm Hg, p < 0.001]. The incidence of a critical systolic blood pressure reduction, defined as a systolic blood pressure reduction ≤–20 mm Hg, was significantly higher in the carperitide group than in the control group (p < 0.001).

There were no significant differences for the primary outcome of the development of CIAKI between the groups (carperitide group: 8.5% vs. control group: 5.7%, p = 0.564) (fig. 2). Of importance, only an increase in serum creatinine >25% occurred as an indicator of CIAKI, and there were no patients who developed CIAKI strictly defined as an increase in serum creatinine of ≥0.5 mg/dl.

Okumura et al.: Effects of Carperitide on Contrast-Induced Acute Kidney Injury with a
Minimum Volume of Contrast in Chronic Kidney Disease Patients
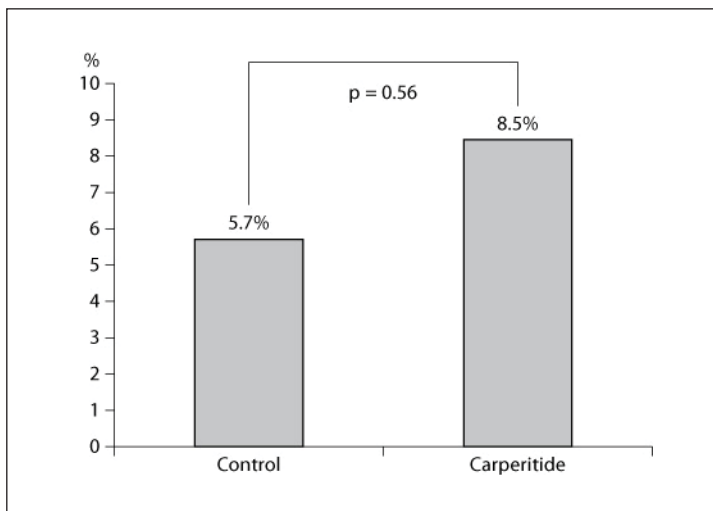
Fig. 2. The incidence of CIAKI was a little higher in the carperitide group than in the control group, but the difference was not statistically significant.

**Table 2.** Contrast volume and changes in blood pressure of study patients

	Carperitide group (n = 59)	Control group (n = 53)	p value
Contrast medium volume, ml	67.4 (38.2)	64.8 (20.5)	0.661
Change in systolic blood pressure, mm Hg	–14 (–20 to –8.5)	–3.5 (–7 to –2)	<0.001
Incidence of hypotension[1], %	31	2	<0.001

Data are presented as means (SD) or medians (interquartile ranges) for continuous variables and percentages for categorical variables. [1] Incidence of hypotension is defined as a systolic blood pressure reduction ≤–20 mm Hg from baseline.

According to the secondary endpoint, the adverse effects of contrast medium on renal function were also similar in both groups. Table 3 shows the changes in renal functional markers. In the carperitide group, there was a significant deterioration in the serum creatinine, eGFR, and serum cystatin C levels compared to the control group at 24–48 h after the administration of the contrast medium (p = 0.002, 0.006, 0.001, respectively). In contrast, the serum creatinine level showed a tendency to decrease in the carperitide group at 1 week after contrast medium use, but not significantly so.

A univariate analysis of the incidence of CIAKI in the carperitide group revealed that hypotension defined as a severe systolic blood pressure reduction by ≤–20 mm Hg was a significant predictor [odds ratio (OR) 15.6 (1.58–154.28), p = 0.019] (table 4). When all variants of the patients' age, diabetes mellitus status, angiotensin II receptor blocker (ARB) and statin use, and hypotension detected by the univariate analysis were included in the multivariate model, hypotension was an independent predictor of the development of CIAKI in the carperitide group [OR 31.87 (1.93–525.58), p = 0.015]. Furthermore, all patients who developed CIAKI in the carperitide group and 75% of the patients who developed CIAKI in both groups were treated with calcium channel blockers. Although the incidence of CIAKI in the carperitide group without hypotension was low, it was comparable to that in the placebo group (2.4 vs. 5.7%, respectively, p = 0.432) (fig. 3).

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308

Okumura et al.: Effects of Carperitide on Contrast-Induced Acute Kidney Injury with a Minimum Volume of Contrast in Chronic Kidney Disease Patients

Fig. 3. The incidence of CIAKI was higher in the control group than in the carperitide group without severe blood pressure reduction, but the difference was not statistically significant.
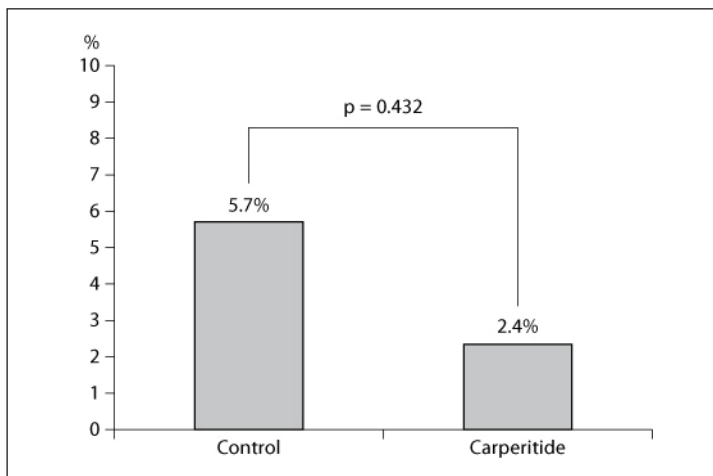
Table 3. Changes from baseline in serum creatinine, eGFR, and serum cystatin C

	Carperitide group (n = 59)	Control group (n = 53)	p value
Serum creatinine, mg/dl			
Baseline	1.16 (0.99–1.27)	1.18 (1–1.44)	0.493
Change within 48 h	0.05 (–0.03 to 0.13)	–0.03 (–0.08 to 0.07)	0.002
Change at 1 week	–0.03 (–0.09 to 0.04)	0.01 (–0.06 to 0.07)	0.054
eGFR, ml/min/1.73 m^2			
Baseline	44.4 (9.2)	45.4 (10.4)	0.574
Change within 48 h	–2.0 (6.1)	0.8 (4.3)	0.006
Change at 1 week	0.9 (5.6)	–0.4 (4.3)	0.169
Serum cystatin C, mg/l			
Baseline	1.47 (1.26–1.64)	1.36 (1.23–1.7)	0.630
Change within 48 h	0.09 (–0.01 to 0.18)	–0.03 (–0.11 to 0.07)	0.001
Change at 1 week	–0.01 (–0.08 to 0.04)	–0.01 (–0.1 to 0.05)	0.242

Data are presented as means (SD) or medians (interquartile ranges).

Table 4. Univariate and multivariate analysis for CIAKI in the carperitide group

	CIAKI, % (+)	CIAKI, % (–)	Univariate analysis OR 95% CI	Univariate analysis p value	Multivariate analysis OR 95% CI	Multivariate analysis p value
Age >70 years	80	78	1.14 (0.12–11.21)	0.909	1.08 (0.1–33.16)	0.960
Diabetes mellitus	80	57	2.97 (0.31–28.35)	0.325	10.49 (0.40–275.51)	0.159
Dyslipidemia	80	69	1.83 (0.19–17.71)	0.599		
Hypertension	80	82	0.91 (0.09–9.03)	0.940		
ARBs	20	59	0.17 (0.02–1.64)	0.126	0.78 (0–1.61)	0.099
Statins	60	70	0.63 (0.10–4.15)	0.630	0.22 (0.13–3.35)	0.274
Incidence of hypotension[1]	80	30	15.6 (1.58–154.28)	0.019	31.87 (1.93–525.58)	0.015
LVEF(≥40%)	80	93	0.32 (0.29–3.59)	0.333		
Contrast medium >65 ml	40	35	1.23 (0.19–8.00)	0.830		
History of myocardial infarction	20	15	1.44 (0.14–14.57)	0.758		

LVEF = Left ventricular ejection fraction; CI = confidence interval.
[1] Incidence of hypotension is defined as a systolic blood pressure reduction ≤–20 mm Hg from baseline.

309

Okumura et al.: Effects of Carperitide on Contrast-Induced Acute Kidney Injury with a Minimum Volume of Contrast in Chronic Kidney Disease Patients

Discussion

The pathogenesis of CIAKI is considered to be linked to the cytotoxic effects of contrast media and renal vasoconstriction. In the present study, we showed that CAG with low-dose contrast medium decreased the incidence of CIAKI by about 50% compared to previous reports and none of our CKD patients with CAG developed strictly defined CIAKI (≥ 0.5 mg/dl serum creatinine), which is reported to be a more sensitive definition for mortality and morbidity in patients with CIAKI [17]. Carperitide, a renal-specific vasodilator, has been reported to have preventive effects on contrast-induced renal injury because of improvement of renal perfusion [18]. Contrary to the previously reported protective effects of carperitide, our current results did not demonstrate the advantages for CIAKI. A sub-analysis of CIAKI in the carperitide group showed an impact of hypotension, which was suggested to disturb the renoprotective effects of carperitide. Also, our sub-analysis revealed that combination therapy using calcium channel antagonists with carperitide could potentially predict the development of CIAKI. Glomerular hypoperfusion induced by systemic arterial pressure reduction due to treatment with dual vasodilators is suggested to result in glomerular dysfunction within 48 h after contrast medium use.

Mehran et al. [19] reported the utility of a CIAKI risk stratification score based on 8 available variables, and we can improve the procedure-related factors including the contrast volume. The present study indicates that decreasing the volume of contrast medium is indispensable for the prophylaxis of CIAKI, especially in CKD patients. When the contrast volume is suppressed to <100 ml, a critical blood pressure reduction exerts adverse effects on the development of CIAKI. The results of our sub-analysis emphasize the need for avoiding excessive use of vasodilators in order to maintain the renal circulation. As the incidence of hypotension was higher in the carperitide group, carperitide use should be avoided when the contrast medium volume is suppressed. The determination of an adaptable dose of carperitide, without hypotension, is essential for an effective and safe use of carperitide in patients with CAG/PCI.

Study Limitations

First, the diagnosis of CIAKI depended on the peak value of the serum creatinine concentration within 48 h after contrast medium use [20]. However, because of our institutional limitations concerning the frequency and timing of blood collection, the degree of the elevation of creatinine might have been underestimated. Second, this study was a single-center study and was not blinded. Third, the incidence of CIAKI was lower than predicted under procedures using a small amount of contrast medium.

Acknowledgments

Disclosure Statement

The authors declare that they have no conflicts of interest.

310

Okumura et al.: Effects of Carperitide on Contrast-Induced Acute Kidney Injury with a Minimum Volume of Contrast in Chronic Kidney Disease Patients

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