Carperitide Increases the Need for Renal Replacement Therapy After Cardiovascular Surgery

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Objectives: **Acute kidney injury is a common complication after aortic surgery. Carperitide, a human atrial natriuretic peptide, was reported to be effective for preventing acute kidney injury after cardiac surgery. However, most studies were from single centers, and results of meta-analyses are subject to publication bias. The aim of the present study was to investigate whether carperitide preserved renal function in patients undergoing cardiovascular surgery.**

Design: **Retrospective cohort study.**

Setting: **Participating hospitals (N = 281) in a national database from 2010 to 2013.**

Participants: **Adult patients (N = 47,032) who underwent cardiovascular surgery.**

Interventions: **None.**

Measurements and Main Results: **The main intervention variable investigated was the use of carperitide on the day of surgery. Assessed outcomes included receiving renal replacement therapy within 21 days of surgery and in-hospital mortality. Data were available for 47,032 patients, of whom 2,186 (4.6%) received carperitide on the day of surgery. Multivariate logistic regression analysis revealed that carperitide was significantly associated with a greater likelihood of receiving renal replacement therapy within 21 days of surgery, but not with in-hospital mortality.**

Conclusions: **In patients undergoing cardiovascular surgery, carperitide significantly increased the odds of receiving renal replacement therapy within 21 days after surgery.**

KEY WORDS: perioperative care, cardiovascular surgery, renal failure, carperitide, mortality, renal replacement therapy, atrial natriuetic peptide

ACUTE KIDNEY INJURY (AKI) is a common complication after cardiovascular surgery, affecting approximately 9% to 39% of patients.[1–3] AKI after cardiovascular surgery has been reported to be associated with longer hospital stay[4] and higher mortality.[5,6] The mortality rate of patients with AKI requiring renal replacement therapy (RRT) after cardiac surgery was reported to be 54%.[7] However, effective interventions to prevent postoperative AKI have not yet been established.[8]

Carperitide, a human atrial natriuretic peptide, was approved for use in patients with acute decompensated heart failure in 1995 in Japan. In 2000, the first randomized trial[9] demonstrated that carperitide preserved postoperative glomerular filtration rate. Several randomized trials[10–12] subsequently demonstrated that carperitide prevented AKI. Furthermore, meta-analyses showed that human atrial natriuretic peptide reduced the occurrence of AKI and the need for RRT after cardiac surgery.[13,14] As a result, this drug is used widely off-label in Japan with the aim of preventing AKI. However, most randomized trials are from single centers, and the results of meta-analyses are subject to publication bias.[13] Also, randomized controlled trials include only selected patients based on strict inclusion criteria and are not always representative of larger populations. No population-based studies have yet been reported. The aim of the present study was to investigate the impact of carperitide on outcomes in patients who underwent cardiovascular surgery, based on a retrospective analysis of data from the Diagnosis Procedure Combination database, which is a nationwide administrative database in Japan.

METHODS

The institutional review board of the University of Tokyo approved this study. Informed consent was waived because of the anonymous nature of the data.

Data Source

Inpatient data for this study were extracted from the Japanese Diagnosis Procedure Combination database.[15] The Diagnosis Procedure Combination is a case-mix inpatient classification system for acute care hospitals linked to health care reimbursement in Japan. More than 1,000 hospitals voluntarily participate in the Diagnosis Procedure Combination system. The database includes data from approximately 7 million inpatients, which represents approximately 50% of all discharges from acute care hospitals in Japan. The Diagnosis Procedure Combination database includes the following data: hospital identification number; patient gender and date of birth; dates of hospitalization and discharge; primary diagnosis, diagnosis precipitating admission, diagnosis consuming the most resources, pre-existing comorbidities at admission, and complications during hospitalization, which were coded with International Classification of Diseases, Tenth Revision codes and text in the Japanese language; procedures and the dates of procedures performed; dates and doses of drugs or blood products prescribed during the hospitalization; duration of anesthesia and cardiopulmonary bypass; and discharge status.

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Patient Data

This study included all adult patients who underwent surgery for thoracic aortic aneurysms, coronary artery bypass grafting, or valve surgery during their hospitalization and were discharged between July 2010 and March 2013. Patients who underwent surgery without cardiopulmonary bypass or underwent surgery of the descending aorta were not included. In addition, the following patients were excluded: patients who underwent emergency surgery for thoracic aortic dissection, impending rupture, or ruptured thoracic aortic aneurysms and other surgery performed on the day of admission; were younger than 18 years; died within 2 days postoperatively; underwent RRT before surgery; underwent cardiovascular surgery more than once; had missing data regarding the duration of cardiopulmonary bypass; and started carperitide at a time other than the day of surgery.

Study Variables

Data specifically regarding the prescription of carperitide on the day of surgery were extracted. Patients prescribed carperitide were categorized according to the prescribed dose. A low dose was defined to be $\leq$1,000 μg on the day of surgery. A high dose was defined to be $>$1,000 μg on the day of surgery.

The presence of comorbidities, including myocardial infarction, congestive heart failure, cerebrovascular disease, chronic pulmonary disease, chronic kidney disease, diabetes mellitus, and liver disease, was assessed. These comorbidities were extracted as components of the Charlson Comorbidity Index based on International Classification of Diseases, Tenth Revision codes using algorithms developed by Quan et al.[16] Hospital volume of cardiovascular surgery was defined as the average number of operations performed in each hospital annually. Hospital volume was categorized into tertiles, with an equal number of patients in each category. Hospital factors included type of hospital (academic or nonacademic) and hospital volume. Procedure-related variables included type of surgery (surgery for thoracic aortic aneurysm, coronary artery bypass grafting, or valve surgery); duration of cardiopulmonary bypass (minutes); and use of dopamine, dobutamine, norepinephrine, and red blood cell transfusion on the day of surgery.

Outcome Measures

Assessed outcomes included receiving RRT within 21 days of surgery and in-hospital mortality. RRT-free 21-day survival,"[17] which was defined as survival for $\geq$21 days after surgery without receiving RRT, also was assessed.

Statistical Analysis

Continuous variables were presented as an average with the SD or the median with the interquartile range. Categoric variables were presented as the number with a percentage. To account for differences in baseline characteristics between patients who did and did not receive carperitide, propensity score analyses were conducted in addition to logistic regression analyses. The propensity score was estimated with a logistic regression model, using baseline characteristics listed in Table 1 as the independent variables. To adjust for clustering within hospitals, generalized estimating equations were fitted with logistic regression models. The established model had a c-statistic of 0.957 (95% confidence interval [CI] = 0.955-0.959). Propensity score matching was performed by nearest neighbor matching without replacement. A caliper was set at 20% of SD of the propensity scores. Differences between 2 groups before and after propensity score matching were assessed by standardized differences. Because the dose of carperitide may affect the outcomes, additional propensity score analyses were performed in which patients with no carperitide were matched separately to patients with low-dose carperitide and high-dose carperitide. Standardized differences of $<$10% were considered negligible imbalances in baseline characteristics between groups.[18] A p value $<$ 0.05 was considered statistically significant. All analyses were performed using IBM SPSS Statistics version 22 (IBM Corp, Armonk, NY).

RESULTS

After application of inclusion and exclusion criteria, 47,032 patients who underwent surgery for thoracic aortic aneurysms, coronary artery bypass grafting, or valve surgery were included in the analysis (Fig 1). The characteristics of the patients are shown in Table 1. Patients receiving carperitide were more likely to be admitted to academic hospitals or hospitals with higher volume. Patients in the carperitide group had fewer myocardial infarctions or a lower incidence of congestive heart failure and more peripheral vascular disease. The rate of patients with chronic renal disease was similar in both groups. More patients underwent surgery for thoracic aortic aneurysm in the carperitide group, and more patients underwent coronary artery bypass grafting and valve surgery in the no-carperitide group. The duration of cardiopulmonary bypass was longer in patients who received carperitide than patients who did not. More patients received norepinephrine and red blood cell transfusions in the carperitide group than in the no-carperitide group.

Crude in-hospital mortality and the proportion of patients who underwent RRT were significantly higher, whereas the rate of RRT-free survival 21 days postoperatively was significantly lower in the carperitide group (Table 2). Multivariate logistic regression analysis revealed that carperitide significantly was associated with receiving RRT (odds ratio = 1.43; 95% CI = 1.27-1.61), but not with in-hospital mortality (odds ratio = 1.04; 95% CI = 0.82-1.32) and RRT-free survival (odds ratio = 0.91; 95% CI = 0.71-1.17) (Table 3). When the dose of carperitide was added to the logistic regression analysis as an independent variable, the odds ratio for receiving RRT was 1.56 (95% CI = 1.26-1.93) in the high-dose carperitide group (Table 4).

Propensity score matching created 2,159 pairs. Patient characteristics were well balanced between the groups. The carperitide group was associated significantly with a higher probability of receiving RRT within 21 days of surgery compared with the no-carperitide group (5.5% *v* 9.0%, p $<$ 0.001), but not with in-hospital mortality (5.8% *v* 5.8%, p = 1.000) or RRT-free survival (95.1% *v* 94.5%, p = 0.371) (Table 2). When the propensity score matching analysis was restricted to patients who received low-dose carperitide or high-dose carperitide, the low-dose group was not associated with