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Effects of low-dose atrial natriuretic peptide infusion on cardiac surgery–associated acute kidney injury: A multicenter randomized controlled trial☆

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ABSTRACT

Purpose: To evaluate the effects of atrial natriuretic peptide (ANP) on renal function and medical costs in patients with acute kidney injury (AKI) associated with cardiac surgery.
Materials and methods: The Japanese trial for AKI in Post-cardiovascular surgery patients by ANP (JAPAN) was a prospective, multicenter, randomized, double-blind, placebo-controlled study conducted in 11 hospitals in Japan. Acute kidney injury was defined as an increase in serum creatinine of at least 0.3 mg/dL within 48 hours. The patients were randomly assigned to receive ANP (0.02 μg kg^{-1} min^{-1}) or placebo. The primary end point was a change in renal function. The secondary end points were a need for renal replacement therapy, the lengths of intensive care unit and hospital stays, and medical costs incurred over the 90-day follow-up.
Results: Of the 77 randomized patients, 37 were in the ANP group and 40 were in the placebo group. Although ANP significantly ($P = .018$) increased urine output, it did not significantly improve renal function compared with placebo. There were no significant differences between the groups in the renal replacement therapy rate, the lengths of the intensive care unit and hospital stays, or medical costs.
Conclusion: Atrial natriuretic peptide infusion did not show a renoprotective effect or cost-saving effect in the treatment of cardiac surgery–associated AKI.

1. Introduction

Cardiac surgery–associated acute kidney injury (AKI) is a common complication after cardiac surgery and has an established link with increased mortality [1-5] and medical costs [6]. In a recent study, AKI associated with a decreased estimated glomerular filtration rate (eGFR) (>25%, >50%, and >75%) within 1 week of surgery, respectively, has been reported to occur in 24% (n = 829), 7% (n = 228), and 3% (n = 119) of cardiac surgery patients (n = 3500), and was an independent predictor of death [1]. The pathogenesis of cardiac surgery–associated AKI is thought to be mediated by a reduction in renal blood flow induced by wide-ranging factors such as exogenous and endogenous toxins, metabolic abnormalities, ischemia and reperfusion injury, neurohormonal activation, proinflammatory and vasoconstrictive mediators, and oxidative stress [2-5]. Surgical procedures and cardiopulmonary bypass (CPB) activate inflammatory mediators, adhesion molecules, and proinflammatory transcription factors, leading to cellular injury and AKI [2]. Perioperative low cardiac output is directly related to AKI risk due to hyperactivity of sympathetic nervous system components such as the renin-angiotensin-aldosterone system, which increases renal vasoconstriction [3].

Atrial natriuretic peptide (ANP) is a potent endogenous natriuretic, diuretic, and vasorelaxant peptide with an important role in regulating blood pressure and fluid homeostasis [7]. It raises the pressure within

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[1] The investigators participating in the Japanese trial for Acute kidney injury in Post-cardiovascular surgery patients by Atrial Natriuretic peptide (JAPAN).

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the glomerular capillaries by dilating afferent renal arterioles and constricting efferent arterioles [8], resulting in increased glomerular filtration and urine output. Atrial natriuretic peptide increases medullary vasa recta blood flow [9] and, by doing so, may protect against medullary ischemia. Atrial natriuretic peptide also preserves glomerular filtration rate (GFR) and reduces renal tissue damage in rat models of acute ischemic renal failure [10]. It confers anti-inflammatory effects by inhibiting nuclear factor (NF) κB activation and cytokine production [11-13]. In recent studies by our group using a rat model of renal ischemia-reperfusion injury, pretreatment and posttreatment with ANP attenuated the messenger RNA expression of proinflammatory cytokines in kidney and lung by inhibiting NF-κB [14,15].

Review articles have shown that ANP infusion induces a diuretic effect with increased creatinine clearance, preserves postoperative renal function, reduces the usage of conventional diuretics, and suppresses the renin-angiotensin-aldosterone system in higher-risk patients after cardiac surgery [16,17]. Two randomized controlled trials (RCTs) in a clinical setting have demonstrated that low-dose ANP infusion improves renal function in patients undergoing coronary artery bypass grafting (CABG) with left ventricular dysfunction [18] and chronic kidney disease [19]. Until now, however, no earlier multicenter RCTs have investigated the effects of ANP infusion in patients with cardiac surgery–associated AKI. We therefore decided to evaluate the effects of ANP on renal function and medical costs in patients with cardiac surgery–associated AKI.

2. Materials and methods

2.1. Study design and patients

The *J*apanese trial for *A*KI in *P*ost-cardiovascular surgery patients by *AN*P (JAPAN) was a prospective, multicenter, randomized, double-blind, placebo-controlled study in patients with AKI after cardiovascular surgery. Patients were enrolled at 11 hospitals in Japan from May 2012 through March 2015 and were followed up for 90 days after enrollment. This study protocol was approved by the ethics committee at each participating institution, starting with Tokyo Medical and Dental University, the coordinating center. This study was performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments. Informed written consent was obtained from all patients. This study was registered with the University Hospital Medical Information Network (UMIN 000006812). Study coordinators at each hospital registered data into the Internet Data and Information Center for Medical Research (INDICE). Patients were assigned by the INDICE randomization system to receive either ANP or placebo. A flowchart of the study design and patient selection is shown in Fig. 1. Inclusion criteria were a patient age of ≥20 years and recent elective cardiac surgery, namely, CABG, valve surgery, thoracic aortic aneurysm surgery, or a combination thereof. The definition of AKI was based on the Kidney Disease: Improving Global Outcomes (KDIGO) criteria: an increase in serum creatinine of at least 0.3 mg/dL from the preoperative level within 48 hours after cardiac surgery [20]. The exclusion criteria were (1) severe hypotension or cardiogenic shock; (2) right ventricular infarction; (3) dehydration; (4) end-stage renal disease; (5) administration of nonsteroidal anti-inflammatory drugs, angiotensin-converting enzyme (ACE) inhibitor, or angiotensin receptor blocker (ARB) within 24 hours before the operation; (6) administration of contrast agent within 3 days before the operation; and (7) extracorporeal membrane oxygenation.

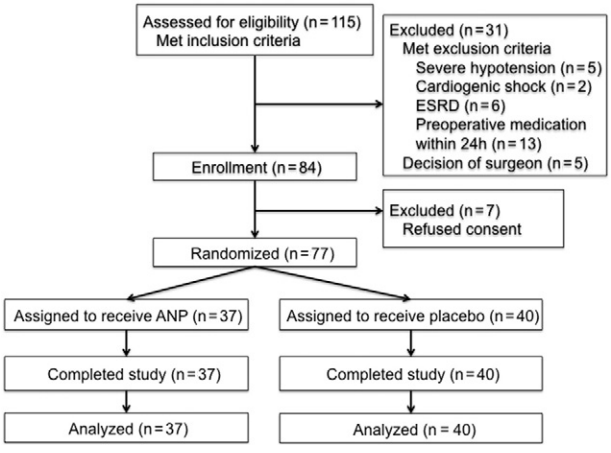

Fig. 1. Flowchart of study design and patient selection for a prospective randomized placebo-controlled study. ESRD indicates end-stage renal disease.

The patients were randomly assigned to receive a low-dose of ANP (carperitide; Daiichi-Sankyo Pharmaceutical, Tokyo, Japan) at the rate of 0.02 μg kg^{-1} min^{-1} (2 mL/h) or placebo (5% glucose, 2 mL/h) by the INDICE randomization system. The infusion of ANP or placebo continued until the serum creatinine level fell back to the preoperative level. The primary end point was a change in renal function over the 90-day follow-up measured by serum levels of creatinine and cystatin C, and creatinine clearance or eGFR. The secondary end points were (1) a need for renal replacement therapy over the 90-day follow-up, (2) the lengths of intensive care unit (ICU) and hospital stays, and (3) medical costs incurred over the 90-day follow-up. Renal replacement therapy was started if patients with AKI met at least one of the following criteria: oliguria (urine output <100 mL in a 6-hour period) unresponsive to fluid resuscitation measures, a serum potassium level higher than 6.5 mmol/L, severe acidemia (pH <7.2), serum urea nitrogen level higher than 70 mg/dL, serum creatinine level higher than 3.4 mg/dL, or the presence of clinically significant organ edema [21].

The diagnostic procedure combination/per-diem payment system was used to calculate total medical costs. Medical costs under diagnostic procedure combination/per-diem payment system consist of inclusive costs and fee-for-service. The inclusive component (D file) covers charges for hospitalization, examinations, and medication, and has a flat-rate per-diem fee based on diagnostic categories. The fee-for-service component (E file) reimburses costs for expensive procedure such as surgeries and renal replacement therapy. Total medical costs (¥) were calculated as 10 × (D file + E file).

Hemodynamics and arrhythmias were recorded during the study period in the ICU. The definition criteria for arrhythmias are atrial fibrillation, atrial flutter, supraventricular tachycardia, premature ventricular contraction, ventricular tachycardia, or ventricular fibrillation.

2.2. Sample size and power calculation

The results from Sezai et al [19] were used to calculate the sample size for this study. A sample size of 87 for each group is estimated to have 80% power to detect a difference in means of 74.25, assuming that the common SD is 196 using a 2-group *t* test with a .05 1-sided significance level. We estimated 194 as the sample size against the loss of about 10% as a dropout rate. Finally, a sample size of 200 was detected as sufficient for this study.

2.3. Statistical analysis

Qualitative data are shown as numbers (percentages) and quantitative data are shown as medians (interquartile ranges). The assessor was blinded for the treatment groups. Although we tried repeated-measures analysis of variance, it was significant for interaction effect between time and variables. Therefore, we could not do repeated-measures analysis of variance. Data were analyzed by the Mann-Whitney *U* test to analyze each pairing of groups. Contingency tables on medical histories and surgical procedures were done by Fisher exact test instead of the χ^2 test. All statistical analyses were performed with EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan), which is a