Vasopressin Does Not Raise Cardiac Enzymes Following Cardiac Surgery: A Randomized Double-Blind Clinical Trial

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Objective: **The aim of this study was to investigate the relationship between intraoperative vasopressin infusion and postoperative cardiac enzymes.**

Design: **A prospective, double-blind, randomized, controlled study.**

Setting: **A single tertiary cardiac center.**

Participants: **One hundred consecutive patients undergoing cardiac surgery with or without cardiopulmonary bypass.**

Interventions: **The study was approved by the Institutional Review Board, and patients provided informed consent to participate. Patients were randomized by computer into 2 equal groups: Vasopressin or control. The blinded study included vasopressin administered at a dose of 1.8 U/h or 1.8 mL/h of normal saline, along with catecholamines. The drug was administered continually during surgery while patients needed catecholamines. The intervention was discontinued upon admission to the intensive care unit when information regarding the true character of the drug was reported to the doctor in charge of patients in the intensive care unit by one of the investigators. Primary outcomes were CK-MB and troponin T levels measured at 0, 6, and 12 hours postoperatively.**

Measurements and Main Results: **Of the 100 patients, 8 were excluded; the remaining 92 were randomized to either the vasopressin (n = 47) or control (n = 45) group. There were no significant differences in demographic data between the groups. Postoperatively at 0, 6, and 12 hours, there were no differences in CK-MB (U/l) (37.5 ± 57.9 *v* 32.0 ± 21.5, 29.4 ± 41.1 *v* 24.4 ± 23.1, and 21.4 ± 21.3 *v.* 21.8 ± 32.4, respectively) and troponin T (752.4 ± 638.2 *v* 762.7 ± 557.1, 753.8 ± 507.3 *v* 777.6 ± 515.0, and 774.6 ± 572.6 *v* 698.7 ± 540.2, respectively) values.**

Conclusions: **Vasopressin infusion has been used to treat catecholamine-unresponsive shock. In this study, intraoperative vasopressin was used safely as a possible first-line drug for treating hypotension; however, it did not increase the levels of cardiac enzymes after cardiac surgery.**

KEY WORDS: vasopressin, cardiac surgery, cardiac enzymes, vasoplegia, vasoconstrictor

VASOPRESSIN EXERTS A NONCATECHOLAMINE-related vasoconstrictive effect through the V_1 receptor; it is used for cardiopulmonary resuscitation[1] and for treating septic patients.[2] The standard dose of vasopressin for septic patients is 0.01-0.04 U/min.[2,3] The VASST study[3] revealed that the efficacy of vasopressin for patients with mild-to-moderately severe sepsis is equivalent or possibly superior to that of norepinephrine. A recent review article reported a superior outcome when vasopressin was administered to patients with vasodilatory shock (vasoplegia) compared with norepinephrine.[4] Low serum vasopressin concentration is associated with postcardiac surgery vasoplegia, and vasopressin administration effectively remedies this.[5,6] A few randomized controlled trials[7–9] have been conducted with patients undergoing coronary artery bypass grafting (CABG) with a high risk of vasoplegia and moderately reduced left ventricular function,[7] as well as patients with moderately reduced left ventricular function[8] and off-pump CABG in stable condition.[9] The dose of vasopressin was fixed at 1.8 U/h in 2 studies[7,8] and flexible (mean value 0.8 U/h) in 1.[9] They reported the decreased frequency of vasoplegia and improved outcomes, including mortality,[7] reduced catecholamine requirements during weaning from cardiopulmonary bypass (CPB), improved hemodynamics,[8] and stabilized heart rate and pulmonary artery pressure.[9] Although all 3 studies targeted patients undergoing CABG, the authors presumed these beneficial effects could be generalized to other cardiac surgery patients. The possible adverse effect of vasopressin is reduced organ perfusion that may affect coronary perfusion,[10] particularly if patients are hypovolemic or in a low-cardiac-output state. On the other hand, catecholamines can cause variable adverse effects, particularly if patients suffer reperfusion injury following cardiac surgery.[11] Because vasopressin reduces the requirement for catecholamines through engagement of V_1 receptors and improving catecholamine sensitivity, it may reduce the adverse effects of catecholamines, particularly on cardiac oxygen balance. However, whether intraoperative vasopressin infusion affects coronary perfusion and oxygen balance remains unknown because of insufficient data.

There has been growing evidence that indicates postoperative levels of cardiac enzymes correlate with prognosis. Peak CK-MB and troponin T levels within 24 hours after CABG are known to correlate with postoperative mortality.[12] Moreover, postoperative troponin level correlates with 30-day mortality among patients undergoing noncardiac surgery.[13] The level of cardiac troponin is associated closely with mortality and echocardiographic findings in patients with sepsis.[14]

These findings suggested that patients' outcomes may be predicted according to levels of cardiac enzymes. If higher catecholamine concentrations potentially cause myocardial damage through inotropic effects and tachycardia, these adverse effects may be mitigated by vasopressin because of its ability to reduce the requirement for catecholamines and to reduce heart rate and increase blood pressure without an inotropic effect.

The authors, therefore, aimed to test the hypothesis that low-dose vasopressin infusion at 1.8 U/h (considered a standard from previous reports) reduced postoperative cardiac enzymes, reflected by improved intraoperative coronary perfusion and oxygen balance, through stabilizing hemodynamic values.

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METHODS

This study was conducted with 100 consecutive cardiac surgical patients in a single cardiac center based in Japan as a randomized, placebo-controlled, double-blind, parallel-group study. The study was approved by the Ethics Committee of the institution, and was conducted in accordance with the standards set forth in the Helsinki Declaration. Informed written consent was obtained from all patients prior to surgery. All cardiac surgical patients over the age of 20 were eligible. Exclusion criteria included patient refusal, no requirement for intervention, and unanticipated adverse effects during surgery. The study was conducted from April 2013-July 2013, and the aim was to enroll 100 consecutive patients.

Patients were randomized by computer into 2 groups: Vasopressin or control. One researcher who was not involved in the surgery made up the drug protocol according to the computer-generated randomization list for each patient. During surgery, the drug was blinded to everyone involved in the surgery. Following anesthesia induction, the study drug (vasopressin 1.8 U/h or normal saline 1.8 ml/h) was administered along with catecholamines to patients requiring hemodynamic support. The study drug was administered continually during the time patients received catecholamines. Patients were weaned off the study drug once all catecholamines were discontinued. Extra vasopressin was administered as required if hemodynamic stability was not achieved using catecholamine support, particularly when the dose of norepinephrine exceeded 8 μg/min. If the study drug was still administered upon the patient's admission to the intensive care unit (ICU), one of the investigators who was not involved in surgery and in evaluating the outcome revealed the true character of the drug to the doctor in charge of the ICU. This was considered the end of the intervention study.

General anesthesia was administered by at least one board-certified anesthesiologist with total intravenous anesthesia, including midazolam, propofol, rocuronium, remifentanil, and fentanyl. Standard monitoring during surgery included electrocardiography, oxygen saturation, capnography, arterial blood pressure, pulmonary artery catheterization, and transesophageal echocardiography. CPB was managed by the perfusionist in charge.

Hemodynamics during surgery were judged unsatisfactory if the following parameters were not achieved: (1) Blood pressure: Systolic pressure 80 to 140 mmHg, mean 55 to 85 mmHg; (2) Heart rate: Off-pump CABG 40-80/min and others 40 to 90/min; (3) Cardiac index (CI): >1.5 L/min/m^2; (4) Venous oxygen saturation (SvO2): $>60\%$.

Appropriate fluid resuscitation was determined according to pulmonary artery catheter values and transesophageal echocardiography and conducted by anesthesiologists, and the perfusionists who decided the appropriate blood component use for each case. The anesthesiologist selected and administered inotropes, including dopamine, dobutamine, milrinone, or epinephrine, either alone or combined. In addition, norepinephrine was administered as a vasoconstrictor alone or with inotropes. For control of heart rate, a beta-blocker was administered if there were no contraindications.

In the current study, the authors defined vasoplegia as the absence of low output (cardiac index $>$ 2.0 L/min/m^2) and refractory catecholamine-resistant vasodilatory shock (could not reach target blood pressure with norepinephrine $>$ 7 μg/min).

Inotropes were discontinued when CPB was initiated, although the study drug and norepinephrine were continued to maintain 50 to 80 mmHg of perfusion pressure. The perfusionist administered phenylephrine, norepinephrine, and extra vasopressin, in this order, as required. Continuous drug infusion was withdrawn during CPB using the same protocol. Standard management techniques during CPB were as follows: Target perfusion pressure 50 to 80 mmHg, CI 2.5 L/min/m^2, temperature 30°C to 34°C (typically 32-34°C), and circulating arrest at 28°C.

Primary outcomes consisted of the myocardial enzyme levels included at 0, 6, and 12 hours postoperatively.

Secondary outcomes: (1) Catecholamine requirements during surgery; (2) hemodynamics during surgery; (3) incidence of predetermined vasoplegia during surgery; (4) incidence of new-onset atrial fibrillation (AF) within 7 postoperative days; (5) incidence of acute kidney injury (AKI) defined by RIFLE criteria within 5 postoperative days; (6) ventilator periods, length of hospitalization, mortality within 30 days, peak C-reactive protein (CRP), arterial lactate concentration, SvO2, and CI upon ICU admission.

After inducing general anesthesia, the anesthesiologists recorded the incidence of insufficient hemodynamics. The total amount of catecholamines required, maximum norepinephrine dose, total amount of drugs administered, and other information were recorded during surgery. Upon ICU admission, the anesthesiologist recorded the arterial blood lactate concentration, SvO2, and CI.

Postoperatively, the investigator recorded levels of myocardial enzymes, CK-MB, and troponin T at 0, 6, and 12 hours, as well as the incidence of postoperative AKI, death within 30 days, length of hospitalization, incidence of clinical myocardial infarction, ventilator periods, and peak CRP levels. Postoperative AF was recorded by one of the investigators who was uninformed of the identity of the study drug. The results of continuous electrocardiograms during the ICU stay were recorded. The incidences of AF were checked at least twice daily or reported to the investigators by the nurses or physicians caring for the patients. Only the researcher who prepared the drug and the ICU caregiver knew the identity of the study drug during the study period. Patients were followed until discharge or for 30 days after surgery.

The authors were unable to define a valid sample size before conducting the study for analyzing the primary outcome. The authors hope to accomplish this in future studies. Vasoplegia was considered in the secondary analysis. Although it lacks a specific definition, vasoplegia is referred to as vasodilatory shock that is refractory to treatment with catecholamines and occurs in approximately 10% to 47% of patients depending on the type of surgery.[15] In a previous randomized controlled trial, the incidence of vasoplegia in a control group was 20%. [15] Therefore, the authors expected a $\geq$ 20% incidence of vasoplegia in the control group because the patients were physically smaller than previously reported patients[7–9] suffering from hemodilution. Therefore, 92 patients were required to detect a 70% reduction at a one-sided 5% significance level and a power of 80%.

Postoperative AF is reported to occur in approximately 30% to 60% of cardiac surgery patients.[16] The authors assumed a 60% incidence in the control group. Although there is no information in the field of cardiac surgery to indicate whether vasopressin reduces AF, it has been reported that there was an approximate 85% reduction in septic patients.[17] If the expected incidence of postoperative AF was 60%, 45 and 91 patients would be required to detect 50% and 35% reductions, respectively, with a one-sided 5% significance level and a power of 80%. The authors anticipated few patients from the initial group of 100 would be excluded from the study.

StatMate version 4 (Advanced Technology for Medicine and Science, Tokyo, Japan) was used to perform statistical analyses. Interim analysis of 50% participants was performed during the study, and the overall significance was more than 0.05 between the groups. Data are expressed as the mean ± standard deviation for normally distributed data or as the median (25%-75% interquartile range) for data that were not normally distributed. Comparisons of continuous variables between groups were performed as appropriate using an unpaired Student t test, Welch's test, or the Mann-Whitney test. Comparisons of categoric data between groups were performed as appropriate using the chi-square test or Fisher's exact test. To describe primary outcomes, the risk ratio (RR) and 95% confidence interval are shown. Patients, physicians involved