Association of Preoperative Uric Acid and Acute Kidney Injury Following Cardiovascular Surgery

Kyoung-Woon Joung, MD, Jun-Young Jo, MD, Wook-Jong Kim, MD, PhD, Dae-Kee Choi, MD, PhD, Ji-Hyun Chin, MD, PhD, Eun-Ho Lee, MD, PhD, and In-Cheol Choi, MD, PhD

Objective: **Recent studies suggested that elevated serum uric acid levels may be associated with the risk of acute kidney injury (AKI) in several settings. However, the effect of uric acid on the risk of AKI after cardiovascular surgery remains uncertain.**

Design: **A retrospective analysis.**

Setting: **A tertiary care university hospital.**

Participants: **All consecutive adult patients (n = 1,019) who underwent cardiovascular surgery between January 2011 and May 2012.**

Interventions: **None.**

Measurements and Main Results: **Preoperative and perioperative data were assessed in the study population. AKI was defined and staged as serum creatinine concentration-based Acute Kidney Injury Network criteria. Univariate and multivariate logistic regression analyses were conducted to evaluate the association between preoperative uric acid and postoperative AKI. Preoperative elevated uric acid (≥6.5 mg/dL) was associated independently with AKI after cardiovascular surgery (odds ratio 1.46; 95% confidence interval 1.04–2.06, p = 0.030). Results were the same in subgroup analyses. Preoperative elevated uric acid (≥6.5 mg/dL) also was associated with a higher incidence of prolonged ICU and hospital stay.**

Conclusions: **Preoperative elevated serum uric acid is an independent risk factor for AKI in patients undergoing cardiovascular surgery. This finding suggests that preoperative measurements of serum uric acid concentration may help stratify risks for AKI in these patients.**

KEY WORDS: acute kidney injury, cardiovascular surgery, risk factors, uric acid, risk stratification

URIC ACID (UA) is an end-product of purine degradation and is excreted in urine. Increased serum level of UA is associated with multiple biologic effects such as endothelial dysfunction, platelet aggregation, increased oxidative stress, and high levels of inflammatory markers.[1–5] Many epidemiologic studies have suggested that hyperuricemia is associated with cardiovascular derangements such as hypertension, coronary artery disease, and cerebrovascular disease.[6–8] Moreover, hyperuricemia is related to the progression of chronic kidney disease, although the chronologic relationship between impaired renal function and hyperuricemia is ambiguous.[9,10]

In addition to chronic kidney disease, hyperuricemia is associated with acute kidney injury (AKI) in various disease states. UA-induced AKI has been reported primarily in patients with large tumor burden and those receiving chemotherapy.[11] In such patients, AKI is caused by hyperuricemia and intratubular precipitation of UA crystals following the rapid release of nucleotides after tumor cell death.[11,12] However, more recent studies suggested that even a slight increase in serum UA levels without intrarenal crystal deposition could be associated with an increased risk of renal dysfunction by various mechanisms.[13–16] Thus, preoperative hyperuricemia may be related to renal dysfunction or promote an increased risk of postoperative AKI. Furthermore, 2 recent clinical studies suggested that preoperative hyperuricemia might be related to postoperative AKI, although these studies were limited by a relatively small sample size (58 and 190 patients).[17,18]

Accordingly, to confirm previous research findings, the authors conducted a large observational study to evaluate the relationship between preoperative hyperuricemia and postoperative AKI in patients undergoing cardiovascular surgery.

METHOD

After the approval from the institutional review board of the authors' institution (2012-0858), they retrospectively assessed all patients aged 20 years or older who underwent cardiovascular surgery between January 1, 2011 and May 31, 2012 in their institution. Patients with missing serum creatinine (Cr) or serum uric acid measurements and those with preoperative dialysis were excluded as were patients who had been treated with allopurinol, those with organ transplantation or nephrectomy, those who underwent endovascular aortic repair surgery, and those who died intraoperatively or within 24 hours postoperatively. For providing continuous assessment and improvement of quality of care, the Department of Anesthesiology and Cardiovascular Surgery keep a prospective database on all patients undergoing cardiovascular surgery. Clinical data for all patients were collected from the computerized databases and from a retrospective review of the computerized patient record system. Data collected included demographics, comorbidities, preoperative medication and laboratory data, perioperative management, morbidity, and mortality. The authors conducted this observational study in accordance with Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines.[19]

As described previously,[20–22] cardiovascular surgery and perioperative management were performed according to institutional standards. The anesthesia protocols are described below. The authors induced general anesthesia using a bolus intravenous (IV) injection of etomidate, 0.2 mg/kg, to stabilize vital signs, followed by the continuous infusion of propofol and remifentanil using a target-control infusion pump (Orchestra® Base Prima; Fresenius Kabi, Brezins, France). For ease and safety of orotracheal intubation, bolus IV injection of 0.8 mg/kg of rocuronium was given. To maintain anesthesia, the authors used a continuous infusion of remifentanil, propofol, and rocuronium. All drugs were stopped at the end of surgery. The anesthetic depth of all patients was monitored using the bispectral index (BIS) monitor (A-2,000, Aspect Medical Systems, Newton, MA), and the effect-site concentration of propofol was titrated to maintain the BIS value between 40 and 60. Effect-site concentration of remifentanil was adjusted to

From the Department of Anesthesiology and Pain Medicine, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Korea.

Address reprint requests to Eun-Ho Lee, MD, PhD, Asan Medical Center, University of Ulsan College of Medicine, Department of Anesthesiology and Pain Medicine, 388-1, Pungnap 2-dong, Songpa-gu, Seoul 138-736, Korea. E-mail: leho@naver.com

1053-0770/2601-0001$36.00/0

http://dx.doi.org/10.1053/j.jvca.2014.04.020

maintain the heart rate and blood pressure within 20% of preoperative values. To adjust the preload, the authors used 0.9% saline and 6% hydroxyethyl starch, 130/0.4 (Voluven, FreseniusKabi, Bad Homburg, Germany). In addition, a packed red blood cell (pRBC) transfusion was performed when hemoglobin concentration was <8 g/dL in all perioperative periods. A cell salvage device was used on all patients (AUTOLOGTM, Medtronic Inc, Minneapolis, MN), and salvaged blood was reinfused between the end of cardiopulmonary bypass (CPB) and the end of surgery. In off-pump surgery, IV heparin was administered at a dose of 150 IU/kg, and target-activated coagulation time (ACT) was 250 to 350 seconds. In on-pump surgery, the dose of IV heparin was 300 IU/kg and target ACT was more than 500 seconds. ACT was checked every 30 minutes, and heparin was added to maintain adequate ACT.

CPB management strategies at the authors' institution are described below. The authors typically used 20% mannitol, 20% albumin, and crystalloid solution (PlasmaLyte A) as priming solutions. They also primed the bypass circuit using pRBC for patients with a preoperative hematocrit value below 30% to prevent excessive hemodilution when CPB was initiated. The transfusion strategy of pRBC during the CPB period was to maintain hematocrit values between 23% and 27%. Mean arterial blood pressure was maintained between 60 mmHg and 70 mmHg during the CPB period, and IV phenylephrine and nicardipine hydrochloride were administered as required. The arterial carbon dioxide tension was maintained throughout bypass at 35 mmHg to 40 mmHg without correction of temperature. The arterial oxygen tension was maintained between 250 mmHg and 300 mmHg. Typically, patients were cooled to a nasopharyngeal temperature of 34°C to 28°C during bypass and rewarmed to a nasopharyngeal or rectal temperature of 37°C prior to separation from bypass. Nonpulsatile perfusion was maintained at 2 to 2.4 L/min/m^2.

Surgical procedures were performed by five experienced surgeons. After all the procedures were performed and completed, patients were transferred to the intensive care unit (ICU). Once respiration recovered spontaneously and arterial blood gas levels were acceptable, the endotracheal tube was removed. All patients were discharged from the ICU when vital signs were stable.

The development of AKI after cardiovascular surgery was considered the primary outcome. Postoperative AKI was defined and staged according to the AKI Network criteria using a change in Cr within the first 48 hours after surgery (Stage I was defined as serum Cr increased more than 0.3 mg/dL or $150\% \leq$ serum Cr $\leq 200\%$ from baseline; stage II was defined as $200\% <$ serum Cr $\leq 300\%$ from baseline; stage III was defined as either serum Cr $> 300\%$ from baseline, serum Cr ≥ 4.0 mg/dL with an acute increase of at least 0.5 mg/dL or the need for renal replacement therapy).[23] The authors did not use the urine output criteria because urine output data of patients were insufficient and could have been affected by the use of diuretics during the perioperative period. To assess immediate postoperative cardiovascular function, the number of inotropes used in the ICU and the maximal cardiovascular component of the sequential organ failure assessment (SOFAc) score within the first 24 hours after surgery were checked.[24] In addition, other postoperative outcome variables, including time to extubation from the end of surgery, length of ICU and hospital stay, and death from any cause occurring during initial hospital stay after surgery or within 30 days of surgery, were evaluated to determine their association with preoperative hyperuricemia.

Serum UA was measured by an enzymatic method, and creatinine was measured by means of a kinetic Jaffe method using an automatic biochemistry analyzer (Cobas® 8000 modular analyzer series; Roche Diagnostics GmbH, Vienna, Austria). Preoperative renal function was determined by estimated glomerular filtration rate (eGFR), which was calculated using the Modification of Diet in Renal Disease equation II (eGFR $= 186 \times$ serum creatinine$^{-1.154} \times$ age$^{-0.203} \times$ [0.742 if female] $\times$ [1.210 if African-American]).[25]

The prevalence of preoperative hyperuricemia was defined as a uric acid concentration ≥ 6.5 mg/dL (which is the average threshold of the gender-based definition of 6.0 mg/dL in women and 7.0 mg/dL in men).[26]

In this study, all continuous variables were expressed as the mean $\pm$ standard deviation or median with interquartile range, and the categoric were frequency and percentages. To compare the differences of the baseline and intraoperative and postoperative characteristics, the authors used the χ^2 test or Fisher's exact test for categoric variables and Student's *t*-test or the Mann-Whitney rank-sum test for continuous variables as appropriate.

To evaluate the relationship between preoperative serum UA levels and AKI after cardiovascular surgery, they performed logistic regression analyses. Initially, all covariates in Table 1 and Table 2 were evaluated independently. In univariate analyses, preoperative serum UA and covariates (age, sex, preoperative serum albumin and total bilirubin level, hematocrit, hypertension, congestive heart failure, eGFR <60 mL/min/1.73 m^2, use of angiotensin-converting enzyme inhibitors and/or angiotensin-receptor blockers, use of diuretics, ejection fraction, European System for Cardiac Operative Risk Evaluation [EuroSCORE], total crystalloid infused during surgery, off-pump surgery, cardiopulmonary bypass time, and packed red blood cells used intraoperatively and for 48 hours after surgery) were associated ($p < 0.05$) significantly with postoperative AKI. These variables were candidates for the multivariate logistic regression models. A backward elimination process ($p < 0.05$ to retain) was used to develop the final multivariate models. Serum UA was analyzed as dichotomous and continuous variables.

In addition, as sensitivity analyses, a priori subgroup analyses were conducted for male patients ($n = 634$), patients with hypertension ($n = 514$), preoperative eGFR <60 mL/min/1.73 m^2 ($n = 149$), preoperative normal renal dysfunction ($n = 870$), or ejection fraction $<50\%$ ($n = 241$), and for those who underwent cardiovascular surgery with cardiopulmonary bypass ($n = 674$). A priori subgroups were defined based on previous studies.[18] Models for subgroup analyses were constructed as logistic regression identical to the final model above. To summarize the strength of the association of each variable with postoperative AKI, adjusted odds ratios (ORs) with 95% confidence intervals (CIs) were calculated. The Hosmer-Lemeshow statistic was used to evaluate model calibration. The discrimination ability and contribution of preoperative uric acid level for predicting postoperative AKI was evaluated by C statistic. Statistical comparison of C statistic between models was performed, as described by Delong et al,[27] and CIs for the difference in c-statistics between models were calculated by bootstrap sampling. The authors also calculated the category-free net reclassification improvement (NRI) and the integrated discrimination improvement (IDI) to quantify the performance and the net benefit of adding uric acid to the model predicting postoperative AKI.[28] All reported p values were 2-sided, and p values < 0.05 were considered statistically significant. All data manipulations and statistical analyses were performed using SAS® Version 9.1 (SAS Institute Inc., Cary, NC) software.

RESULTS

Between January 1, 2011 and May 31, 2012, a total of 1,094 patients underwent cardiovascular surgery at the authors' institution. After excluding patients who met any of the exclusion criteria ($n = 75$), data for 1,019 patients were analyzed (Fig 1). The baseline and perioperative characteristics of this study population are presented in Table 1 and Table 2. Patients consisted of 634 males (62.2%) and 385 females (37.8%),with a median age of 63.0 (54.0-70.0) years. The mean preoperative UA concentration was 5.8 ± 1.8 mg/dL (range, 1.3-14.0 mg/dL), and a total of 319 of the 1,019 patients (31.3%) had a serum UA level ≥ 6.5 mg/dL. These patients