Acute Kidney Injury in Patients Undergoing Open Abdominal Aortic Aneurysm Repair: A Pilot Observational Trial

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Objectives: Acute kidney injury (AKI) is a frequent complication after open repair of abdominal aortic aneurysms (AAA). Little research has been done to determine whether intraoperative hemodynamic events may precipitate AKI. Novel biomarkers also may aid in the earlier diagnosis of AKI.

Design: A pilot prospective observational trial.

Setting: A single tertiary academic medical center.

Participants: Participants were 40 adult patients undergoing open repair of infrarenal AAA.

Interventions: Intraoperative hemodynamic monitoring of heart rate, mean arterial pressure, central venous pressure, and cardiac index was performed on a continuous basis. Blood samples were obtained at baseline and at 24 hours postoperatively for inflammatory biomarkers, including neutrophil gelatinase-associated lipocalin (NGAL).

Measurements and Main Results: AKI occurred in 20% of patients (8 of 40). Hypotension, including duration (defined as the length of time mean arterial pressure was <65 mmHg) and magnitude (the area under the curve of a mean arterial pressure <65 mmHg), was the only factor associated with postoperative AKI. Urinary NGAL at the conclusion of surgery had excellent ability to predict the development of AKI (area under the curve 0.84, 95% confidence interval = 0.70-0.97). The cytokines pentraxin 3 (PTX3), interleukin-1 receptor antagonist (IL1-RA), macrophage chemotactic protein (MCP), suppressor of tumorigenicity 2 (ST-2), and interleukin-10 (IL-10) also had good ability to predict the development of AKI in the immediate postoperative period.

Conclusions: AKI occurs frequently in patients undergoing open repair of AAA. Intraoperative hypotension was the only factor that predicted the development of subsequent AKI. Urinary NGAL and several novel inflammatory biomarkers demonstrated good ability to predict its development. Novel biomarkers also may aid in the early diagnosis of AKI.
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IN THE UNITED STATES, abdominal aortic aneurysms (AAAs) are diagnosed in 190,000 patients per year, and $>50,000$ of these patients undergo aneurysm repair.[1] Elective repair of AAA is associated with increased morbidity and mortality compared with other surgical procedures.[2] Acute kidney injury (AKI) is an infrequent complication after most surgical procedures, occurring in approximately 1% of surgical patients.[3] However, as a result of the significant alterations in renal blood flow during aortic cross-clamping, the incidence of AKI is reported to be 20% to 25% in patients undergoing aneurysmectomy.[4–6]

There have been several refinements in the definition of AKI. With the creation of the RIFLE (Risk, Injury, Failure, Loss, End-Stage Renal Disease[7]) and AKIN (Acute Kidney Injury Network[8]) scoring systems, the diagnosis of AKI has become more standardized and amenable to research. An important caveat of both of these classifications is that they use elevation of serum creatinine as a definition of AKI. However, by the time these minor changes in serum creatinine occur, renal damage already has occurred. These minor increases in serum creatinine are associated with increased morbidity and mortality,[9,10] which has led to widespread recognition of the need for improved biomarkers that could act as early prognostic biomarkers of AKI.

In murine models, neutrophil gelatinase-associated lipocalin (NGAL) is the most rapidly induced protein in ischemic and nephrotoxic AKI. It is used increasingly as an early predictor of AKI.[11–13] The use of NGAL in predicting kidney injury has been studied in several populations, but there have been no studies to date looking at NGAL as a marker of AKI in patients undergoing open AAA repair.[14,15] It is well known that surgery is associated with a robust inflammatory response. There is also mounting evidence that there is an inflammatory component to AKI in addition to hemodynamic and direct nephrotoxic factors.[16]

The primary objective of this study was to determine if several novel candidate proinflammatory and anti-inflammatory biomarkers (including NGAL) are early predictors of AKI (as defined by the AKIN criteria) in patients undergoing open repair of an AAA. The authors also attempted to determine if intraoperative decreases in mean arterial pressure (MAP) <65 mmHg, cardiac index (CI), or central venous pressure (CVP) were associated with the development of AKI.

METHODS

This trial is registered at ClinicalTrials.gov (ClinicalTrials.gov Identifier NCT01681251). The data collection for this study was based on a randomized controlled trial comparing stroke volume variation–guided fluid administration with clinician-directed fluid administration in patients undergoing open repair of AAA. After approval from the Research Ethics Board, all patients at the authors' institution >18 years old who were American Society of Anesthesiologists physical classification I-III presenting for elective open repair of infrarenal AAA were approached. Written informed consent was obtained from all patients. Patients were excluded from the

trial if they met any of the following criteria: age > 80 years old, weight > 120 kg, known or suspected aortic insufficiency, renal dysfunction (serum creatinine > 150 μmol/L), active congestive heart failure, or atrial fibrillation. The weight, aortic insufficiency, and atrial fibrillation exclusion criteria were included because the minimally invasive cardiac output monitor that was used (FloTrac/Vigeleo system; Edwards Lifesciences, Irvine, CA) was inaccurate in these conditions. Patients with pre-existing renal dysfunction were excluded because they might have elevations in the studied inflammatory biomarkers at baseline.

Anesthetic technique was at the discretion of the attending anesthesiologist. At the authors' institution, this procedure usually consists of general anesthesia, with the placement of a thoracic epidural catheter before induction to facilitate postoperative analgesia. Standard Canadian Anesthesiologists' Society monitors, with the addition of an arterial cannula and central venous access with an 8.5F cannula, were placed in all patients. In addition, the FloTrac/Vigeleo minimally invasive cardiac output monitor was used in all patients. None of the patients underwent the placement of a supraceliac clamp, and all clamps were infrarenal.

Fluid administration consisted of lactated Ringer's solution, or 130/0.4 hydroxyethyl starch (HES) solution (Voluven; Fresenius Kabi, Bad Homburg, Germany). No other colloid was used. The type and rate of fluid administration were at the discretion of the attending anesthesiologist. Typically, HES is administered before aortic cross-clamp removal. Autologous blood was salvaged and returned to the patient.

Intraoperative hemodynamic data (including heart rate, MAP, cardiac output, CI, stroke volume variation, CVP, and end-tidal carbon dioxide) were collected at 60 Hz by TrendFace Solo software (ixellence GmbH, Wildau, Germany). The authors chose MAP ≤ 65 mmHg, CI ≤ 2.4 L/min/m^2, and CVP ≤ 8 mmHg a priori as thresholds to describe low arterial pressure, cardiac flow, and volume status. These values were chosen because they are published widely as being normal hemodynamic values.[17]

Means of the per-second values were calculated to obtain data for every minute of the case (done offline using Microsoft Excel [Redmond, WA]). Intraoperative data collected included operative duration, aortic cross-clamp time, fluid administration (crystalloid, colloid, blood products), and fluid losses (blood and urine output).

Blood samples were analyzed preoperatively, immediately postoperatively, 6 hours postoperatively, and 24 hours postoperatively by enzyme-linked immunosorbent assay for the following biomarkers associated with inflammation: pentraxin 3 (PTX3), interleukin-10 (IL-10), suppressor of tumorigenicity 2 (ST-2), macrophage chemotactic protein 1 (MCP-1/CCL2), interleukin-1 receptor antagonist (IL1-RA), and soluble tumor necrosis factor receptor II (sTNFr-II). Urine also was analyzed for the presence of NGAL. In a pilot trial, the authors determined the kinetics of these cytokines and determined that the peak response occurred 24 hours postoperatively.

Cytokines were analyzed by the following method: Analyte levels in cryopreserved serum were determined using Meso Scale Discovery (MSD, Gaithersburg, MD) electrochemiluminescence detection to quantify binding events on patterned

arrays using minor modifications of the manufacturer's protocol. To provide uniformity in comparing data among different vendors' lots of standards, constant internal laboratory standards (purchased from Peprotech, Rocky Hill, NJ, and R&D Systems, Minneapolis, MN) were established and used throughout the study. Briefly, samples and standards were incubated on singleplex MSD plates for 3 hours (instead of 2 hours), and the plate was incubated with detection antibody for 3 hours (instead of 2 hours) before wash. All other steps were as per manufacturer's recommendations. Analysis was on a SECTOR Imager 2400 instrument (MSD). The operator was blinded to the nature of all samples during processing, with subsequent statistical analysis also performed independently. Interassay variation was generally 4% to 10%. Sufficient samples were not always obtained for each individual to be quantified for each analyte at each time point. Assays for MSD plates that were unavailable were performed by ultrasensitive enzyme-linked immunosorbent assay as described.[18,19] Briefly, titrations of 4 twofold dilutions of each serum were assessed with reagents from BioLegend (San Diego, CA) as described. Interassay enzyme-linked immunosorbent assay variability was generally $< 10\%$.

AKI was defined using the creatinine component of the AKIN guidelines.[8] Briefly, AKI was defined as an abrupt (< 48 hours) reduction in kidney function manifesting either as an absolute increase in serum creatinine (> 26.4 μmol/L) or as a percentage increase in serum creatinine of $\geq 50\%$. The injury was staged as AKIN I (increase in serum creatinine > 26.4 μmol/L or $> 150\%$ from baseline), AKIN 2 (increase in serum creatinine $> 200\%$ from baseline), or AKIN 3 (increase in serum creatinine to $> 300\%$ from baseline).

Statistical Analysis

Because this was a pilot observational study of the aforementioned goal-directed therapy trial, a power analysis was not conducted. Demographic, hemodynamic, and fluid data are represented as mean $\pm$ SD. With respect to cytokine levels, normality was tested with the D'Agostino-Pearson omnibus normality test. Peak cytokine responses were analyzed between groups using a Mann-Whitney test (because none of the cytokines had a normal distribution). For cytokines that demonstrated significant between-group differences, receiver operating characteristic curves were created to determine the sensitivity and specificity of the cytokine in question. Cytokine results were expressed as median [interquartile range]. Categoric variables were analyzed with Fisher exact test. Between-group continuous variables were analyzed with a Student t-test. Results were considered statistically significant if p < 0.05. Analysis was performed using GraphPad Prism Software Version 6.0d for Mac (GraphPad Software, Inc, San Diego, CA).

RESULTS

Patients were recruited between September 2011 and January 2013. As defined by the AKIN criteria, 20% (8 of 40) of patients with AAA developed AKI. Baseline demographic data are presented in Table 1, and patient flow is presented in Figure 1. At the beginning of the surgery, there