Predictors of Acute Kidney Injury in Cardiac Transplantation

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ABSTRACT

Background. Acute kidney injury (AKI) is an outcome that represents a significant increase in morbidity and mortality rates; however, limited information exists about the incidence of AKI after cardiac transplantation.

Methods. This single-center, retrospective study from 2009 to 2014 analyzed pre-, intra-, and post-operative characteristics of 111 patients who underwent orthotopic cardiac transplantation to identify risk factors for AKI and validate findings of existing literature.

Results. AKI based on the RIFLE criteria (risk, injury, failure, loss, and end-stage) occurred in 65 patients (58.6%) during the hospitalization period, with 38 patients requiring early dialysis. Risk factors for AKI were longer cardiopulmonary bypass duration ($P = .008$), higher packed cell ($P = .004$) and cryoprecipitate ($P = .022$) transfusions, and post-operative bleeding with subsequent surgical re-exploration ($P = .008$). The development of AKI was also associated with longer inotropic ($P \leq .001$) and ventilation duration ($P \leq .001$) as well as higher mortality rates ($P = .048$).

Conclusions. AKI after cardiac transplantation is prevalent and prognostically significant. Although there is yet to be a strategy that conclusively demonstrated its ability to prevent AKI after cardiac surgery, therapies targeted at modifiable risk factors may offer protection against this outcome.

CARDIAC transplantation is currently the only available therapeutic option that has been shown to have a positive impact on survival in patients with end-stage cardiac failure and severe coronary artery disease when all other treatment options are exhausted [1]. Despite advances in surgical techniques and immunosuppressive regimen, cardiac transplantation continues to be associated with significant complications, particularly acute kidney injury (AKI), which may progress into chronic kidney disease (CKD).

On the basis of the 2013 registry from the International Society for Heart and Lung Transplantation, renal dysfunction occurs in 26% of patients in the first year after cardiac transplantation, with 1.5% necessitating chronic dialysis. The numbers are even higher in the 5-year period, in which renal dysfunction occurs in 52% of transplant recipients, with a 2.9% chance of requiring chronic dialysis [2]. When AKI is severe enough to require dialysis, early mortality rates escalate to 50% to 80% from 5% to 10% in patients without AKI [3]. Despite these rates, few studies that have examined the incidence of AKI occurring within the first month of cardiac transplantation. In addition, the number of studies examining risk factors using the consensual term "AKI" is lacking [4]. Many studies use the term "acute renal failure"; however, the definitions and parameters vary between studies, making it difficult to standardize and review findings.

The objectives of this study were: (1) to validate findings of previous studies related to the topic by use of the RIFLE (risk, injury, failure, loss, and end-stage) criteria [5] and (2) to investigate new factors, both modifiable and non-modifiable, that contribute strongly to the incidence of AKI.

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METHODS

Study Cohort

This retrospective study involved 130 patients who underwent cardiac transplantation during the period of 2009 to early 2014 at St. Vincent's Mater Hospital, Sydney, Australia. The study was approved by the hospital research ethics committee, which waived the need for written informed consent. A database search was performed to identify patients who underwent orthotopic cardiac transplantation during the stipulated time period. The patients were then de-identified. The authors excluded patients with multi-organ transplants, re-transplantation, pre-operative AKI, dialysis, or septic shock. Pediatric cardiac transplant patients were not included in this study. Of all the patients who were included in the study, 1 patient was not included because of a simultaneous heart and kidney transplant, and 18 patients had a significant amount of missing data.

Defining AKI Parameters

The primary aim of the study was to determine the frequency of post-operative AKI and the identification of independent predictors for the development of the complication. On the basis of the RIFLE criteria, AKI was defined as a $\geq 1.5\times$ elevation in serum creatinine (sCr) levels [5]. All available sCr data were reviewed through electronic medical records: baseline sCr was obtained pre-operatively on the day of the surgery, and the largest increase in sCr post-operatively within a 1-week span was used to determine the incidence of AKI. In addition, patients who required dialysis in the intensive care unit (ICU) within the post-operative week were also considered to have AKI.

Clinical Variables

Through the use of standardized data collection forms, patient and operation data were extracted from the electronic medical records and manually from the patient's files. The following demographic variables were collected: age, sex, height, weight, body surface area (BSA), body mass index (BMI), indication for transplant, previous sternotomy, and presence of any mechanical assist device. Pre-operative variables included sCr, estimated glomerular filtration rate (eGFR), and hemoglobin before surgery; these also collected from laboratory values on the day of surgery from the electronic medical records. Pre-operative eGFR was calculated from pre-operative sCr values by use of the Modification of Diet in Renal Disease Study equation, adjusted for each 1.73 m^2 of BSA [6].

Intra-operative variables evaluated were operation duration, cardiopulmonary bypass (CPB) duration, cross-clamp duration, donor ischemic time, transfusions after CPB (including packed cells [PC; contains red blood cells], fresh-frozen plasma, platelets, prothrombinex, and cryoprecipitate), inotropic support (including adrenaline [Ad], noradrenaline [NAd], vasopressin, isoprenaline), and furosemide.

Post-operative variables evaluated were ICU stay, inotropic and ventilation duration in the ICU, use of dialysis, maximum sCr in the first week, use of extracorporeal membrane oxygenation (ECMO), urine output in the first 24 hours, graft rejection, incidence of post-operative bleeding in the first 24 hours, length of hospital stay, mortality status, and cause of death.

Immunosuppression Protocol

A standardized approach to immunosuppressive therapy is used at St. Vincent's Mater Hospital. Before surgery, patients receive oral mycophenolate mofetil 1.5 g immediately; they then receive a number of medications at induction of anesthesia, including intravenous (IV) Vitamin K 10 mg, IV methyprednisolone 500 g and IV cephalozin 500 g. The patients also receive IV basilizimab 20 mg, with a subsequent dose on post-operative day 4, if recorded sCr is above 120 μmol/L, or if they have undergone explantation of a left ventricular assist device (LVAD), biventricular assist device (BiVAD), or total artificial heart. Intra-operatively, IV methylprednisolone 500 g and IV cephalozin 500 g are given off-bypass. On post-operative day 1, patients receive a test dose of oral tacrolimus 0.5 mg, 2 doses of IV mycophenolate mofetil 1 g, and 3 doses of IV methylprednisolone 125 mg. If sCr is >140 μmol/L, tacrolimus is held off until sCr values are <140 μmol/L. From day 2 onward, patients initially receive 2 doses of IV methylprednisolone, with oral prednisolone 0.6 mg/kg/day in 2 divided doses until 2 weeks after transplant; weaning is facilitated by use of 0.1 mg/kg/day each week until complete withdrawal. Patients also receive 2 doses of IV mycophenolate mofetil 1 g and 2 doses of oral tacrolimus as charted daily. A trough tacrolimus level of 8 to 12 μg is targeted by day 7 and decreased thereafter.

Statistical Analysis

Statistical analysis was performed by use of IBM SPSS statistics software version 20.0 (SPSS Inc., Chicago, Ill, United States). Results are presented as value ± standard deviation or percentage, depending on the type of data and statistical test used. Univariate analysis by use of the independent t test was performed to detect any associations between individual variables of a numeric type and the incidence of AKI, in which a 2-sided P value of <.05 is considered statistically significant, with 95% confidence intervals. Categorical data were analyzed by use of the Pearson χ^2 test when appropriate. In addition, the Mann-Whitney test was also used for data that are not normally distributed, expressed in mean rank values. Multivariate regression analysis was not conducted because of the smaller sample size [7].

RESULTS

Between January 2009 and April 2014, 130 patients underwent orthotopic cardiac transplantation. Nineteen patients were excluded: 18 patients had inadequate data in the records and 1 patient had a concurrent cardiac and renal transplant. AKI, based on the RIFLE criteria, occurred in 65 patients (58.6%) during the hospitalization period, with 38 patients requiring dialysis (58.4% of AKI patients; 34% of all patients). AKI is further stratified into risk (n = 22), injury (n = 24), and failure (n = 19) in the criteria. The use of dialysis is subject to individual cases and not based on a specific sCr threshold.

There was no significant difference between patients who had development of AKI and those who did not with respect to patient age, sex, BSA, BMI, presence of mechanical assist device, pre-operative sCr, eGFR, and hemoglobin. In addition, similar values within the aforementioned characteristics were observed between both groups. Although there are higher rates of previous sternotomy in patients with AKI, it was not of statistical significance (Table 1).

Intra-operatively, patients who underwent a longer operation have higher tendencies to develop AKI (450 ± 120 compared with 386 ± 75 in non-AKI patients, $P = .003$). A similar pattern can be observed in patients with a longer