Risk Factors for and Outcomes of Acute Kidney Injury in Neonates Undergoing Complex Cardiac Surgery

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Objective To characterize the epidemiology of and identify risk factors for neonatal cardiac surgery–associated acute kidney injury (CS-AKI) and determine its impact on clinical outcomes.

Study design Using secondary analysis of data from an ongoing multiprovincial prospective cohort study, we studied 264 neonates undergoing complex cardiac repair. CS-AKI was defined based on the Acute Kidney Injury Network (AKIN) definition. We used regression modeling and survival analysis (adjusting for covariates) to evaluate associations.

Results CS-AKI occurred in 64% of the neonates in our study cohort. Lower age, longer cardiopulmonary bypass time, hypothermic circulatory arrest, type of repair, lower preoperative serum creatinine (SCr) level, lower gestational age, and preoperative ventilation were independent risk factors for developing CS-AKI. Neonates with CS-AKI had longer times to extubation, intensive care discharge, and hospital discharge, after adjusting for covariates. Mortality was significantly increased in neonates with AKIN stage 2 or higher CS-AKI. The neonates with CS-AKI had a lower *z*-score for height at 2-year follow-up and were seen by more specialists.

Conclusion Neonatal CS-AKI is common and independently predicts important clinical outcomes, including mortality. Many risk factors are similar to those in older children, but some are unique to neonates. The observation that lower baseline SCr predicts CS-AKI merits further study. The AKIN definition, based on preoperative SCr value, is a reasonable method for defining CS-AKI in neonates. Many previous studies of CS-AKI have excluded neonates; we suggest that future intervention studies on approaches to reducing CS-AKI incidence and improving outcomes should include neonates. *(J Pediatr 2013;162:120-7)*.

Acute kidney injury (AKI) occurs in 30%-45% of children after cardiac surgery[1,2] and is predictive of short-term mortality and morbidity in various critically ill pediatric populations.[3-7] Despite the abundant research on pediatric AKI, most studies have excluded neonates.[8,9] AKI was found to independently predict mortality in very low birth weight neonates and neonates receiving extracorporeal membrane oxygenation (ECMO).[4,10]

Neonates with congenital heart defects represent a large proportion of admissions to pediatric intensive care units (PICUs). Complex defects necessitate repair early in life, and little is known about the effect of open-heart surgery with cardiopulmonary bypass (CPB) on the neonatal kidney. Less is known about the impact of cardiac surgery–associated AKI (CS-AKI) on clinical outcomes. The present study aimed to describe and characterize the epidemiology of CS-AKI in neonates, identify risk factors for CS-AKI, and determine whether CS-AKI is independently associated with short-term outcomes (eg, length of stay, duration of postoperative ventilation, in-hospital mortality) or long-term mortality, health services utilization, and growth.

Methods

This was a secondary analysis of data from an ongoing, multiprovincial (British Columbia, Alberta, Saskatchewan, and Manitoba) prospective cohort study performed by the Registry and Follow-Up of Complex Pediatric Therapies Program

AKI	Acute kidney injury
AKIN	Acute Kidney Injury Network
AUC	Area under the receiver operating characteristic curve
CPB	Cardiopulmonary bypass
CS-AKI	Cardiac surgery–associated acute kidney injury
DHCA	Deep hypothermic circulatory arrest
ECMO	Extracorporeal membrane oxygenation
PICU	Pediatric intensive care unit
SCr	Serum creatinine
TAPVD	Total anomalous pulmonary venous drainage
TGA	Transposition of the great arteries

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of Western Canada. Infants who needed complex congenital cardiac repair at age ≤6 weeks were eligible for entry into this inception cohort. Subjects were followed from cardiac surgery throughout hospitalization and then for several years after discharge.[11-13] All consecutive patients who underwent biventricular cardiac repair with CPB between January 2002 and December 2009 were included. Patients without preoperative serum creatinine (SCr) data or who received dialysis preoperatively were excluded. Ethics Board approval was obtained from each site.

Relevant preoperative, intraoperative, and postoperative variables from the Registry and Follow-Up of Complex Pediatric Therapies Program database were evaluated. Preoperative variables included gestational age (weeks), sex, length and weight percentiles at surgery, age at surgery (days), use of preoperative ventilation, peak preoperative lactate, last SCr measured before surgery, and surgical group, defined as transposition of the great arteries (TGA), simple total anomalous pulmonary venous drainage (TAPVD), miscellaneous lesions (truncus arteriosus, hypoplastic aortic arch, interrupted aortic arch, complex anomalies involving the great arteries or mitral valve), or any lesion in the context of a chromosomal abnormality. For descriptive purposes, the Risk Adjustment for Congenital Heart Surgery 1 score was calculated retrospectively. This consensus-based scoring system categorizes surgical complexity in the setting of limited primary data collection.[14,15]

Intraoperative variables included CPB time (minutes), deep hypothermic circulatory arrest (DHCA), and aortic cross-clamp time (minutes). Postoperative variables included peak SCr, use of dialysis, peak lactate, and peak inotrope score, calculated by (dopamine + dobutamine) + (100) (epinephrine + norepinephrine + phenylephrine) and categorized as <10, 10-14, 15-19, 20-24, or >25 μg/kg/min.[16] Measurements were made at 3 points postoperatively: postoperative day 1 (day 1), postoperative days 2-5 (day 2-5), and postoperative day 6 until hospital discharge (day 6+). SCr was measured using the Jaffe reaction. For samples with an icteric index >6 (corresponding to a serum bilirubin level of >200 umol/L), enzymatic creatinine was measured; there is no significant interference in the Jaffe reaction at a bilirubin level <200 umol/L. Use of postoperative ECMO at any time was recorded.

Two-year outcome variables included death (and when it occurred), number of physician specialists seen, number of doctor visits (including emergency department visits but excluding routine checkups), number of cardiac-related hospitalizations, number of non–cardiac-related hospitalizations, and height and weight (absolute, percentile, and *z*-score). We also recorded the 4-year mortality outcomes for those children undergoing surgery before 2007.

AKI was defined based on Acute Kidney Injury Network (AKIN) criteria[17]: peak postoperative SCr increase by ≥50% or by ≥26.5 μmol/L from the last SCr drawn before surgery or dialysis. We could not use the specific AKIN criteria of "SCr rise within 48 hours," so we instead used peak postoperative SCr recorded at 3 time intervals as described earlier. We further categorized AKI based on severity as stage 1, stage 2, and stage 3 in accordance with AKIN criteria.[17]

Short-term outcomes were lengths of postoperative PICU and hospital stays, duration of postoperative ventilation, and hospital mortality. Long-term outcomes were mortality, growth, and health care utilization (as defined earlier).

CS-AKI Risk Factors

We used backward stepwise multiple logistic regression analysis (*P* value for entry into the model = .05; *P* value for removal = .10) to evaluate independent risk factors for CS-AKI. The following risk factors were considered for the CS-AKI prediction model: gestational age, sex, preoperative ventilation, highest preoperative inotrope score, highest preoperative lactate level, weight percentile at surgery, age at surgery, surgical group, CPB time, aortic cross-clamp time, use of DHCA, and preoperative SCr. Preoperative SCr rather than preoperative estimated glomerular filtration rate was assessed in the model, because an estimated glomerular filtration equation has not been validated in neonates. We adjusted for age at surgery, the main confounder of the association between preoperative SCr and postoperative AKI. All potential predictors were assessed for colinearity before inclusion in regression. Area under the receiver operating characteristic curve (AUC) was calculated to predict AKI in the final predictive model. Continuous variables that were not normally distributed were log-transformed before being included in modeling.

AKI as a Predictor of Short-Term Outcomes

We evaluated the associations between CS-AKI and death-censored length of postoperative PICU stay, postoperative hospital stay, and ventilator-days using multiple Cox proportional hazards modeling. All models were adjusted for gestational age, age at surgery, sex, surgical group, duration of CPB, use of DHCA, requirement for postoperative ECMO, peak postoperative inotrope score, and duration of ventilation (excluded in analysis of ventilator-days outcome). We evaluated the association between CS-AKI and in-hospital mortality by multiple logistic regression, adjusting for the same covariates.

AKI as a Predictor of Long-Term Outcomes

We evaluated the association between CS-AKI and 2-year health care utilization outcomes using Poisson regression, adjusting for gestation, age at surgery, surgical group, preoperative ventilation, highest lactate value, and postoperative ECMO. These variables were previously shown to be associated with longer-term outcomes in this cohort.[11,12,18] We explored the association between CS-AKI and growth measures at 2 years using multiple linear regression, adjusting for gestational age, age at surgery, surgical group, and height or weight percentile at surgery.

Statistical Analyses

Long-term mortality was evaluated by Cox proportional hazards modeling. Variables included in multiple regression