Caffeine Exposure and Risk of Acute Kidney Injury in a Retrospective Cohort of Very Low Birth Weight Neonates

J. Bryan Carmody, MD, MPH[1], Matthew W. Harer, MD[2], Anna R. Denotti, MD[3], Jonathan R. Swanson, MD, MS[2], and Jennifer R. Charlton, MD, MS[4]

Objective To evaluate the association between caffeine exposure and acute kidney injury (AKI) in very low birth weight (VLBW; ≤1500 g) neonates.

Study design We retrospectively reviewed a cohort of 140 VLBW neonates consecutively admitted to the University of Virginia's neonatal intensive care unit from March 2011 to June 2012, excluding only those admitted >2 days of age or who died at <2 days after birth. We separately analyzed a subgroup of 44 neonates who received prolonged invasive respiratory support (mechanical ventilation for first 7 days after birth). The exposure of interest was caffeine exposure in the first week after birth. The primary outcome was AKI within the first 10 days after birth according to the Kidney Disease: Improving Global Outcomes system, modified to include only serum creatinine.

Results Caffeine exposure occurred in 72.1% of all patients and 54.5% of those who received prolonged invasive respiratory support. AKI occurred less frequently in neonates who received caffeine (all patients: 17.8% vs 43.6%; $P = .002$; prolonged invasive respiratory support: 29.2% vs 75.0%; $P = .002$). Caffeine exposure was associated with decreased odds for AKI in logistic regression models adjusted for sex, birth weight, gestational age, small for gestational age status, illness severity on admission, and receipt of indomethacin, invasive ventilation, dopamine, aminoglycosides, and vancomycin (all patients: OR 0.22; 95% CI 0.07-0.75, $P = .02$; prolonged invasive respiratory support subgroup: OR 0.06; 95% CI 0.01-0.57, $P = .02$).

Conclusions In a cohort of VLBW neonates, those exposed to caffeine were less likely to experience AKI. *(J Pediatr 2016;172:63-8)*.

Acute kidney injury (AKI) is common in the neonatal intensive care unit (NICU). Between 18% and 40% of very low birth weight (VLBW; <1500 g) infants experience AKI,[1,2] a frequency higher than in other hospitalized populations.[3] As in older pediatric and adult patients, AKI in VLBW infants is associated with increased morbidity and mortality.[1,2,4]

In spite of the burden of AKI, specific therapies remain scarce. Many initially promising therapies have failed to show benefit in clinical trials.[5] One exception is theophylline. To date, there have been 4 randomized, placebo-controlled trials, involving both term neonates with birth asphyxia[6-8] and preterm neonates ≤32 weeks gestational age with respiratory distress syndrome.[9] In each trial, neonates who received theophylline had greater urine output and increased glomerular filtration rate (GFR) compared with those who received placebo.

Historically, theophylline was widely used in the treatment of apnea of prematurity. Today, its use has largely been replaced by another adenosine antagonist, caffeine,[10] which offers similar efficacy, but more favorable pharmacokinetics, and fewer adverse effects.[11] However, the relationship between caffeine and AKI has never been investigated. The objective of this study was to determine whether VLBW neonates exposed to caffeine in the first week after birth were less likely to experience AKI within the first 10 days after birth.

Methods

We reviewed all VLBW neonates admitted to the University of Virginia's level IV NICU from March 2011-June 2012. This timeframe was chosen so that data extraction could be accomplished using a newly implemented electronic medical record. All neonates with birth weight ≤1500 g were initially included. Neonates

AKI	Acute kidney injury
CRIB II	Updated clinical risk index for babies
GFR	Glomerular filtration rate
KDIGO	Kidney Disease: Improving Global Outcomes
NICU	Neonatal intensive care unit
SGA	Small for gestational age
VLBW	Very low birth weight

From the [1]Division of Nephrology, Department of Pediatrics, Eastern Virginia Medical School, Norfolk, VA; [2]Division of Neonatology, Department of Pediatrics, University of Virginia Children's Hospital, Charlottesville, VA; [3]Department of Pediatrics, Ospedale Regionale per le Microcitemie, University of Cagliari, Cagliari, Italy; and [4]Division of Nephrology, Department of Pediatrics, University of Virginia Children's Hospital, Charlottesville, VA

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who survived for <2 days were excluded because there were often insufficient numbers of serum creatinine measurements to classify these patients as having AKI. In addition, patients admitted at >2 days of age were excluded because medication administration and laboratory data prior to transfer were frequently inaccessible. The Institutional Review Board at the University of Virginia approved the study protocol and waived the need for consent.

Data were collected from the electronic medical record and included patient demographics, gestational age, birth weight, Apgar scores, laboratory results, length of stay, mortality, medication exposures, and respiratory support. Neonates were classified as small (SGA), appropriate, or large for gestational age using previously reported reference standards.[12] Illness severity at admission was assessed using the updated clinical risk index for babies (CRIB II) score.[13]

AKI was defined and staged using the Kidney Disease: Improving Global Outcomes (KDIGO) definition with 2 modifications, as previously proposed for use in neonates[14] (**Table I**). First, because neonates often have nonoliguric renal failure, only the change in serum creatinine was included. Second, a peak creatinine of ≥2.5 mg/dL was used for stage 3 AKI rather than the adult cut-off of ≥4.0 mg/dL.

Because the elimination half-life of caffeine in premature neonates is long (mean: 101 hours[15]), we assessed all serum creatinine measurements in the first 10 days of life when identifying AKI. Serum creatinine was measured using an alkaline picrate (Jaffe) method traceable to isotope dilution mass spectrometry.[16] All laboratory measurements were performed in the core laboratory at the University of Virginia Medical Center.

Caffeine exposure was determined by review of the inpatient medication administration record. Caffeine was prescribed at the discretion of the attending neonatologist according to the University of Virginia's institutional protocol. A loading dose of 20 mg/kg of intravenous caffeine was administered, followed by an intravenous 5 mg/kg daily maintenance dose. When enteral feedings reached a volume of 100 mL/kg/d, the route of administration was converted to oral. In cases of refractory apnea and bradycardia, and at the discretion of the attending neonatologist, an additional caffeine loading dose of 10 mg/kg was administered, followed by a higher daily maintenance dose. Caffeine levels were only obtained in cases where rapid metabolism or toxicity were concerns.

Table I. Modified KDIGO definition for AKI used in the study

AKI stage	Definition
0	No significant change in Cr
1	↑ Cr by 0.3 mg/dL within 48 h **or**
	↑ in Cr by 150% to <200% from previous trough
2	↑ in Cr by 200% to <300% of previous trough
3	↑ in Cr ≥300% of previous trough **or**
	Cr ≥2.5 mg/dL **or**
	Renal replacement therapy

Cr, serum creatinine.

To assess the association between caffeine and AKI in a more clinically homogenous group of neonates, we separately analyzed a subgroup of neonates who received prolonged invasive respiratory support. Neonates who were intubated and received mechanical ventilation for each of the first 7 days after birth were considered to have received prolonged invasive respiratory support.

Statistical Analyses

Continuous variables were compared using the Mann-Whitney *U* or Student *t* test and categorical variables were compared using χ^2 or Fisher exact tests as appropriate. Univariable and multivariable logistic regression models were created to determine the association between caffeine exposure and AKI. Candidate variables for multivariable regression were identified based on biological plausibility or $P < .20$ in univariable analysis. Final selected multivariable models were constructed using stepwise regression with backward elimination among all candidate variables. Number needed to be exposed was estimated from the aOR obtained in the final selected logistic regression models using methods previously described.[17] Multicollinearity was assessed by calculating the tolerance statistic, with values <0.20 indicating excessive multicollinearity. A 2-sided significance level of 0.05 was set for hypothesis testing. All statistical analyses were performed using IBM SPSS v 22 (Armonk, New York).

Results

A total of 154 VLBW neonates were admitted to the NICU from March 2011 to June 2012. Fourteen patients were excluded (died <2 days after birth, n = 8; admitted to NICU >2 days after birth, n = 6). The remaining 140 neonates constituted the study population. Their demographics are shown in **Table II**.

In the first week after birth, 101 neonates (72% of the study population) received caffeine; 79% of these received their first dose within the first 48 hours after birth. The median cumulative caffeine dose received in the first week after birth was 45 mg/kg (IQR 40-50 mg/kg). Among the 17 neonates with a measured serum caffeine level, the median was 16.4 μg/mL (IQR 13.1-18.7 μg/mL). Compared with neonates who did not receive caffeine, those who received caffeine were more likely to require invasive ventilation, but less likely to receive pressor support with dopamine or be classified as SGA (**Table II**).

AKI occurred within the first 10 days in 35 patients (25.0%). The median age at AKI was 5 days (IQR 3-8 days). Most AKI was mild: 25 neonates (71.4%) reached KDIGO stage 1, 8 (22.9%) reached stage 2, and 2 (5.7%) reached stage 3. No neonate received dialysis. Among neonates experiencing AKI, the median peak serum creatinine was 1.2 mg/dL (IQR 1.0-1.4 mg/dL).