Acute Kidney Injury in Asphyxiated Newborns Treated with Therapeutic Hypothermia

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Objective To test the hypothesis that acute kidney injury (AKI) would be independently associated with increased morbidity and mortality.

Study design A total of 96 consecutively cooled infants were reviewed retrospectively. Modified Acute Kidney Injury Network criteria were used to classify AKI based on absolute rise in serum creatinine (SCr) level from a previous trough (stage I, rise in SCr of 0.3 mg/dL or SCr 150-<200%; stage II, rise in SCr of 200-<300%; stage III, rise in SCr of ≥300%, SCr 2.5 mg/dL, or dialysis). Outcomes were mortality, duration of neonatal intensive care unit (NICU) stay, and duration of mechanical ventilation.

Results AKI occurred in 36 of 96 infants (38%). Overall mortality was 7% and was higher for those with AKI, with the difference approaching statistical significance (14% vs 3% in those without AKI; $P = .099$). Patients with AKI stayed longer in the NICU (mean, 15.4 ± 9.3 days vs 11 ± 5.9 days; $P = .014$) and required prolonged mechanical ventilation (mean, 9.7 ± 5.9 days vs 4.8 ± 3.7 days; $P < .001$). On multivariate analysis, AKI remained predictive of prolonged duration of mechanical ventilation and prolonged NICU stay.

Conclusion We used the Acute Kidney Injury Network definition for AKI in asphyxiated newborns undergoing therapeutic hypothermia to demonstrate that the incidence of AKI remains high, but lower than rates published before the advent of therapeutic hypothermia. We highlight the importance of recognizing AKI in asphyxiated newborns undergoing therapeutic hypothermia, along with the potential benefits of early recognition. *(J Pediatr 2013;162:725-9)*.

Perinatal asphyxia remains a common problem in the neonatal intensive care unit (NICU). Newborns with perinatal asphyxia often develop multiorgan dysfunction affecting virtually every organ system.[1] The treatment for perinatal asphyxia has evolved over the years to include therapeutic hypothermia, which has improved outcomes for these patients.[2-4]

Acute kidney injury (AKI) is a common occurrence in neonates with perinatal asphyxia.[5] Before the advent of therapeutic hypothermia, the incidence of AKI was high, affecting 47-72% of neonates with varying degrees of perinatal asphyxia.[6-10] Previous studies relied on differing definitions of AKI based on an arbitrary serum creatinine (SCr) threshold, often >1.5 mg/dL, hindering comparison of studies. Furthermore, to date no study has included patients treated with therapeutic hypothermia.

Defining AKI in neonates remains a challenge, stemming in part from the presence of maternal creatinine in the neonatal period.[11] Jetton et al[12] proposed a modification of the adult Acute Kidney Injury Network Criteria (AKIN) definition of AKI[13] as a standardized definition of AKI for neonates based on a rise in SCr from a previously documented low rather than on an absolute SCr threshold, to allow for better characterization of the incidence, epidemiology, and outcomes. A similar definition was used to study AKI in very low birth weight neonates,[14] neonates with congenital diaphragmatic hernia requiring extracorporeal membrane oxygenation,[15] neonates with perinatal asphyxia not receiving therapeutic hypothermia,[8] and infants with congenital heart disease.[16] No studies in neonates receiving therapeutic hypothermia for perinatal asphyxia have been reported to date.

To examine the incidence of AKI and the association between AKI and clinical outcomes, we performed a retrospective chart review of neonates treated with hypothermia at the University of Michigan. We evaluated the incidence and time course of AKI in asphyxiated newborns treated with therapeutic hypothermia using modified AKIN criteria. We hypothesized that AKI in asphyxiated newborns treated with therapeutic hypothermia would be independently associated with increased duration of mechanical ventilation, increased length of NICU stay, and increased mortality.

AKI	Acute kidney injury
AKIN	Acute Kidney Injury Network
NICU	Neonatal intensive care unit
SCr	Serum creatinine

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Methods

We conducted a retrospective review of all consecutive neonates treated with therapeutic hypothermia for perinatal asphyxia between 2003 and 2010 at the University of Michigan. The University of Michigan's Institutional Review Board approved this study and waived the need for consent.

Both whole-body cooling and selective head cooling were used during the study period. The entry and exclusion criteria for cooling have been reported previously.[17] Before 2009, patients received either selective head cooling or whole-body cooling; after 2009, whole-body cooling was the more common treatment modality. Monitoring and treatment during cooling were provided in accordance with Cool Cap and National Institute of Child Health and Human Development whole-body cooling protocols.[2,3]

Infant demographic data collected included gestational age, birth weight, and sex. Perinatal data included cesarean delivery, clinically identifiable intrapartum sentinel event (ie, placental abruption, cord prolapse, cord avulsion, vasa previa, ruptured uterus, maternal cardiopulmonary arrest, difficult delivery with shoulder dystocia), birth location, resuscitation details (asystole or chest compressions at birth), umbilical cord pH, umbilical cord base deficit, seizure occurring within 6 hours after birth, and Apgar scores at 1 and 5 minutes after birth. Characteristics of the hospital course include the need for vasopressor support, transfusions, dialysis, or mechanical ventilation; presence of persistent pulmonary hypertension; and exposure to gentamicin or vancomycin.

During therapeutic hypothermia, laboratory test results (including renal function, electrolyte levels, and liver function tests) were assessed before the start of cooling (baseline); at 24, 48, and 72 hours during cooling; and then on days 5, 7, and 10 of life as clinically indicated.

AKI was defined using an SCr-based modification of the AKIN criteria, consistent with previous reports (Table I). As reported previously, modifications to these criteria included excluding urine output (because AKI in neonates is often nonoliguric) and setting a SCr cutoff value of 2.5 mg/dL for stage III, to proportionally reflect a comparable degree of kidney dysfunction indicated by an SCr level of 4 mg/dL in adults.[13,14] The criteria were further modified such that an infant had to have a minimum SCr of >0.5 to be classified as having AKI. Our exclusion of the AKIN criterion specifying that the rise in SCr must occur over a period of 48 hours reflects recent changes that have replaced this with a period of 7 days in the recently published Kidney Disease Improving Global Outcomes AKI guidelines.[18] The outcomes of interest included duration of ventilation, length of NICU stay, duration of hospitalization, and survival to NICU discharge.

Table I. Definition of AKI categories*

AKI stage	Criteria
0	No change in Cr
1	↑ SCr 0.3 mg/dL or ↑ SCr 150-<200% from previous trough value
2	↑ SCr 200-<300% from previous trough value
3	↑ SCr ≥300% from previous trough value, SCr 2.5 mg/dL, or dialysis

Cr, creatinine.
*Adapted from Jetton et al.[13]

General population descriptive statistics (mean, SD, proportions) were analyzed for the entire cohort and segregated into patients with AKI and those without AKI (Table II). All continuous variables were found to be within acceptable ranges, based on skewness and kurtosis, to allow analysis as normally distributed. Univariate and multivariate analyses were performed using both parametric and nonparametric procedures as appropriate. Data are reported as mean and SD were reported for continuous parametric data and as frequency for nonparametric data. Univariate comparisons between groups were done using the independent-samples *t* test or Pearson χ^2 test. A *P* value ≤.05 was considered statistically significant for all analyses. Variables identified as being clinically significant for the development of AKI on univariate analysis were retained for multivariate analysis. Linear regression was used to evaluate the association between AKI and patient outcomes (duration of mechanical ventilation and length of NICU stay) while controlling for the other independent covariates retained in each model. All statistical analyses were performed using SPSS 18.0 (IBM, Armonk, New York).

Results

A total of 96 patients underwent therapeutic hypothermia between 2003 and 2010 at the University of Michigan, including 53 who received whole-body cooling and 43 who received selective head cooling (Table II). Eighty-four patients had been transferred from an outside institution for therapeutic hypothermia. Eighty-seven patients had been exposed to gentamicin. Fifty-two patients had experienced a clinically identifiable sentinel event around the time of birth; the most common of these events included placental abruption (n = 18), difficult delivery (n = 8), cord prolapse (n = 7), and uterine rupture (n = 4).

AKI was identified in 36 of 96 patients (38%) during the study period. Based on the modified AKIN criteria, 16 patients had stage I AKI, 7 had stage II AKI, and 13 had stage III AKI. Three patients underwent renal replacement therapy during the study, 1 of whom was discharged on peritoneal dialysis and eventually underwent renal transplantation for cortical necrosis. The remaining 2 patients requiring renal replacement therapy died. Patients who developed AKI were significantly more likely to have asystole around the time of birth (*P* = .049), clinical seizures before initiation of cooling (*P* = .039), persistent pulmonary hypertension (*P* = .018), elevated gentamicin level (*P* = .015), elevated vancomycin level (*P* = .011), the need for pressor support (*P* < .001), and the need for transfusions (*P* < .001). There was no statistically significant difference in the development of AKI between neonates treated with whole-body cooling and those treated with selective head cooling (38% vs 33%; *P* = .958). Otherwise, there were no significant differences in the demographic