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Neonatal Acute Kidney Injury and the Risk of Intraventricular Hemorrhage in the Very Low Birth Weight Infant

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Abstract

Despite improvements in survival of premature infants, many have comorbid conditions. The role of the kidney in multiorgan dysfunction is unclear, particularly in regard to intraventricular hemorrhage (IVH). We hypothesized that infants diagnosed with acute kidney injury (AKI) have an increased risk of IVH independent of gestational age (GA) and other variables associated with both comorbidities. This prospective cohort study consisted of 125 infants with a birth weight 1,200 g and/or GA $\leq$ 31 weeks. A definition of AKI was used from KDIGO, not including urine output as nonoliguria is common in this population. IVH was based on serial head ultrasounds. Neonates with AKI had a higher trend towards having IVH compared to those without [14/35 (40%) vs. 22/83 (26.5%), $p = 0.1$]. Infants with AKI were more likely to have stage 2 IVH or higher than those without AKI [12/36 (33.3%) vs. 6/82 (7.3%); $p < 0.01$]. AKI was associated with a 3.6-fold increased risk of a grade 2 or higher IVH [hazard ratio (HR) 3.55, 95% confidence interval (CI) 1.39–9.07] and over 4-fold increase in risk of a grade 3 or higher IVH (HR 4.34, 95% CI 1.43–13.21). While there was no association between AKI and IVH overall, those with AKI had a higher hazard ratio to develop a grade 2 or higher IVH even when controlling for birth weight, antenatal steroid use, and 5-min Apgar score. Future studies are indicated to expand sample size and to control for other clinical variables that could be associated with both AKI and IVH.

Keywords

Acute kidney injury; Intraventricular hemorrhage; Very low birth weight; Extreme prematurity

Introduction

Despite improvements in survival of premature infants, many are faced with chronic neurodevelopmental problems stemming from complications related to prematurity. The most common neurological sequela in premature infants is intraventricular hemorrhage

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(IVH). The long-term effects of IVH are significant resulting in poor developmental outcomes including cerebral palsy, hearing impairment, and blindness [1, 2]. Frequently, IVH occurs spontaneously; however, very low birth weight (VLBW) infants are particularly susceptible due to the immature development of the subependymal germinal matrix (SEGM) which is the site of origin for IVH [3]. As the fetus develops, the SEGM decreases in size, and a collagenous vascular sheath support structure develops, stabilizing these vessels [4, 5].

Studies support that the initiation of hemorrhage is largely due to alterations of cerebral perfusion pressure and blood flow [6, 7]. The ability of the neonate to control cerebrovascular autoregulation declines with decreasing gestational age (GA). In addition, the sick preterm infant transitions to a more pressure-passive cerebral circulation [8]. Multiple factors can impair this autoregulation and are risk factors for IVH. In addition to birth weight (BW) and GA, they include mode of delivery, Apgar score (1 and 5 min), need for delivery room resuscitation, administration of surfactant, refractory hypotension or hypertensive injury, hyperviscous state, early sepsis, respiratory distress syndrome, pneumothorax, asphyxia, and reperfusion injury [1, 9–11]. Also, maternal factors have been identified: pregnancy-induced hypertension, premature and/or prolonged rupture of membranes, and maternal infection. Because of the integral role of the kidney with blood pressure regulation and in turn cerebral perfusion and blood flow, its role may be important in the development of IVH. Whether abrupt changes in kidney function during the first week of life are associated with IVH has yet to be investigated.

The incidence of acute kidney injury (AKI) in VLBW infants (i.e. <1,500 g) is relevant, and its association with increased mortality risk has been well documented and recently reviewed [12–15]. While AKI is an independent risk factor for poor outcomes in critically ill infants, there is a growing interest in its role in multiorgan dysfunction. Particularly, organs such as the brain, heart, lungs, liver, and intestines can be subjected to damage in the presence of AKI through numerous proinflammatory mechanisms [16]. Studies have shown that significant systemic and brain inflammation in mouse models of ischemia/reperfusion can lead to disruption of the blood-brain barrier [17, 18]. An association between AKI and brain outcomes in term neonates has been reported by Sarkar et al. [19], whereby they showed that AKI is independently associated with hypoxic-ischemic lesions observed on MRI in term infants that received therapeutic hypothermia for severe perinatal asphyxia [20]. To our knowledge, there are no previous studies exploring the relationship between kidney and brain injury in VLBW infants.

Because the kidney has a critical role in maintaining blood pressure, fluid balance, electrolyte homeostasis, and modulating the immune system during multiorgan failure, it is possible that premature infants with AKI are at risk to develop IVH. We performed a prospective cohort study to improve our understanding of the associations between AKI and IVH. We hypothesized that infants diagnosed with AKI will have an increased risk of IVH independent of GA and other possible confounders.

Methods

Study Population

This prospective cohort study was conducted in the Regional Newborn Intensive Care Unit (RNICU) located on the University of Alabama at Birmingham (UAB) campus between February 2012 and June 2013. The study population consisted of infants with BW $\geq$ 1,200 g and/or GA $\geq$ 31 weeks. Infants were excluded if they had a known congenital abnormality of the kidney or urinary tract. We followed enrolled infants from the time of birth until 36 weeks corrected GA or hospital discharge, whichever occurred first. Parental informed consent was obtained from parents or guardians. UAB's Institutional Review Board approved the study.

Variable Definitions

The neonatal AKI definition used was from KDIGO (Kidney Disease: Improving Global Outcomes) as previously described by Jetton and Askenazi [20] (table 1). For this study, we did not include urine output criteria because it is often difficult to measure urine output in premature infants, and nonoliguric AKI is very common in this population. Since serum creatinine (SCr) decreases in neonates after birth and is dependent on GA, baseline SCr was defined as the lowest previous SCr value. Stage 1 AKI was defined as a rise in SCr of at least 0.3 mg/dl from the baseline value or an increase in SCr by $\geq$ 150–200%. Stage 2 AKI was defined as a $\geq$ 200–300% increase in SCr, and stage 3 AKI was defined as a rise in SCr of at least 2.5 mg/dl or an increase in SCr by $\geq$ 200%. SCr was obtained on days 1, 2, 3, 4, and 12 from most infants in addition to any clinically indicated measured values. The median number of SCr values obtained for each patient during the first 2 weeks of life was 5 (range 2–14).

IVH is defined as bleeding within the germinal matrix, and the most common imaging technique used to diagnose is the cranial ultrasound [1]. Head ultrasounds were obtained as part of routine care at the end of week 1 and again week 4 of life, and interpretations were based on reports by institutional radiologists. If a grade 3 or 4 IVH was detected, ultrasounds were obtained bi-monthly after the first diagnosis.

Infant demographic data were obtained and included GA, BW, head circumference, race, sex, and Apgar scores at 1 and 5 min. In addition, infant intervention data were collected including umbilical artery catheter (UAC), antibiotic, surfactant, ventilator support, and indomethacin administration. Maternal demographic data included history of hypertension, preeclampsia, drug abuse, and use of prenatal maternal steroid administration.

Statistical Analysis

A log-rank test estimated from Kaplan-Meier analysis was used to examine whether demographic, clinical, and maternal characteristics were associated with time to IVH. A Cox proportional hazards model was used to estimate hazard ratios (HRs) and associated 95% confidence intervals (95% CIs) for the association between AKI and IVH. For purposes of the analysis, AKI was entered into the model as a time-varying covariate. To control for potential confounders, we chose BW, 5-min Apgar score, and maternal antenatal steroids

based on previous studies on risk factors for AKI and IVH in premature infants [6, 14]. Separate models were created for IVH grade 1 or higher, grade 2 or higher, and grade 3 or higher. SAS v9.3 was used for all analyses.

Results

Of the 284 screened infants who met the inclusion criteria, 75 were not interested, 76 were not available, and 8 were transferred from an outside hospital. One hundred and twenty-five infants were consented, with 7 excluded due to incomplete data resulting in 118 infants in the cohort. No significant differences in GA, BW, and 5-min Apgar scores were detected between included and excluded infants (fig. 1).

AKI within the first 15 days of life was documented in 36/118 (30.5%) infants (n = 31 with stage 1 AKI, n = 2 with stage 2 AKI, and n = 3 with stage 3 AKI). IVH was found in 35/118 (29.6%) of infants (n = 17 with grade 1 IVH, n = 5 with grade 2 IVH, n = 9 with grade 3 IVH, and n = 4 with grade 4 IVH). There was no difference in regard to race or gender between infants with and without IVH. As shown in table 2, infants with IVH had a lower mean GA ($p < 0.03$), lower BW ($p < 0.04$), smaller head circumference ($p < 0.04$), and lower 5-min Apgar scores ($p < 0.01$) compared to those without IVH. In regard to clinical course, those with IVH were more likely to have a UAC (30/83, 36.1%, $p < 0.05$), receive surfactant (42/83, 50.6%, $p < 0.05$), and have been on high-frequency oscillator ventilatory support (HFOV; 7/35, 20.0%, $p < 0.01$). Those with IVH were less likely to be born to mothers who received antenatal steroids (32/35, 91.4%, $p < 0.01$). Lastly, infants with IVH had a lower rate of survival [25/35 (80.6%) vs. 61/83 (89.7%), $p < 0.05$] (table 2).

Table 3 also shows the distribution between any AKI and any IVH. Infants with AKI had a higher trend towards also having IVH compared to those without AKI [14/35 (40%) vs. 22/83 (26.5%), $p = 0.1$]. When evaluating the association between AKI and IVH grade 2 or higher, infants with AKI were more likely to have stage 2 IVH or higher than those without AKI [12/36 (33.3%) vs. 6/82 (7.3%), $p < 0.01$] (table 3). Though there was no association between AKI and IVH of any grade, AKI was associated with a 3.6-fold increased hazard of a grade 2 or higher IVH (HR 3.55, 95% CI 1.39–9.07) and over 4-fold increased hazard of a grade 3 or higher IVH (HR 4.34, 95% CI 1.43–13.21). These associations remained significant for both a grade 2 or higher (HR 3.39, 95% CI 1.31–8.77) and a grade 3 or higher IVH (HR 3.97, 95% CI 1.28–12.32) after adjusting for BW, antenatal steroid use, and Apgar scores at 5 min (table 3).

Discussion

To our knowledge, this is the first study describing the association between AKI and IVH in the premature infant. Previous studies have shown numerous risk factors for each, including those overlapping risk factors of lower GA and BW, perinatal hypoxia, lower Apgar scores, infant sepsis, medically treated patent ductus arteriosus, and antenatal steroids [1, 9, 13, 20–22]. Our study found similar findings that those diagnosed with IVH had lower GA and BW, lower Apgar scores (5 min in our study), and less use of antenatal steroids. In addition, we also found an association with smaller head circumference, use of surfactant, HFOV, and

presence of UAC with IVH. Lastly, it supported the increased risk of mortality associated with both, also found in other research.

While there was no clinically significant association between AKI and IVH overall, we did find a higher trend toward IVH among those with AKI, though it remains unclear whether this trend is due to similar risk factors. For instance, other factors that contribute to AKI are numerous including the use of nephrotoxic agents and recurrent infections that can lead to multiorgan damage [21, 23] and in turn may alter cerebral perfusion pressure and blood flow leading to IVH damage. However, our study does show an association with AKI and a higher severity grade of IVH. While it may be argued that those infants with AKI and IVH are more likely to be clinically ill, the role of the kidney in maintaining blood pressure and fluid balance (both contributors to IVH risk) appears to have some contribution based on the increased HRs we found while controlling for BW, antenatal steroid use, and Apgar scores at 5 min.

Gupta et al. [24] demonstrated that the severity of renal injury is associated with the degree of brain asphyxia, and Sarkar et al. [19] has demonstrated those neonates with hypoxic-ischemic encephalopathy had worse MRI findings in the presence of AKI after cooling therapy as compared to those without renal injury. These findings lead to our hypothesis that AKI could potentially be an independent risk factor for IVH.

The results of the current study should be viewed in light of certain strengths and limitations. First, multiple measurements of SCr allowed AKI be included as a time-varying covariate in statistical models. This improved the probability that the exposure of AKI was known to occur prior to IVH. That said, no measurements of SCr were taken from day 5 to 11 of life. Thus, there still exists a probability that AKI occurred following IVH. Secondly, the role of antenatal steroids in the risk of IVH is relevant, and numerous studies have shown a reduction in severe IVH. In our study, 29.6% of infants had some grade of IVH with 11% (13/118) with grade 3 or higher, and 57% of the infants in our study received a full course of antenatal steroids. However, 43% of our infants had none or an incomplete antenatal steroid course, which is a limitation to our study as this may be a contributory factor in the incidence of IVH. Little is known regarding the role of antenatal steroids on kidney development. Jahnukainen et al. [25] showed that antenatal steroids result in increases in mean arterial blood pressure, blood flow, and glomerular filtration rate in numerous animal models resulting in accelerated functional maturation. Some have postulated that this accelerated maturation contributes to premature cessation of renal development, and therefore increases the risk of kidney injury. Nonetheless, little data exists on the possible link between earlier cessation of nephrogenesis and later development of kidney injury in the human subject. Lastly, our study was limited by sample size; thus, there still exists the possibility that the reported results are biased by residual confounders as more variables could not be entered into statistical models. Unmeasured variables that could be confounders of the association between AKI and IVH include various markers of sepsis or multiorgan damage that were not able to be fully evaluated based on the retrospective nature of the study. For instance, the need for delivery room resuscitation (epinephrine and chest compressions), refractory hypotension, presence of a hemodynamically patent ductus arteriosus, and use of mechanical ventilation including the use of high-frequency ventilation

as noted by Sarkar et al. [22] as risk factors for IVH that may also contribute to AKI. We were able to review the use of high-frequency oscillator ventilation in our study population and found 9.3% (11/118) of the infants had at some time been on high-frequency ventilation, and 20% (7/35) of those with a diagnosis of IVH having been on HFOV, the latter being clinically significant ($p < 0.01$).

The definition of AKI is empiric. Thus, it is possible that the rise in SCr we see simply documents that there was a higher net negative balance during the first week of life. Large multicenter studies will be needed to further understand this relationship. Also, numerous novel bio-markers of neonatal AKI may be more sensitive to understand how the kidney and brain communicate [26].

While AKI and IVH are both independently associated with increases in mortality, it seems that the concomitant presence of AKI also worsens morbidity, in this case severity of IVH [14, 15]. Because the kidney has an integral role in maintaining homeostatic factors in the neonate, including the brain, this relationship could be a potential risk factor for IVH.

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Fig. 1.
Flowchart for enrollment. HUS = Head ultrasound.

Table 1

KDIGO classification of AKI for neonates

AKI stage	SCr
1	0.3 mg/dl from lowest previous value or 150 – 200% from lowest previous value
2	200 – 300% from lowest previous value
3	2.5 mg/dl or 300% from lowest previous value

Baseline SCr was defined as the lowest previous SCr value because SCr decreases in neonates after birth and is dependent on GA.

Table 2

Comparison of demographic, clinical, and maternal characteristics among neonates with and without subsequent IVH diagnosis

	IVH (n = 35)	No IVH (n = 83)	p value
<i>Demographics</i>			
Race			
Black	20 (57.1)	43 (51.8)	0.8404
White	12 (34.3)	35 (42.2)	
Hispanic	2 (5.7)	3 (3.6)	
Other	1 (2.9)	2 (2.4)	
Gender			
Female	17 (48.6)	43 (51.8)	0.4740
Male	18 (51.4)	40 (48.2)	
GA			
Mean $\pm$ SD, weeks	26.1 $\pm$ 2.6	27.6 $\pm$ 2.0	0.0002
<28 weeks	26.1 (65.7)	37 (44.6)	0.0238
28 weeks	12 (34.3)	46 (55.4)	
BW			
Mean $\pm$ SD, g	850.1 $\pm$ 271.8	100.3 $\pm$ 311.4	0.0169
<1,000 g	23 (65.7)	39 (47.0)	0.0351
1,000 g	12 (34.3)	44 (53.0)	
Head circumference			
Mean $\pm$ SD, cm	23.4 $\pm$ 2.5	25.0 $\pm$ 2.8	0.0047
<25 cm	23 (65.7)	38 (45.8)	0.0309
25 cm	12 (34.3)	45 (54.2)	
<i>Clinical characteristics</i>			
Apgar 1 min	2.5 (0 – 8)	5 (0 – 8)	0.0664
Apgar 5 min	6 (0 – 8)	7 (0 – 8)	0.0077
UAC	19 (54.3)	30 (36.1)	0.0469
Antibiotics	35 (100.0)	85 (100.0)	–
Surfactant	25 (71.4)	42 (50.6)	0.0472
Indomethacin	18 (51.4)	29 (34.9)	0.1280
HFOV	7 (20.0)	4 (4.8)	0.0096
AKI	14 (40.0)	22 (26.5)	0.1
Survived to 36 weeks post-conception	25 (80.6)	61 (89.7)	0.0439
<i>Maternal characteristics</i>			
Hypertension	9 (25.7)	25 (30.1)	0.6027
Preeclampsia	9 (25.7)	24 (28.9)	0.6991
Antenatal steroid	32 (91.4)	82 (98.8)	0.0095
Antenatal indomethacin	4 (11.4)	9 (10.8)	0.7728
Prenatal care	33 (94.3)	78 (94.0)	0.9212

	IVH (n = 35)	No IVH (n = 83)	p value
Drug abuse	2 (5.7)	5 (6.0)	0.9997

p values estimated from a log-rank test from Kaplan-Meier analysis. Values are presented as n (%), with the exception of Apgar scores reported as median (range), or as stated.

Table 3

Crude and adjusted HRs and associated CIs for the association between AKI and IVH

IVH grade	No AKI (n = 82) n (risk %)	AKI (n = 36)		
		n (risk %)	crude HR (95% CI)	adjusted HR (95% CI)
1	21 (25.6)	14 (38.9)	1.49 (0.73 – 3.07)	1.46 (0.71 – 3.02)
2	6 (7.3)	12 (33.3)	3.55 (1.39 – 9.07)	3.39 (1.31 – 8.77)
3	3 (3.7)	10 (27.8)	4.34 (1.43 – 13.21)	3.97 (1.28 – 12.32)

The HRs were estimated from a Cox proportional hazards regression and adjusted for BW, maternal antenatal steroid use, and Apgar scores at 5 min. AKI entered into model as a time-dependent covariate.