The incidence of Acute Kidney Injury in preterm infants treated with early high dose caffeine

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Abstract

Background and Objectives

Acute kidney injury (AKI) is common in neonates and associated with increased morbidity and mortality, longer hospitalization, and a higher risk for future kidney damage. Caffeine treatment, commonly used to treat apnea of prematurity, was reported to be associated with decreased AKI occurrence. However, previous studies lack uniformity regarding the dosage and timing of the administration of the drug.

The objective of this study was to assess the incidence of AKI in VLBW preterm infants treated with early high dose caffeine, and to identify risk factors associated with AKI.

Methods

A retrospective cohort study of very low birth weight preterm infants admitted to the Neonatal Intensive Care Unit (NICU) at the Shaare Zedek Medical Center between Jan. 1, 2017 and Dec. 31, 2019. AKI was defined according to the neonatal AKI KDIGO classification, based on an elevation of serum creatinine levels or a decrease in urine output. High dose Caffeine (20 mg/kg bolus, administrated in the first hour of life, followed by a maintenance dose of 10 mg/kg/day) was universally administrated to all VLBW preterm infants born less than 32 weeks of gestation. Infants with inadequate data regarding urine output or less than two serum creatinine measurements were excluded.

Results

During the study period 311 VLBW infants were admitted, all had adequate serum creatinine and urine output data. 301 met the inclusion criteria, 41 infants (13.6%) were diagnosed with AKI, while only 12 (4%) during the first week of life, a significantly lower incidence in comparison to previous reports (p - value < 0.0001). Sixteen infants (5.1%) had more than one AKI episode. Seven infants (17%) had AKI stage 1 and 17 infants had stage 2 and 3 (41.5%).

AKI was associated with lower gestational age and male sex (p value = 0.002 and 0.03, respectively).

Conclusions

The incidence of AKI in a cohort of VLBW infants, treated with early high dose Caffeine was significantly lower as compared to previous studies, especially in the first week of life.

Introduction

Nephrogenesis commences at the 5th gestational week, completes at weeks 34–36 of gestation[1] and continues minimally and inefficiently after preterm birth. Accordingly, preterm infants can have a reduced nephron number which can result in decreased renal reserve later in life[2]. There are previous studies linking prematurity and low birth weight to chronic kidney disease[3]. In addition, during the first few weeks

of life, the kidneys are vulnerable to the effect of various noxious factors such as exposure to nephrotoxic medications, hypoxia, hemodynamic instability and infections[4].

Acute kidney injury (AKI) is defined as sudden reduced kidney function that results in a decline in glomerular filtration rate (GFR). AKI in preterm infants is associated with prolonged hospitalization, higher morbidity and mortality rate and elevated risk for chronic kidney disease[2,5]. AKI is common among preterm infants [6] and is reported between 18–40% in previous studies[7,8].

In the Jetton et al. AWAKEN study that included 2000 neonates, AKI incidence was 30% in all infants, and 33.5% in very low birth weight (VLBW) group[9]. Other studies using only creatinine criteria reported an AKI incidence rate of 18%-40% in VLBW from birth to discharge from the NICU (or up to week 36 of pregnancy)[7,8]. Using only creatinine criteria, without urine output criteria, may underestimate the true AKI incidence. Results from another study focusing on extremely low birth weight (ELBW) neonates, showed an even higher AKI incidence rate of 56%[10]. In previous reports AKI rates are significantly higher in the first week of life, with 21% percent of neonates experiencing AKI in the first week of life[12].

Caffeine citrate, a methylxanthine that was initially used to treat apnea of prematurity, was shown to have additional beneficial effects. Two large studies found a clear association between caffeine treatment and reduction in AKI incidence (17.8% vs 43.6% and 11.2% vs 31.6%)[12,13]. The caffeine protocol was not uniform across participating sites precluding reaching any conclusions on the optimal caffeine protocol.

A general decrease in AKI incidence was reported by Chen et al. (2021) who compared AKI in very premature neonates (up to 29 weeks of pregnancy) and neonates born in weeks 29–32 of pregnancy during the years 2008–2015. In the neonates born prior to 29 weeks, the occurrence decreased from 56–17%[14]. Benchmarking AKI trends and current incidence can point to protective interventions.

In the present study we aim to evaluate the current incidence of AKI in a cohort of VLBW neonates treated with early high-dose caffeine.

Methods

All neonates that were hospitalized in the neonatal intensive care unit at Shaare Zedek Medical Center from January 1st 2017 to December 31st 2019, with a birth weight less than 1500 grams (VLBW) were included in this retrospective cohort study.

Exclusion criteria included newborns with inadequate data (less than two serum creatinine levels or less than two full urine reports), newborns hospitalized for less than 48 hours or admitted after one week of age and newborns with major congenital or chromosomal anomalies. Infant and maternal data were retrieved from our electronic medical records. Urine output is routinely reported quantitatively in the intensive care unit and qualitatively after transfer to the step-down unit, which occurs when the infant is

stable and at least 33 weeks corrected age. We excluded the daily urine report of the first day of life from the analysis. Clinical Risk Index for Babies scoring system (CRIB II) was used as a marker for severity[15].

AKI was defined and severity classified according to the neonatal KDIGO criteria[16] combined stage was assigned based on the higher grade of either criterion (Table 1).

Table 1
Neonatal AKI KDIGO Classification

Stage	Serum creatinine	Urine output
0	No change or rise $<$ 0.3 mg/dL	$\geq$ 0.5 mL/kg/h
1	SCr rise $\geq$ 0.3 mg/dL within 48 h or rise $\geq$ 1.5–1.9 $\times$ reference SCr* within 7 d	$<$ 0.5 mL/kg/h for 6 to 12 h
2	SCr rise $\geq$ 2-2.9 $\times$ reference SCr**	$<$0.5 mL/kg/h for $\geq$ 12h
3	SCr rise $\geq$ 3 $\times$ reference SCr** or SCr $\geq$ 2.5 mg/dL or receipt of dialysis	$<$0.3 mL/kg/h for $\geq$ 24 h or anuria for $\geq$ 12 h

* The lowest SCr value in the last 7 days,
**The lowest previous SCr value.

Statistical analysis was performed using IBM SPSS 26.0 statistics software package (IBM SPSS Statistics for Windows, Version 26.0. Armonk, NY). To compare distributions of perinatal factors and neonatal morbidities between infants with and without AKI, Chi-square test was used for categorical variables and t-test for continuous variables. Multivariable logistic regression analysis was used to assess the independent effect of AKI on mortality.

Ethical approval for the study was provided by the Institutional Review Board, which waived the need for informed consent based on the strict maintenance of participants' anonymity.

Results

During the study period 311 eligible newborns were admitted to the NICU. Of these, 8 were excluded from the study due to birth defects, and two neonates were excluded because they were admitted later than 7

days of life. A total of 301 neonates were included in the final analysis. There were no exclusions for missing data.

Patients' characteristics presented in Table 2. Patients with AKI were born earlier with lower Apgar scores and higher CRIB II scores.

Table 2
Patients' characteristics.

	AKI patients	No AKI patients	P value
Birth weight* (gm)	827.6 (211.4)	11973. (226.4)	0.000
Gestational age* (weeks)	260. (0.38)	29.8 (2.51)	0.000
Sex^			
Male	14 (34.2%)	134(51.5%)	0.04
Apgar score*			
1 min > 7	14 (34.1%)	164 (63.6%)	0.001
5 min > 7	27 (65.9%)	228 (88.4%)	0.001
CRIB II score*	11.6 (3.06)	6.4 (3.06)	0.000
Maternal risk factors^			
Eclampsia	4 (9.8%)	17 (6.5%)	0.5
chorioamnionitis	3 (7.3%)	25 (9.6%)	0.78
PPROM	12 (29.3%)	55 (21.2%)	0.24
Placenta			
abruption/previa	15 (36.5%)	55 (21.2%)	0.031

(* - mean, SD, ^- number (percent))

Forty-one neonates out of 301 tested (13.6%) had at least one event of AKI during hospitalization. Of them 30 (73%) neonates met both creatinine and urine output criteria, 9 (22%) had non-oliguric renal failure and 2 (5%) infants were diagnosed with AKI based solely on urine output. 16 newborns (39%) had two or more events. Seven neonates (17%) had AKI stage 1, the remaining 34 were equally divided between stage 2 and 3 (17, 41.5%).

There were 73 AKI episodes during the study period (stage 1: 26 (35%), stage 2: 29 (40%) and stage 3: 18 (25%)). A correlation between AKI severity and fulfilling both AKI criteria is depicted in **Fig. 1**.

AKI occurrence in the first week of life was 4% (12 of 301 neonates).

Compared to previous reports, we found significantly lower AKI incidence (13.6% vs. 18–40%; p < 0.001, p < 0.048 respectively). More so in early onset AKI (4% vs 14.4–25.5%, p value < 0.001). In our data 29% of all AKI cases occurred in the first week of life as compared to about two thirds in previous reports (p < 0.001).

Risk factors associated with acute kidney injury

Risk factors associated with AKI are presented in Table 3. In univariate analysis sepsis, PDA, BPD and NEC were more prevalent in the AKI group. AKI infants had higher mortality rate (58% of AKI infants versus 2.3% of non-AKI infants (p < 0.001)). In multivariate analysis CRIB II score and AKI remained significant risk factors for mortality (p < 0.001). Mortality rate were correlated with AKI severity as presented in **Fig. 2**.

Table 3
Risk factors and prognosis associated with AKI

	AKI (n = 41)	**No AKI (n = 260)**	**P-value**
Sepsis^	10 (24.4%)	12 (5.1%)	0.01
PDA^	31 (75.6%)	54 (20.8%)	0.00
BPD^	17 (41.5%)	47 (18.1%)	0.02
NEC ^	22 (53.7%)	21 (8.1%)	< 0.0001
Mortality^	24 (58.5%)	6 (2.3%)	< 0.0001
Length of hospitalization among survivors* (days, SD)	187.2 (107.3)	60.8 (29.6)	< 0.0001
Weight at discharge* (kg)	2.44 (1.74)	2.64 (0.87)	0.484

(*- mean, SD, ^- number (percent))

Discussion

Our study shows low AKI rates in VLBW neonates. The rate of AKI during the entire hospitalization period was 13.6% versus 18–40% in previous studies. The AKI rate during the first week of life was even lower as compared to previous studies (4% versus 21%). More so, in our data 29% of all AKI cases occurred in the first week of life as compared to about two thirds in previous reports (p < 0.001). AKI was found to be associated with higher mortality (58.5% vs. 2.3%, p < 0.0001). Both creatinine and urine output criteria for the diagnosis of AKI were met in most newborns (73%), and in 4.9% AKI urine output criteria was solely met.

Similar to other studies, gestational age, birth weight, Apgar score, CRIB II score and sepsis were found to be associated with AKI. Neonatal morbidities, such as PDA, IVH and NEC and longer hospitalization were

also significantly associated with AKI.

Lower AKI rates found in this study are in line with recently published studies[14], reporting lower incidence of AKI possibly explained by improved neonatal care.

Under-diagnosis of AKI in our cohort is less likely due to the multitude of creatinine measurements, full urine output reports and adequate data on all enrolled neonates.

This study is limited by its retrospective design. The lack of proper controls that were not exposed to caffeine allows us to only speculate about the protective effect of caffeine against AKI in preterm infants. Clearly, the lower incidence of AKI can be a result is multiple factors, however, caffeine's rule is supported by other studies. [13,18–19]. Furthermore, caffeine's nephro-protective effect is plausible given its effect on the kidneys including increased renal blood flow and tissue oxygenation[22], enhanced sodium excretion, and elevating glomerular filtration rate[20]. Methylxanthines, such as caffeine and aminophylline, were correlated with decreased AKI incidence in asphyxiated term infants[23], preterm cohort[13], in VLBW infants[12] and specifically in preterms diagnosed with NEC[17]. Harer et al. reported an early AKI incidence of 11.2% in caffeine treated preterm infants, as compared to 31.6% in caffeine naive infants[15]. However, the timing of caffeine in their study was not uniform, and doses were not presented. Herein lies the importance of the present work which described the incidence of AKI in a cohort of VLBW infants universally treated with early high dose caffeine.

Our main goal was to better describe the current rate of AKI among premature infants treated with early high dose of caffeine. Preterm infants are a vulnerable population with increased risk for future kidney disease. Monitoring AKI incidence is critical for identifying appropriate measurements to prevent kidney insults. Further studies are needed to support the protective effect of early caffeine treatment.

Abbreviations

AKI- Acute kidney injury, RDS - Respiratory distress syndrome, VLBW - Very low birth weight, CRIB- Clinical Risk Index for Babies scoring system, Scr- serum creatinine GA - Gestational age, SGA- small for gestational age, AGA- appropriate for gestational age, LGA- large for gestational age, PPROM- premature rupture of membranes EC - Necrotizing enterocolitis, IVH - Intraventricular hemorrhage, BPD - Bronchopulmonary dysplasia, PDA – Patent ductus arteriosus, UOP-Urine output.

Declarations

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Efrat Ben-Shalom and Yaacov Frishberg: contributed substantially to the design of the study, analysis and interpretation of the data, revision of the article for important intellectual content and has approved the final version of the article.

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Figures

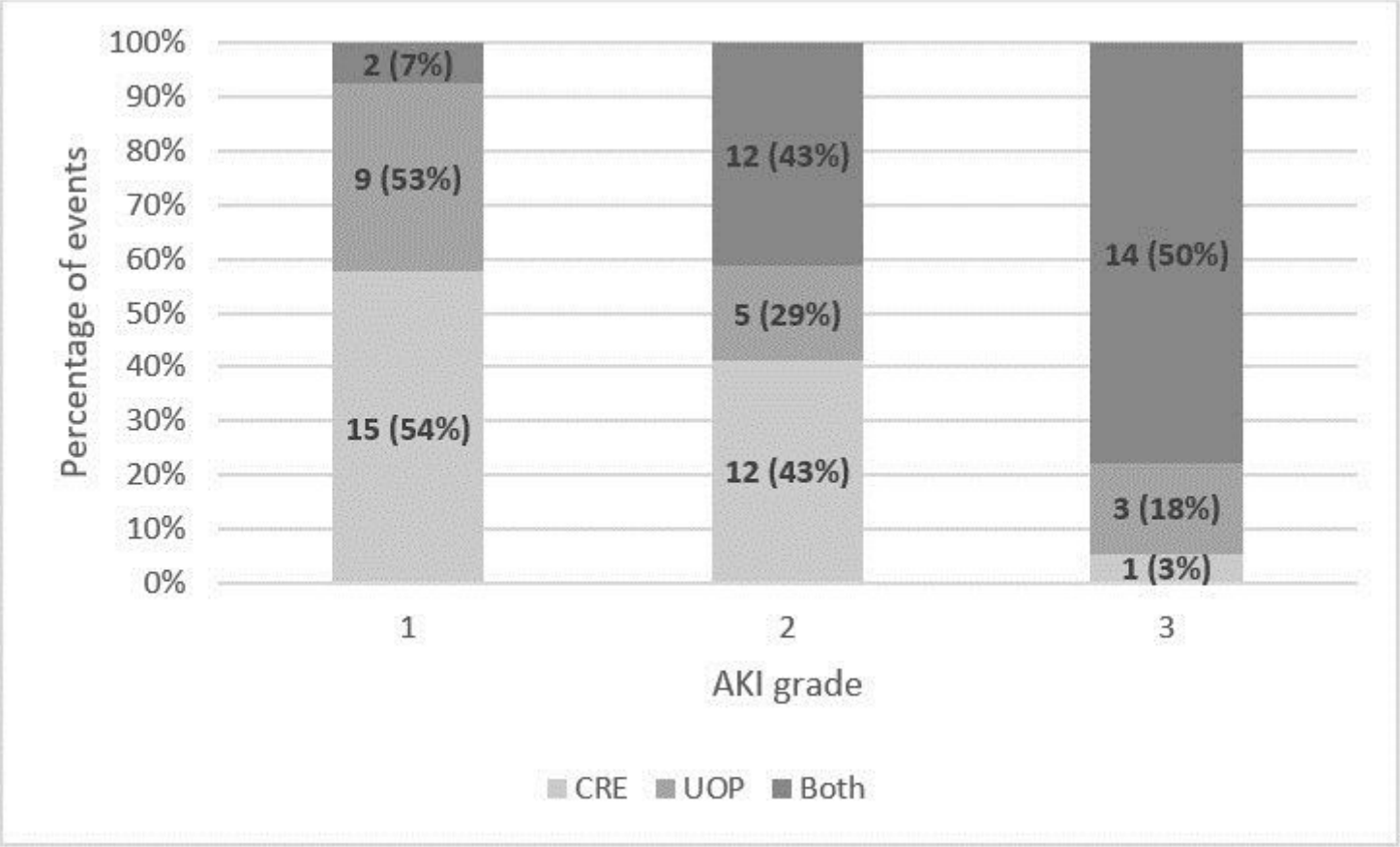

Figure 1

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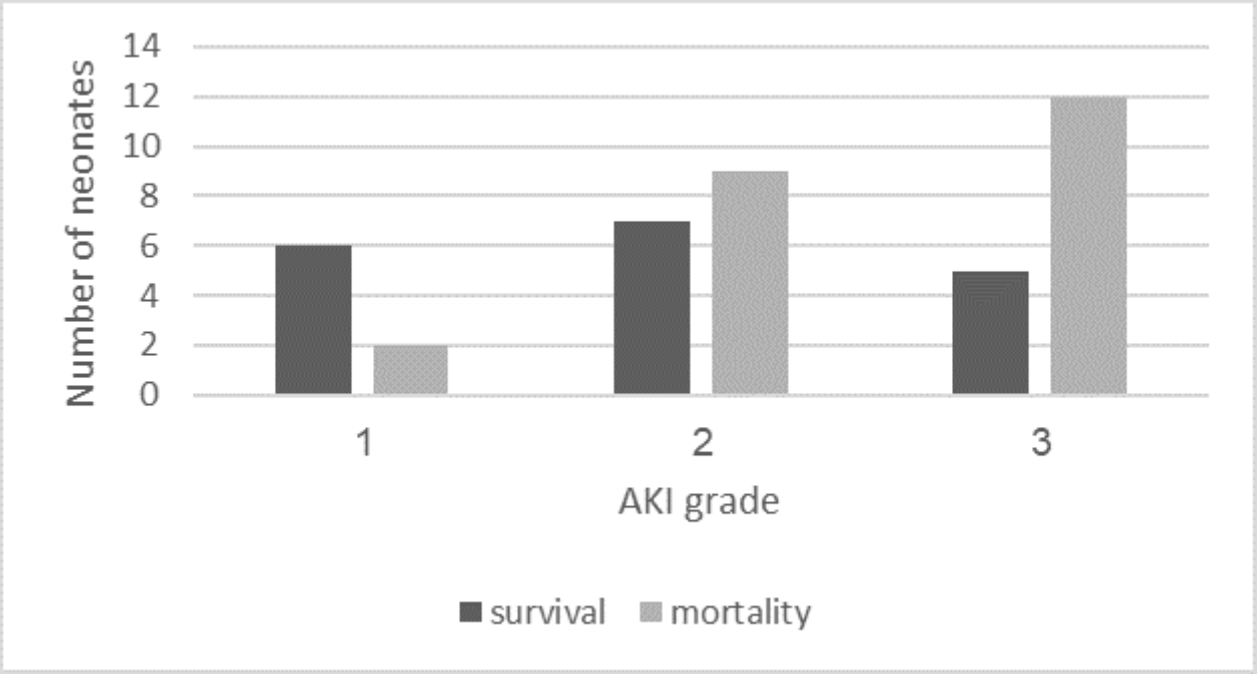

Figure 2

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